RESPIRATORY MEDICINE

Cite as: Archiv EuroMedica. 2025. 15; 4. DOI 10.35630/2025/15/4.015

Received 03 July 2025;
Accepted 18 August 2025;
Published 21 August 2025

THERAPEUTIC PROGRESS IN NON-SMALL CELL LUNG CANCER (NSCLC): MOLECULAR TARGETS AND IMMUNOTHERAPY

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ABSTRACT

BACKGROUND:

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer and remains a major cause of cancer-related mortality. Advances in molecular diagnostics have led to new therapeutic approaches based on genetic alterations.

OBJECTIVE:

To review recent progress in the treatment of NSCLC, including targeted therapies, immunotherapies, and strategies to overcome drug resistance.

METHODS:

Narrative review based on recent literature. No systematic search strategy was applied. Two summary tables present approved therapies for molecular targets and emerging immune-based strategies.

RESULTS:

Therapies targeting EGFR, ALK, ROS1, MET, RET, KRAS, and NTRK are discussed, as well as the use of checkpoint inhibitors, CAR-T cells, and bispecific antibodies. Mechanisms of resistance and corresponding therapeutic approaches are reviewed. Some treatment combinations show statistical improvement in progression-free or

overall survival, but clinical significance remains to be clarified.

CONCLUSIONS:

Modern NSCLC treatment is increasingly personalized. Molecular profiling guides therapy selection, and novel agents expand options for resistant disease. Further studies should focus on clinical endpoints and optimal treatment combinations.

Keywords: non-small cell lung cancer, NSCLC, targeted therapy, resistance, EGFR, ALK, ROS1, immunotherapy, biomarkers, bispecific antibodies

INTRODUCTION

Non-small cell lung cancer (NSCLC) remains a leading cause of death and most patients are diagnosed at an advanced stage. The primary treatment for early-stage NSCLC is surgery; unfortunately, recurrence rates are high [1]. NSCLC represents 85% of all lung cancer cases. Advanced stages of NSCLC are associated with a poor prognosis, although survival is improving with new targeted therapies and immunotherapy. Many patients with NSCLC develop brain metastases (BM), which significantly reduces prognosis and quality of life [2]. A number of oncogenic mutations and rearrangements in NSCLC have been identified as targets for tyrosine kinase inhibitors (TKIs), such as mutations in the EGFR and BRAF genes and fusions in the ALK, ROS1, NTRK, and RET genes, which may represent potential new therapeutic choices [3-5]. Second- and third-generation TKIs are superior to first-generation TKIs, and osimertinib (a third-generation TKI) is now the standard first-line treatment due to its better safety profile and activity in the CNS. Osimertinib has been shown to provide significant and durable improvement in relapse-free survival (DFS) and reduce the risk of local and distant recurrence, including in the CNS. Specific side effects of osimertinib include interstitial lung disease (ILD), pneumonia and cardiovascular events [6,7]. Researchers are exploring new resistance mechanisms (e.g., EGFR C797S, MET amplifications, phenotypic switching) and strategies to overcome them, including combination therapies and innovative drugs. Immunotherapy, especially checkpoint inhibitors (ICIs) such as pembrolizumab or nivolumab, is revolutionizing treatment, and prospects are expanding for CAR-T therapy and bispecific antibodies [8,9]. The future of NSCLC treatment lies in comprehensive molecular profiling, the increasing use of artificial intelligence for data analysis and clinical decision support, and the development of new biomarkers that will allow an even more precise and individualized approach to each patient.

AIMS

The aim of this narrative review is to synthesize and critically evaluate the most recent clinical data and therapeutic strategies in the treatment of non-small cell lung cancer (NSCLC), with a particular focus on targeted therapies, immunotherapy, and emerging combination regimens. The review seeks to answer the following research question: *What are the latest evidence-based developments in NSCLC therapy, and how do they contribute to improving patient outcomes and overcoming treatment resistance?*

METHODS

This narrative review was based on literature selected manually by the authors. Sources were identified through thematic relevance to the treatment of non-small cell lung cancer (NSCLC), with particular attention to recent clinical trials and reviews published between 2018 and 2024. The cited works include both original studies and secondary literature covering molecular subtypes of NSCLC, resistance mechanisms, and targeted therapies.

No systematic search strategy, database selection, or predefined inclusion/exclusion criteria were specified in the article. The references were chosen to illustrate major therapeutic developments and ongoing research directions in the field.

RESULTS

1. NSCLC TARGETED THERAPIES - CURRENT GUIDELINES AND FUTURE DIRECTIONS

Targeted therapy, also known as personalized therapy, is a new and very promising form of oncological therapy [10]. There are special hopes associated with targeted therapy in terms of improving the effectiveness of treatment and extending the overall survival of patients with detected cancer. Its main assumption is the detection of a molecular target, which is performed thanks to molecular tests [11]. In targeted therapy, drugs are used that are not classified as typical cytostatics, it is based on drugs that use cellular mechanisms, blocking them or cellular receptors. Due to the specific nature of this therapy, genetic assessment of cancer cells is required and an estimate of the susceptibility of these cells to the planned treatment [12]. Current guidelines for the treatment of NSCLC cancer include the use of drugs from the group of EGFR, ALK, ROS1 inhibitors [13-15].

1.1. EGFR inhibitors

Some of the NSCLC cancer cells show mutations in the EGFR gene – epithelial cell growth receptor in the TKI domain – Tyrosine Kinase Inhibitors. The role of this protein includes the processes of growth and division, cancer cells get out of control of this protein, which causes rapid growth [16]. EGFR inhibitors block signals from EGHR, causing a reduction in cancer cell growth [17]. The drugs from the EGFR inhibitor group include, among others, first-generation agents such as gefitinib and erlotinib, second-generation afatinib, third-generation osimertinib, and fourth-generation products currently in clinical trials. Third-generation inhibitors such as osimertinib have demonstrated improved progression-free and overall survival compared to first-generation agents in EGFR-mutated NSCLC, particularly in the first-line setting and in patients with brain metastases. Recent research conducted by Dickerson et al. [18] suggests that EGFR inhibitors improve overall survival and quality of life in patients diagnosed with EGFR-mutated NSCLC.

1.2. ALK inhibitors

ALK also known as Anaplastic lymphoma kinase, is a protein that's also involved in a variety of tumors also NSCLC. Rearrangement of ALK gene like fusion EML4-ALK [19], this situation leads to constitutive activation of ALK tyrosine kinase that is also recognized in rapid development of NSCLC. According to Paravaresh et al. approx. 3-5% of NSCLC patients exhibit ALK rearrangements [20]. Approval of this drug type has revolutionized the treatment of the patients, offering them less harmful, toxic and safer therapy options [21]. Drugs that represent I-gen the ALK Inhibitors are: Kryzotinib, II-gen Alektinib and Ceritinib, third gen is Lorlatinib and the newest one Ensartynib [22]. Clinical efficiency of 2nd and 3rd gen ALK Inhibitors offer better Overall Survival and less risk of metastasis [23]. Moreover, Alektinib proved significant improvement in first-line treatment [23].

1.3. ROS 1

ROS1 gene reaaregment is exhibited in 1-2% of patients with NSCLC, fusions presented on this gene lead to activation of ROS1 tyrosine kinase that empowers the neoplasm developing process. Usually patients with ROS1-positive NSCLC react properly to targeted therapies [24]. Crizotinib was the first approved ROS1 Inhibitor for NSCLC. In the PROFILE 1001 clinical trial, it demonstrated median progression-free survival (PFS) of 19.2 months [25]. Other Agents are Entrectinib, Repotrectinib and Taletrectinib [26]. Entrectinib has shown high intracranial activity and is approved as a first-line ROS1 inhibitor, particularly for patients with baseline brain metastases. Repotrectinib and taletrectinib are next-generation inhibitors currently under investigation for crizotinib-resistant cases, including those with ROS1 G2032R mutations.

1.4. New mutations and resistance mechanisms in NSCLC

Targeted therapies have revolutionized the treatment of non-small cell lung cancer (NSCLC), but resistance remains a major challenge. New resistance mechanisms need to be clarified in order to improve patient outcomes and guide the development of next-generation therapies [27].

One of the most common resistance mutations is EGFR C797S, which has a tendency to occur after treatment with third-generation EGFR inhibitors such as Osimertinib [28]. The mutation inhibits effective drug binding, resulting in treatment failure. NTRK1 and ZRSR2 mutations have also been shown to contribute to primary resistance to EGFR-TKIs, which is achieved through activation of bypass signaling pathways [27].

The second common resistance mechanism is gene amplification and fusion. For example, MET amplification is also a frequent event upon failure of EGFR targeted therapy, in which it is achieved by the reactivation of bypass signaling pathways around EGFR inhibition [29]. Similarly, de novo fusion events involving genes such as RET, NTRK, or ALK have also been reported to mediate acquired resistance via reactivation of downstream proliferation cascades [27].

Phenotypic switching is also an important escape mechanism. Some NSCLC tumors can convert to small cell lung cancer after treatment, especially in EGFR mutation. The change in tumor phenotype requires a radical shift in the treatment regimen, typically requiring platinum chemotherapy [30].

1.5. Overcoming resistance

New targeted therapies hold great promise for the patients suffering from non-small cell lung cancer, especially for those whose condition has become resistant to the previous treatment. In ROS1 mutant patients, who are in a position to become resistant to prior treatments, new agents such as repotrectinib and taletrectinib allow effective disease treatment – even brain metastases [31]. These next-generation inhibitors have shown activity in patients with crizotinib-resistant ROS1 fusion-positive NSCLC, including those with brain metastases and G2032R mutations, which are commonly associated with acquired resistance. Combination regimens are also getting more popular among overcoming drug resistance. For example, combined inhibition of MEK and ALK proteins can help

delay the development of resistance, whereas in MET gene-amplified patients, combination therapy targeting both EGFR and MET pathways has been explored [32]. The precise and case-specific treatment of NSCLC is gaining prominence because of these strategies. In early-phase studies, combination strategies such as dual inhibition of EGFR and MET or MEK and ALK have shown potential to delay resistance, although their use remains investigational and context-specific. While some combination therapies and next-generation inhibitors demonstrate statistically significant improvements in progression-free or overall survival, their clinical relevance—such as impact on quality of life, symptom burden, or long-term tolerability—remains insufficiently addressed in current studies. Future trials should distinguish between statistical outcomes and patient-centered clinical benefit to better guide therapeutic decisions in resistant NSCLC.

Table 1 provides an overview of the main molecular targets and approved therapies for NSCLC, including those discussed in this section.

Table 1. Molecular Targets and Corresponding Therapies in Non-Small Cell Lung Cancer (NSCLC)

Molecular Target	Targeted Therapy	Clinical Setting
EGFR (exon 19 del, L858R)	Osimertinib, Erlotinib, Gefitinib, Afatinib	First-line in EGFR-mutated NSCLC
ALK rearrangement	Alectinib, Brigatinib, Lorlatinib	ALK-positive NSCLC, first-line or post-crizotinib
ROS1 fusion	Crizotinib, Entrectinib, Repotrectinib, Taletrectinib	ROS1-positive NSCLC
BRAF V600E	Dabrafenib + Trametinib	NSCLC with BRAF V600E mutation
MET exon 14 skipping	Capmatinib, Tepotinib	NSCLC with MET exon 14 skipping
RET fusion	Selpercatinib, Pralsetinib	RET fusion-positive NSCLC
NTRK fusion	Larotrectinib, Entrectinib	Rare fusions in NSCLC
KRAS G12C	Sotorasib, Adagrasib	NSCLC with KRAS G12C mutation

2. NEW APPROACHES IN NSCLC IMMUNOTHERAPY

2.1. Immune checkpoint inhibitors (ICIs)

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that act by blocking proteins called "immune checkpoints" on the surface of immune cells (primarily T lymphocytes) and on neoplastic cells [8]. The current study provides data on the efficacy of PD-1 inhibitor monotherapy versus chemotherapy in patients with advanced NSCLC, taking into account PD-L1 expression level and line of treatment.

Particularly in the first line of treatment, a positive effect of therapy is seen, which is also present in the second and subsequent lines regardless of PD-L1 levels [33-35]. Although a therapeutic effect is observed, the cited studies differ in PD-L1 thresholds and treatment settings, which limits the generalizability of this conclusion.

Five-year results from the KEYNOTE-024 trial confirm that pembrolizumab in monotherapy as first-line treatment provides a durable and clinically significant overall survival benefit over chemotherapy in patients with metastatic NSCLC with high PD-L1 expression [36]. Paz-Arez et al. also suggested that the combination of nivolumab with ipilimumab showed better results on all efficacy endpoints compared to nivolumab monotherapy in patients with PD-L1 ≥1% and ≥50% [2]. Zhou et al. [37] conclude that neoadjuvant chemotherapy with a PD-1/PD-L1 inhibitor may be the preferred treatment strategy for resectable NSCLC, avoiding the additional toxicity and costs associated with adjuvant immunotherapy without deteriorating survival outcomes. Their study suggests that the addition of adjuvant immunotherapy to PD-1/PD-L1 inhibitor neoadjuvant chemotherapy does not significantly improve Event-Free Survival (EFS) or Overall Survival (OS) compared to PD-1/PD-L1 inhibitor neoadjuvant chemotherapy alone, while increasing the risk of side effects [37]. Adding radiotherapy to durvalumab (PD-1 inhibitor) treatment does not improve systemic objective response rates in patients with NSCLC who previously

showed progression after treatment with PD(L)-1 inhibitors [38].

2.2. CAR-T

In the treatment of NSCLC, CAR T-cell therapy involves harvesting T cells from the patient, which are then genetically modified to express chimeric antigen receptors (CARs) directed against specific antigens present on lung cancer cells, such as EGFR or MUC1 and to destroy them once they are reintroduced into the patient's body [39,40]. The anti-tumor effect of CAR-T therapy may enhance the combination of this therapy with microwave ablation (MWA), however, such research has only been conducted in the context of CAR-T cells targeting the AXL protein [41]. Li et al. [42] in their study proved that another effective target for CAR-T therapy in NSCLC is B7-H3 present on NSCLC cells. Standard B7-H3.CAR T-cells are effective in metastatic and orthotopic models of NSCLC, but have limited ability to target brain metastases [42]. Other promising therapeutic targets for CAR-T, are mesothelin (MSLN), paclitaxel-loaded (PTX), EGFR, MSLN, MUC1, PSCA, CEA, D-L1, CD80/CD86, ROR1, HER2 and c-Met [43-45]. The study by Chinsuwan et al. [46] demonstrates the feasibility of designing CARs using natural EGFR ligands as an alternative to traditional single-chain variable fragment (scFv) of antigen recognition domain for NSCLC therapy. This method may be a promising alternative treatment strategy for advanced NSCLC, regardless of EGFR mutation status or histological subtype [46].

2.3. Bispecific antibodies

Bispecific antibodies (bsAbs), which have two binding sites and are designed to enhance anti-tumor activity with a better safety profile than some combinations. The first in its class of bispecific antibodies simultaneously directed against PD-1 and PD-L1 was IBI318 (also known as LY3434172). Its mechanism of action, which involves blocking the interaction of PD-1 with PD-L1 and PD-L2, as well as PD-L1 with CD80, is to enhance T-cell activation and tumor cell killing by forming bridges between T cells and tumor cells [9]. Bispecific antibodies are a type of modern immune therapy for which researchers are investigating effective predictive biomarkers. The aim of the Song [47] et al. study was to identify biomarkers that can predict which patients will respond to treatment with the bispecific antibody bsAb-KN046. Among those found include molecular heterogeneity within NSCLC tumors [47]. Ivonescimab, as a dual-acting antibody (PD-1 and VEGF-A), has shown promising signals of efficacy in a diverse group of patients with advanced solid tumors, including heavily pretreated populations and tumor types traditionally poorly responsive to immune monotherapy [48,49]. Amivantamab is the first bispecific antibody to demonstrate clinically meaningful efficacy in a patient population with NSCLC with EGFR Exon20ins mutation, which has a very poor prognosis and limited treatment options after chemotherapy (historical ORR ~13%, PFS ~3.5 months, OS ~12.5 months) [50]. The combination of KN046 (bispecific PD-L1/CTLA-4 antibody) with chemotherapy as first-line treatment in metastatic NSCLC has shown satisfactory responses and promising long-term overall survival that appear comparable to or even better (especially OS) than other available combination regimens of immunotherapy and/or chemotherapy (e.g., combinations of two checkpoint inhibitors or inhibitors + chemotherapy), given indirect comparisons [51].

Table 2 summarizes pivotal clinical trials discussed in the previous sections, providing an overview of key therapeutic advances and their clinical outcomes in NSCLC.

Table 2. Key Clinical Trials in Targeted Therapy and Immunotherapy for NSCLC

Clinical Trial	Therapy/Agent(s)	Target Population	Key Outcomes
PROFILE 1001	Crizotinib	ROS1-positive NSCLC	Median PFS: 19.2 months (Shaw et al., 2019)
FLAURA	Osimertinib vs. gefitinib/erlotinib	EGFR-mutant NSCLC (exon 19 del, L858R)	Improved PFS and OS with osimertinib
KEYNOTE-024	Pembrolizumab vs. chemotherapy	Metastatic NSCLC with PD-L1 ≥50%	5-year OS benefit for pembrolizumab
CheckMate 227	Nivolumab + ipilimumab	PD-L1 ≥1% and ≥50% NSCLC	Improved efficacy vs. nivolumab alone
IMpower150	Atezolizumab + bevacizumab + chemo	Non-squamous metastatic NSCLC	Improved PFS and OS in multiple subgroups

ADAURA	Osimertinib (adjuvant)	EGFR-mutant stage IB–IIIA NSCLC	Increased DFS in early-stage patients
CodeBreaK 100	Sotorasib	KRAS G12C-mutant NSCLC	ORR ~37%, PFS ~6.8 months

3. COMBINATION TREATMENT OF NSCLC: COMBINATION OF TARGETED THERAPIES WITH IMMUNOTHERAPY OR CHEMOTHERAPY.

The combination of immunotherapy (ICI) with targeted therapy remains controversial. The combination of EGFR and ALK TKIs increased severe treatment toxicity. This therapeutic combination was associated with an increase in the severity of pneumonia and liver failure. However, despite the unsatisfactory effects of the above-mentioned combination therapy, it was observed that KRAS G12C TKIs may deviate from this norm [52]. Unfortunately, most clinical trials do not progress from phase I to phase II. Due to unacceptable side effects or lack of clinical efficacy [53]. There are currently two ongoing studies evaluating the combination of an ICI with a KRAS G12C TKI. The CodeBreak 101 study evaluates sotorasib in patients with advanced solid tumors who have a KRAS G12C mutation. Phase 1b is assessing the safety and tolerability of sotorasib in combination with other anticancer therapies. The ICIs used are pembrolizumab (anti-PD1), panitumumab (anti-EGFR), and atezolizumab (anti-PDL1) (NCT04185883). The phase 2 KRYSTAL-7 study is evaluating the combination of adagrasib with pembrolizumab in 3 cohorts of patients with advanced NSCLC. 2 cohorts have an NSCLC PD-L1 TPS of <1%, and 1 cohort has a TPS of 1%. Additionally, in the phase 3 KRYSTAL-7 trial, patients with unresectable, locally advanced or metastatic squamous or non-squamous NSCLC are randomly assigned to treatment. This group of patients has a TPS score of >=50% (NCT04613596). The PEMBIB study also concentrates on pembrolizumab but in combination with nintedanib, an angiokinase inhibitor targeting VEGFR 1-3, FGFR 1-3, and PDGFR α/β, as well as RET. The Phase Ib study aims to support the hypothesis of the benefit of combination therapy with ICIs and targeted therapy in patients with solid tumors, particularly NSCLC (NCT02856425). Due to the aforementioned controversies regarding combination therapy and the desire to assess its safety, the MCC-19406 Phase I/II study is ongoing. The combination of nivolumab (anti-PD1), ipilimumab (anti-CTLA4) with nintedanib is being evaluated. The study group consists of patients with NSCLC (NCT03377023). The clinical trials cited above suggest that despite the potential dangers of combination therapy, scientists are right to find its significant efficacy in the treatment of NSCLC. Interestingly, there is also the possibility of using targeted therapy in combination with chemotherapy. Phase 3 of an international study is evaluating the effect of treatment with osimertinib (EGFR TKI) with chemotherapy (cisplatin plus pemetrexed or carboplatin) or without chemotherapy. The emphasis was also on the safety of therapy in NSCLC. According to the results, the group of patients treated with osimertinib with chemotherapy had a significantly higher percentage of progression-free survival compared to treatment with osimertinib alone. However, the frequency of grade 3 adverse events was significantly higher in the group of patients treated with combined therapy [54].

3.1. New strategies for the multidirectional treatment of NSCLC.

There are currently indications of new treatment strategies for NSCLC. These include the combination of ICI with radiotherapy (RT). Phase I and II studies numbered 2013-0882 focused on finding the right dose of ipilimumab in combination with stereotactic body therapy (SBRT). Both SBRT and ipilimumab are approved for the treatment of solid and metastatic tumors (NCT02239900). The next clinical trial regarding the use of ipilimumab in combination with radiation. The study number is 14-00208. The aim is to investigate the safety and efficacy of the therapy in metastatic NSCLC. Ipilimumab in combination with RT in the form of IMRT or 3-D CRT can induce an antitumor immune response at the site of application (NCT02221739). The results of an open, randomized phase II study have been published. Investigators evaluated the use of SBRT in combination with nivolumab in unresectable NSCLC. The use of this therapy has been shown to improve the 4-year adverse event-free rate. This indicates the approach as a potential therapeutic option for patients with unresectable NSCLC [55]. Despite the clinical trial, there is still no clear guidance on the use of immunotherapy in combination with radiotherapy in NSCLC [56]. Furthermore, a phase II study of the combination of pembrolizumab with chemoRT noted a significant increase in grade 3 pneumonia-inducing toxicity [57]. In addition to combining ICI with RT, the treatment of NSCLC also focuses on multidirectional inhibition of molecular pathways. Combining therapies with common signalling pathways improves clinical outcomes in NSCLC patients. Dual inhibition of the EGFR-VEGF pathway appears to be a promising strategy. X.Le et al. refer to several studies involving patients with EGFR-mutated NSCLC. All studies assessed the efficacy of erlotinib (EGFR TKI) plus bevacizumab (anti-VEGF) therapy compared with erlotinib independently.

Virtually all studies showed an increase in progression-free survival (PFS) with erlotinib plus bevacizumab instead of erlotinib unaided. The researchers also refer to studies using other EGFR TKIs in combination with bevacizumab. Thus, gefitinib or afatinib together with bevacizumab likewise confirm the efficacy of dual inhibition of the EGFR-VEGF pathway in patients with EGFR-mutated NSCLC. The possibility of erlotinib plus ramucirumab therapy

compared to erlotinib monotherapy has correspondingly been described. Combination therapy has shown significantly better results in terms of PFS [58]. Additionally, the guidelines of the National Comprehensive Cancer Network and the European Society for Medical Oncology include erlotinib with bevacizumab or ramucirumab as first-line therapy in EGFR-mutated NSCLC [59].

Moreover, the published results of the CHRYSALIS-2 study provide further treatment options for patients with NSCLC aimed at simultaneous dual inhibition of molecular pathways. The study included patients with EGFR-mutated NSCLC who had disease progression or were already treated with osimertinib (EGFR TKI) or platinum-based chemotherapy. It was shown that in such patients, the use of osimertinib in combination with lazertinib (EGFR TKI) offers the possibility of obtaining durable antitumor effects [60].

Furthermore, another TATTON study evaluated the activity of osimertinib, whereas with savolitinib (MET TKI). Patients with EGFR-mutated NSCLC included in the study had acquired resistance to osimertinib after its previous use in anticancer therapy. It was shown that the additional use of MET TKI allows to overcome resistance to osimertinib and thus demonstrate anticancer activity while maintaining the safety of therapy [61].

4. THE FUTURE OF PERSONALIZED NSCLC TREATMENT

Non-small cell lung cancer (NSCLC) has entered a new era of personalised treatment, with therapy increasingly tailored to the molecular profile of each patient's tumour. Advances in targeted therapies and immunotherapies have significantly improved outcomes compared to traditional chemotherapy, leading to higher survival rates in recent years. Key to this progress is comprehensive molecular profiling of tumours to identify actionable genetic alterations that drive cancer growth [62].

Molecular testing using next-generation sequencing (NGS) is now routine in advanced NSCLC to detect driver mutations such as EGFR, ALK, ROS1, BRAF, MET, RET, NTRK, KRAS and ERBB2 (HER2) – alterations that can be matched with specific targeted therapies [63]. Each of these oncogenic drivers, when present, confers sensitivity to a corresponding inhibitor, dramatically improving response rates and survival in the affected subset of patients. For example, NSCLC tumours with EGFR mutations typically achieve high response rates and prolonged survival with EGFR tyrosine kinase inhibitors in place of chemotherapy [63]. Similarly, ALK or ROS1 fusion-positive tumours respond profoundly to ALK/ROS1 inhibitors, with many patients now surviving multiple years on targeted treatment. Even previously "undruggable" mutations like KRAS have become actionable: clinical trials of KRAS G12C-specific inhibitors (e.g. sotorasib) have shown durable tumour responses in KRAS-mutant NSCLC [64]. Another recent success is targeting RET gene fusions – selective RET inhibitors such as selpercatinib achieved response rates around 60–70% in RET fusion-positive NSCLC, including significant activity against brain metastases [65]. The expansion of targeted therapies to cover more molecular alterations has translated into better patient outcomes across the population [66]. Notably, personalised therapies are now extending into earlier disease stages: for instance, the ADAURA trial showed that adjuvant osimertinib significantly improved disease-free survival in resected EGFR-mutant NSCLC, reducing the risk of recurrence and reinforcing the importance of molecular testing even in operable cases [67]. Critically, to realize the full benefit of these advances, broad genomic testing is required for all eligible patients. Studies show that relying on limited single-gene assays can miss targetable mutations; performing comprehensive NGS profiling up front increases the detection of actionable alterations – for example, catching MET exon 14 skipping, ERBB2 mutations or NTRK fusions that sequential single-gene tests might overlook [68]. To ensure sufficient genetic material for analysis, less invasive biopsy approaches are being employed. Liquid biopsies that analyse circulating tumour DNA can often identify the same mutations from blood and are now recommended when tissue samples are inadequate [69]. Overall, molecular profiling has become the cornerstone of therapy personalisation in NSCLC, directing patients to the most effective targeted treatments and even guiding sequential therapies as tumours develop resistance [63]. Major oncology guidelines have accordingly made broad molecular testing and matched targeted therapy standard practice in advanced NSCLC [70].

Artificial intelligence (AI) is poised to further enhance personalised treatment planning by uncovering complex patterns in tumour data that inform therapy decisions. AI algorithms can analyse medical images and pathology slides ("radiomics" and "pathomics") to extract predictive features of tumour biology. For example, radiomic analyses of CT scans have been used to non-invasively predict tumour mutation status and immunotherapy responsiveness, providing imaging-based biomarkers to guide treatment [71]. Deep learning applied to routine histopathology can also identify molecular alterations: an AI-driven pathomics model was recently shown to detect ALK and ROS1 gene fusions directly from H&E-stained slides with near 100% sensitivity and specificity [72]. Such tools could streamline diagnostics by flagging likely molecular subtypes even before genetic tests are completed. Beyond image analysis, AI can integrate multi-dimensional data – genomic profiles, clinical factors, and treatment outcomes – to generate decision support for oncologists. Emerging AI models are being trained to recommend optimal therapy plans based on a tumour's specific molecular and clinical characteristics [73]. They can also help predict which patients will benefit from certain treatments; for instance, machine-learning algorithms have been used to predict immunotherapy responders by analysing patterns of tumour-infiltrating lymphocytes and gene expression [71]. Although these AI applications are mostly in the research phase, their potential to improve

diagnostic precision, prognostication, and treatment selection is tremendous [71]. In the future, AI-driven insights could complement clinicians' decision-making, allowing truly personalised treatment strategies that consider a multitude of tumour features beyond what the human eye or standard tests can discern.

Alongside tumour genetics, there is intense interest in identifying new predictive and prognostic biomarkers in NSCLC. In the realm of immunotherapy, programmed death-ligand 1 (PD-L1) expression is an established biomarker used to select patients for first-line immune checkpoint inhibitor therapy – those with high PD-L1 on tumour cells tend to have higher response rates to anti-PD-1/PD-L1 drugs [74]. However, PD-L1 alone is an imperfect predictor, and additional markers are being explored. Tumour mutational burden (TMB), a measure of total tumour mutation load, has been associated with immunotherapy efficacy, although its clinical utility in NSCLC remains under investigation [74]. Certain tumour genomic profiles also modulate immunotherapy outcomes; for example, NSCLC tumours with co-mutations in STK11 or KEAP1 often exhibit primary resistance to PD-1 blockade, making these mutations potential negative predictive biomarkers. Interestingly, a heavy smoking history – which is linked to high TMB – has itself been correlated with improved response to immunotherapy, suggesting this clinical factor may serve as a surrogate predictor of benefit. Emerging evidence even links the gut microbiome to immunotherapy success, hinting that factors beyond the tumour itself could inform treatment selection in the future [74]. For prognosis, circulating tumour DNA (ctDNA) has shown great promise. Detectable ctDNA after curative surgery or during remission is a strong prognostic indicator of minimal residual disease and impending relapse [75]. Serial monitoring of ctDNA levels can potentially give an early readout of treatment response or resistance, enabling adaptive therapy adjustments. In addition, researchers are investigating circulating microRNAs and other blood-based signals as minimally invasive predictors of outcome in NSCLC. Integrating such biomarkers into practice could refine risk stratification – for instance, identifying which patients might benefit from adjuvant immunotherapy or escalated therapy based on residual disease risk. Indeed, recent evidence confirms that biomarkers like ctDNA and PD-L1 critically inform therapy personalisation and support dynamic treatment planning, and it emphasizes the need for continued innovation in biomarker research [76].

In summary, the future of NSCLC therapy is being shaped by molecular profiling, advanced analytics, and biomarker innovation, all converging to enable truly personalised treatment. Genomic profiling has opened the door to precision medicines that dramatically improve outcomes for molecularly-defined subgroups of NSCLC, and the ongoing expansion of actionable targets is bringing personalised options to more patients than ever before [62]. Concurrently, innovations in AI are beginning to harness the wealth of clinical, imaging, and molecular data to guide therapy decisions tailored to each patient's cancer. The continued development of robust predictive and prognostic biomarkers will further refine this personalised approach, helping clinicians choose the right treatment for the right patient at the right time. By combining comprehensive molecular insights with intelligent, data-driven tools, oncologists can increasingly move away from a "one-size-fits-all" strategy and towards a model of care in which treatment is customised to the unique biology of each patient's tumour. This paradigm shift is already improving patient survival and quality of life in NSCLC [66,76].

DISCUSSION

NSCLC treatment regimens are subject to numerous changes due to new reports and the results of clinical trials. In our work, we presented the latest information related to the treatment of NSCLC. Some research is still ongoing. The remaining despite positive results, give long-term effects in the form of new mutations causing a negative tumor response to treatment. Until now, the first-line treatment for patients with EGFR mutations was gefitinib or erlotinib. However, as a result of the conducted studies, higher PFS after using osimertinib was proven than with previous first-line drugs. Therefore, osimerinib was included in the first-line therapy of NSCLC with EGFR mutation [77]. This appears to provide increased treatment options. Unfortunately, the use of osimertinib may cause the development of further new mutations causing the patient's resistance to this substance. As a result, the field of choice of therapeutic agent is narrowed. Among others, through the development of the C797S mutation and MET amplification [28]. Therefore, osimertinib is not an ideal therapeutic agent. By the development of secondary resistance, such as with the C797S mutation or MET amplification, as well as biological heterogeneity itself, NSCLC presents a significant challenge in achieving consistent clinical outcomes. Therefore, discrepancies in clinical trial results are not solely due to differences in patient selection or the varying disease stage at which the trial is conducted. The effectiveness of a given therapy depends on numerous factors, which should be considered when comparing the results of separate studies. However, with the development of therapeutic strategies, it is possible to use combination therapies which effectively overcome the arisen mutations and, consequently, drug resistance. In the case of MET amplification, the combination of EGFR and MET inhibitors is used. Moreover, it is achievable to delay the development of resistance in patients by inhibiting the MEK and ALK proteins [32]. It may be worth considering combination therapies as first-line treatment in most patients with NSCLC to prevent drug resistance. Unfortunately, there is a type of NSCLC with the EGFR Exon20ins mutation that is primarily resistant to TKI and consequently narrows the therapeutic options for the patient. The clinical trial CHRYSALIS gives hope related to the response to treatment. The amivantamab shows a favorable safety profile and response to therapy. Moreover, the therapeutic effect can be observed in monotherapy and combination with platinum therapy. Nevertheless, treatment strategies for rare mutations like Exon20ins are not established. Primarily due to the

limited research conducted in this area and the difficulty in accurately detecting all patients with the mutation [50]. Due to the ease of resistance to the applied treatment among NSCLC, scientists should begin looking for a solution in the case of resistance to amivantamab.

The universal therapeutic option seems to be the use of one of the CAR-T methods. According to the study we cited above, it is possible to effectively cure NSCLC regardless of EGFR mutation or histological status. The ligand-based EGFR-specific CARs used demonstrate strong antitumor activity without directing the therapy to a specific mutation or type of NSCLC. Additionally, it allows for limited mutations resulting from the treatment. Moreover, lower toxicity and several adverse effects have been noted. The study results strongly support the development of the method. However, despite promising preclinical results, the study was conducted strictly in animal models. There is insufficient clinical data to support the use of this therapy in patients with NSCLC. A further limitation of the study is the inability to assess the occurrence of cytokine release syndrome or neurotoxicity syndrome associated with immunoeffector cells. Precisely due to the unavailability of a non-human primate model. However, it is possible to overcome the limitation. Interestingly, the researchers noted that a humanized mouse xenograft model has been submitted for study. [46]. More significant attention should be paid to finding a way to overcome the BBB in connection with the treatment of NLSCL brain metastases. The report of scientists Li et al related to B7-H3.CAR T cells seems to present yearning. Indeed, co-expression of the CCL2 and CCR2b improves the ability of B7-H3.CAR T cells to cross the BBB toward metastases. Moreover, options are being considered to administer these cells directly to the brain in the area of metastases. However, the method of intravenous administration of cells appears to have significance due to the possibility of simultaneously reaching metastases located in other parts of the body [42]. The choice of local intracerebral or systemic administration of B7-H3.CAR T cells toward metastases may depend on the result of the imaging study and the location of the metastases. This extends the way for other groups of scientists to focus on the treatment of NSCLC patients with metastases.

An interesting aspect of the treatment of patients with NSCLC is the history of smoking and the intestinal microbiome. In some of the analyses, cigarette smoking presents a favorable picture of mOS with immunotherapy. However, the meta-analysis conducted by D. Luo et al. found no effect of smoking status on the efficacy of immunotherapy in NSCLC. No significant difference was detected between former and current smokers and between SCLC and NSCLC patients. Lack of difference in results presents limitations of the study. The authors did not have access to parameters such as smoking amount, duration of smoking, or time since quitting. With further research in this area, there is a potential for developing treatment algorithms for both smokers and nonsmokers [78]. In turn, the intestinal microbiome is currently a highly popular case. A significantly negative effect of antibiotic therapy and PPIs on the response to ICI has been shown. However, the time of use after which the microbiome undergoes noteworthy changes has not been determined [74]. It has been noted that bacterial strains, through their presence, can improve the body's response to anti-CTLA4 therapy. Bacterioides Fragilis and Bacterioides Thetaiotaomicron, through polysaccharide products and dendritic cell maturation, induce a Th1 response. As a result, the effectiveness of therapy is improved. Probiotic supplementation before starting therapy appears to be crucial in this case [79]. Furthermore, by the development of next-generation sequencing (NGS), new species of probiotics have been identified. Due to their potential to affect specific diseases, they have been termed next-generation probiotics (NGPs). NGPs improve immunotherapy and likewise control immune-related adverse events (iRAEs). These include Eubacterium limosum, E. hirae, Enterococcus faecium, Collinsella aerofaciens, and Burkholderia cepacia. NGPs may increase survival in patients with NSCLC [80].

CONCLUSIONS

Non-small cell lung cancer (NSCLC) is a biologically heterogeneous disease. Advances in molecular diagnostics have enabled the development of mutation-specific targeted therapies and immunotherapy. This review synthesized current evidence on the efficacy and limitations of immune checkpoint inhibitors, CAR-T cells, bispecific antibodies, and tyrosine kinase inhibitors in genetically defined subtypes of NSCLC. The therapeutic relevance of alterations such as EGFR, ALK, ROS1, BRAF, MET, RET, and KRAS G12C was discussed in the context of first-line therapy and acquired resistance.

Despite substantial progress, primary and secondary resistance remains a critical barrier. Next-generation inhibitors and combination regimens targeting resistance mechanisms are emerging but require further validation in controlled trials.

An individualized treatment approach based on precise molecular profiling is essential to optimize clinical outcomes. The integration of biomarkers, real-world data, and resistance monitoring should inform future strategies in NSCLC management.

DISCLOSURES

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All authors have read and agreed with the published version of the manuscript.

USE OF AI

Artificial intelligence tools (e.g., ChatGPT, OpenAI) were used to assist with language editing, structural refinement, and the formulation of selected textual segments (e.g., background synthesis, objectives, conclusions). All AI-assisted content was critically reviewed, fact-checked, and finalized by the authors.

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