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Review Article

Molecular Targeting in Non-Small Cell Lung Cancer: Advances in EGFR, ROS1, ALK, and MET Pathways

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Abstract

Non-small cell lung cancer (NSCLC) remains a prevalent and deadly malignancy, presenting a substantial global health challenge. Significant progress has been achieved in the last few decades regarding the comprehension of the complex molecular mechanisms that underlie NSCLC. This extensive literature review analyzes the present understanding of the molecular pathways associated with non-small cell lung cancer (NSCLC) and emphasizes the potential of molecular targeting as a favorable therapeutic approach. We conduct a detailed analysis of key molecular targets and discuss the impact of emerging therapeutic modalities on the treatment landscape of NSCLC. Furthermore, we explore potential avenues for future research in this rapidly advancing field, emphasizing the importance of ongoing research and innovation in managing NSCLC and advancing precision medicine.

Keywords: Non-small cell lung cancer; molecular targeting; targeted therapies; precision medicine; resistance mechanisms; biomarkers; clinical trials;

Introduction

Non-small cell lung cancer (NSCLC) represents the predominant subtype of lung cancer, accounting for approximately 85% of all cases [1-2]. Despite significant advancements in diagnostic techniques and therapeutic interventions, NSCLC remains a principal cause of cancer-related mortality worldwide. The complexity of the molecular pathways involved in the pathogenesis of NSCLC necessitates a deep understanding of these mechanisms. Such knowledge is essential for the development and optimization of targeted therapies, which hold the potential to improve patient outcomes significantly [1, 3].

Mechanisms of Oncogenesis during abnormal genetic alterations (AGA)

There are many abnormal genetic aberrations already identified in NSCLC, at least for ten of them we have identified a targeted therapy while for the others research is ongoing. Epidermal growth factor receptor (EGFR) is a dimeric membrane protein and is expressed in more than 60% of NSCLCs. Binding to its ligand facilitates the formation of a dimer and phosphorylation of the tyrosine residues. The process activates the intracellular downstream signaling through MAPD and PI3K pathways, leading to cancer cell proliferation, differentiation, migration, and survival [1, 4]. Approximately 20% of NSCLC patients carry activating mutations in EGFR [4-6]. The most common mutations in non-small cell lung cancer (NSCLC) include deletions in exon 19 (Ex19del) and the L858R point mutation within exon 21. EGFR mutations are more prevalent among individuals of East Asian ethnicity, females, and never-smokers, and are more frequently identified in adenocarcinoma subtypes [1,3,7]. Interestingly, current research suggests that NSCLC patients with EGFR mutations exhibit a better overall survival (OS) outcome compared to those with wild-type EGFR, regardless of whether they receive targeted EGFR therapy. EGFR mutation appears to be an independent predictor of better outcomes. EGFR-mutated NSCLC cells are highly sensitive to EGFR Tyrosine Kinase

inhibitors (TKI) [3]. There are additional EGFR mutations that are less common in exons 18 and 20 that respond to the TKI afatinib [4] or insertion in exon 20 that conferee a poor response to TKI and have now new therapies like chemothereapy and amivantamab a bispecific antibody [5].

Anaplastic lymphoma kinase (ALK) is a transmembrane receptor tyrosine kinase predominantly expressed in the central and peripheral nervous systems of developing embryos, with expression levels significantly decreasing after birth. ALK gene rearrangements occur in approximately 3-8% of non-small cell lung cancer (NSCLC) cases, particularly in adenocarcinomas, affecting predominantly younger patients, males, and never or light smokers. The EML4 and ALK genes are closely located on the short arm of chromosome 2. The intrachromosomal rearrangement resulting in the EML4-ALK translocation leads to the constitutive dimerization of the ALK kinase domain, which activates downstream cell signaling pathways responsible for inhibiting apoptosis and promoting cellular proliferation. Research has suggested that the ALK fusion gene tends to be mutually exclusive with EGFR and KRAS mutations. Consequently, targeting the EML4-ALK fusion gene has been a focus in the treatment of NSCLC [1, 6]. The proto-oncogene tyrosine-protein kinase (ROS) participates in embryonic development and acts as an initiator of signaling events for the differentiation of epithelial tissues. The incidence of ROS1 rearrangement is about 1-2% among NSCLC patients [6,7]. It is more reported in females, nonsmokers, and younger age. ROS rearrangement, by forming phosphotyrosine-recruitment sites in the terminal tail of ROS, leads to protein kinase-activity dysregulation and abnormal activation of signaling pathways involved in cell proliferation, growth, and survival [8]. However, ROS1 rearrangements are not associated with poor prognosis. It is reported to have a higher incidence of the development of thromboembolic events when compared to EGRF or KRAS mutation and the general NSCLC population despite no mortality differences being found [9,10].

Mesenchymal-Epithelial Transition (MET)

The Mesenchymal-Epithelial Transition (MET) proto-oncogene, which encodes a receptor tyrosine kinase, is a transmembrane receptor expressed in the epithelial cells of multiple organs, including the liver, pancreas, and bone marrow. MET recognizes hepatocyte growth factor (HGF) as a ligand and regulates essential cellular processes. Acting as both a pleiotropic factor and a cytokine, HGF promotes cell proliferation, survival, differentiation, and morphogenesis [11-13].

Current studies indicate that diverse oncogenic alterations of MET, including mutations, amplification, overexpression, chromosomal rearrangements, and fusions, contribute to the development of cancer. MET exon 14 skipping is the most prevalent point mutation identified in non-small cell lung cancer (NSCLC), and it is associated with a poor prognosis [11, 14].

The purpose of this paper is to review the most significant clinical data available for key genetic aberrations in lung cancer, examining the benefits of the latest therapies on clinical outcomes and the adverse effects that patients may experience during treatment.

EGFR

EGFR tyrosine kinase inhibitors (TKIs) are recommended as the first-line treatment for advanced non-small cell lung cancer (NSCLC) patients with EGFR-activating mutations. Additional EGFR mutations that lead to TKI resistance frequently contribute to disease progression. Although lung cancer remains challenging to treat and is usually incurable in its advanced stages, the discovery of EGFR-activating mutations has transformed the perception and management of this disease. The response to EGFR TKIs has fostered hope that lung cancer might become curable in the future.

In 2017, Soria et al. published the results of the FLAURA trial, which evaluated the efficacy of osimertinib compared to standard EGFR tyrosine kinase inhibitors (TKIs), gefitinib or erlotinib, in the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). The study included patients who had not received prior treatment and were confirmed to have EGFR exon 19 deletions or L858R mutations. Importantly, the inclusion criteria allowed for patients with central nervous system (CNS) metastases, provided they were in a stable neurological condition.

The trial demonstrated a significant improvement in median progression-free survival (PFS) with osimertinib, which was 18.9 months compared to 10.2 months for patients treated with standard EGFR-TKIs (hazard ratio for disease progression or death, 0.46; 95% confidence interval [CI], 0.37 to 0.57; P<0.001). Furthermore, the overall survival (OS) rate at 18 months was notably higher in the osimertinib group at 83% (95% CI, 78 to 87) versus 71% (95% CI, 65 to 76) in the standard EGFR-TKI group (hazard ratio for death, 0.63; 95% CI, 0.45 to 0.88; P = 0.007, although nonsignificant in the interim analysis). Adverse events of grade 3 or higher occurred less frequently with osimertinib than with standard EGFR-TKIs (34% vs. 45%). These results were pivotal in establishing osimertinib as a first-line treatment option for patients with EGFR-mutated advanced NSCLC.

Notably, resistance to first- and second-generation EGFR tyrosine kinase inhibitors (TKIs), primarily due to the T790M mutation, typically emerges within 8-14 months of treatment initiation. The third-generation TKI, osimertinib, was developed to address this issue. Fourth-generation drugs, which are still under development, are anticipated to overcome multiple resistance

mechanisms, including those observed with third-generation TKIs. The ADAURA trial, led by Wu et al., evaluated the efficacy of osimertinib in patients with completely resected EGFR mutation–positive non-squamous NSCLC. The primary endpoint was disease-free survival (DFS) among patients with stage II to IIIA disease. A total of 682 patients were randomized in a 1:1 ratio to receive either osimertinib or placebo for three years. At 24 months, the DFS rate in the osimertinib group was 89% (95% CI, 85 to 92) compared to 52% in the placebo group (95% CI, 46 to 58), with an overall hazard ratio for disease recurrence or death of 0.20 (99.12% CI, 0.14 to 0.30; P<0.001). Additionally, at the same time point, 98% of patients in the osimertinib group (95% CI, 95 to 99) and 85% of those in the placebo group (95% CI, 80 to 89) were alive without central nervous system disease, with an overall hazard ratio for disease recurrence or death of 0.18 (95% CI, 0.10 to 0.33).

The authors concluded that in patients with stage IB to IIIA EGFR mutation–positive NSCLC, DFS was significantly longer for those receiving osimertinib compared to those who received placebo. The latest updates from this trial also suggest a minimal, yet statistically significant, improvement in overall survival (OS).

Trials are currently assessing the role of added chemotherapy for metastatic disease to improve outcomes, but the results have been mixed so far. Longer-term survival data are necessary before incorporating chemotherapy into the initial treatment strategy for EGFR-mutant NSCLC. In the FLAURA2 trial, an open-label study involving 557 patients with advanced EGFR-mutated NSCLC, the initial treatment combining osimertinib with platinum-pemetrexed chemotherapy showed an improvement in progression-free survival (PFS) compared to osimertinib alone (29.4 months versus 19.9 months). At 24 months, overall survival (OS) data were immature, but there was a nonsignificant trend favoring the osimertinib-chemotherapy combination (hazard ratio 0.9, 95% CI 0.65-1.24). However, grade =3 adverse events were more common in the osimertinib-chemotherapy group (64% versus 27%). These findings suggest a potential benefit in PFS with the addition of chemotherapy to osimertinib treatment, though the increase in severe adverse effects and the lack of significant improvement in OS at the interim analysis warrant cautious interpretation and further investigation.

An open-label, randomized phase 2 clinical trial evaluated the efficacy of osimertinib alone versus its combination with carboplatin-pemetrexed in patients with EGFR mutation-positive NSCLC who experienced disease progression associated with the T790M resistance mutation during first-line EGFR-TKI therapy. The study found that the median progression-free survival (PFS) was 15.8 months for the osimertinib monotherapy group compared to 14.6 months for the combination therapy group, with a hazard ratio of 1.09 (95% confidence interval: 0.51-2.32; P = .83). Median overall survival (OS) was not reached in either group. The overall response rate was 71.4% in the osimertinib monotherapy group and 53.6% in the combination group. The frequency and severity of known adverse events in the combination group were comparable to those previously reported for carboplatin and pemetrexed, and no novel adverse events were observed during the study. The addition of chemotherapy to osimertinib as a second-line treatment did not prolong survival but was found to be generally tolerable. This suggests that while the combination therapy does not offer a significant survival benefit over osimertinib monotherapy, it remains a viable treatment option for patients who can tolerate the regimen.

A phase II study done assessed the efficacy of osimertinib in patients with EGFR mutation-positive NSCLC in whom systemic disease (T790M-negative) progressed after treatment with first- or second-generation EGFR TKIs and platinum-based chemotherapy. The primary end point was overall response rate (ORR). From August 2020 to February 2021, 55 patients from 15 institutions were enrolled in the study. The ORR for primary analysis was achieved in 16 patients (29.1 %; 95 % CI, 17.6-42.9), which exceeded the threshold response rate necessary for analysis. Stable disease (SD) was found in 16 patients (29.1 %), and progressive disease, in 18 (32.7 %). The median length of PFS was 4.07 months (95 % CI 2.10-4.30), and the rate of 12-month PFS was 17.3 %. Osimertinib demonstrated modest antitumor activity against progressive EGFR T790M-negative disease [17].

The BOOSTER trial, an open-label randomized phase II study, investigated the efficacy and safety of combining osimertinib with antiangiogenic therapy using bevacizumab in patients with EGFR-mutant advanced NSCLC who acquired T790M mutations after failure on previous EGFR TKI therapy. The primary endpoint of the trial was investigator-assessed progression-free survival (PFS), while secondary endpoints included overall survival (OS), objective response rate (ORR), and adverse events (AEs). Between May 2017 and February 2019, 155 patients were randomized into two groups: 78 received the combination therapy of osimertinib 80 mg daily and bevacizumab 15 mg/kg every 3 weeks, and 77 received osimertinib alone. After a median follow-up of 33.8 months (interquartile range: 26.5-37.6 months), 129 (83.2%) PFS events were reported in the intention-to-treat population.

The results showed no significant difference in median PFS between the combination therapy group (15.4 months; 95% CI: 9.2-18.0 months) and the osimertinib alone group (12.3 months; 95% CI: 6.2-17.2 months; stratified log-rank P = 0.83), with a hazard ratio (HR) of 0.96 (95% CI: 0.68-1.37). Median OS was also similar between the groups, being 24.0 months (95% CI: 17.8-32.1 months) in the combination arm and 24.3 months (95% CI: 16.9-37.0 months) in the osimertinib arm (stratified log-rank P = 0.91), with an HR of 1.03 (95% CI: 0.67-1.56). The study

shows no significant improvements in progression-free survival (PFS) or overall survival (OS) compared to osimertinib alone for the broader patient population. However, an exploratory analysis highlighted a notable interaction between smoking history and treatment efficacy for PFS. Specifically, smokers benefited more from the combination therapy, showing a hazard ratio (HR) of 0.52 (95% CI: 0.30-0.90), indicating a reduced risk of disease progression or death, whereas never smokers had an HR of 1.47 (95% CI: 0.92-2.33), suggesting a potential disadvantage.

The objective response rate (ORR) was consistent across both treatment arms at 55%, but the median time to treatment failure was significantly shorter in the combination group than in the osimertinib-alone group (8.2 months vs. 10.8 months, respectively; P = 0.0074). This finding suggests that while the combination therapy may initially inhibit tumor growth effectively, its benefits may diminish quicker than with osimertinib alone.

Regarding safety, the incidence of grade =3 treatment-related adverse events (TRAEs) was higher in the combination therapy group (47%) compared to the osimertinib-alone group (18%). This aligns with previous reports, underscoring that while the combination of osimertinib and bevacizumab is tolerable, it poses a higher risk of severe side effects.

The differential impact of the combination therapy based on smoking status underscores the complexity of lung cancer treatment and suggests that personalized approaches could be crucial in optimizing therapeutic strategies. Further research is necessary to understand the mechanisms behind these differences and to determine optimal dosing strategies or alternative combinations of targeted therapies, particularly for specific patient subgroups like smokers.

Resistance to EGFR tyrosine kinase inhibitors (TKIs) in the treatment of non-small cell lung cancer (NSCLC) can be classified into two main categories: intrinsic (or primary) resistance and extrinsic (or secondary) resistance. Intrinsic resistance refers to the initial ineffectiveness of EGFR-TKIs, even in the presence of EGFR mutations that typically predict a favorable response to these drugs. Although the exact mechanisms underlying intrinsic resistance are not fully understood, it has been associated with non-classical sensitizing EGFR mutations that do not respond to standard EGFR-TKIs as effectively as classical mutations like exon 19 deletions or the L858R mutation in exon 21.

Secondary or acquired resistance, on the other hand, typically develops after prolonged exposure to EGFR-TKIs. Several molecular mechanisms contribute to this type of resistance. Among these, mutations in exon 20 of the EGFR gene, particularly exon 20 insertions, are notable for their role in conferring resistance to first- and second-generation EGFR-TKIs. These exon 20 insertions occur in approximately 1-10% of cases and represent a significant challenge in the management of EGFR-mutant NSCLC, necessitating alternative therapeutic strategies or the development of next-generation inhibitors that can effectively target these resistant mutations.

Ongoing research is exploring novel combination therapies that can circumvent medication resistance due to EGFR mutations, a prevalent issue in the treatment of non-small cell lung cancer (NSCLC). Among these studies, the MARIPOSA trial (NCT04487080) is a phase 3, multicenter, randomized study that compares the efficacy and safety of the combination therapy of amivantamab and lazertinib versus single-agent osimertinib as first-line treatment for patients with EGFR-mutant NSCLC. Amivantamab is an EGFR-MET bispecific antibody with immune cell-directing activity, which targets both activating and resistance EGFR mutations as well as MET mutations and amplifications.

In another study, the ongoing CHRYSALIS trial (NCT02609776), amivantamab in combination with lazertinib, a potent, brain-penetrant third-generation EGFR TKI, has shown antitumor activity in both treatment-naive patients and those who have relapsed on osimertinib. Further demonstrating the potential of these innovative approaches, a phase I study conducted in October 2023 examined the use of amivantamab plus chemotherapy for advanced NSCLC with EGFR exon 20 insertions. In a randomized trial involving 308 patients with advanced NSCLC harboring EGFR exon 20 insertions and who had not received previous systemic therapy, those assigned to the targeted combination of amivantamab and chemotherapy experienced a significantly longer progression-free survival compared to those receiving chemotherapy alone (11.4 versus 6.7 months).

These findings suggest that integrating targeted agents like amivantamab with either novel TKIs like lazertinib or with chemotherapy could represent a promising strategy to overcome resistance mechanisms in EGFR-mutant NSCLC, potentially leading to improved clinical outcomes for this challenging patient population [19].

In summary, there are exciting developments ongoing for patients with EGFR-mutated non-small cell lung cancer (NSCLC). The treatment landscape is evolving from the use of osimertinib as monotherapy to exploring its use in combination with chemotherapy. Furthermore, the potential introduction of new therapeutic agents like amivantamab and lazertinib as frontline treatments represents a significant advancement. These innovative approaches aim to enhance treatment efficacy, manage resistance mechanisms, and improve clinical outcomes.

Medication	Trials	Primary Endpoint
Osimertinib vs Gefitinib/ Erlotinib	FLAURA	PFS 18.9 months vs. 10.2 months; hazard ratio for disease progression or death, 0.46; 95% confidence interval [CI], 0.37 to 0.57; P<0.001)
Osimertinib or placebo	ADAURA	DFS was not reached (95% CI, could not be calculated to could not be calculated) in the osimertinib group and 27.5 months (95% CI, 22.0 to 35.0) in the placebo group.
Osimertinib vs Osimertinib + chemotherapy	FLAURA 2	PFS was 25.5 months in the osimertinib–chemotherapy group vs 16.7 in the osimertinib group (hazard ratio for disease progression or death, 0.62; 95% CI, 0.49 to 0.79; P<0.001)
Osimertinib vs pemetrexed plus carboplatin/cisplatin	AURA3	PFS benefit previously seen did not result in a statistically significant improvement in OS with an HR of 0.87 (95% CI 0.67e1.12; P < 0.277) and median OS of 26.8 months for osimertinib versus 22.5 months for platinum-pemetrexed.
Osimertinib + bevacizumab	BOOSTER	PFS between the combination (15.4 months; 95% CI 9.2-18.0 months) and the osimertinib arms (12.3 months; 95% CI 6.2-17.2 months) [log-rank P < 0.71; HR (95% CI): 0.94 (0.66-1.33)]

Table 1: Landmark trial of EGFR targeted therapy**.**

ALK

The therapeutic landscape has been significantly changed with the introduction of ALK inhibitors to clinical trials and encouraging improvements in patient prognoses since the identification of EML4-ALK fusion in non-small cell lung cancer (NSCLC). Cryzotinib was initially recognized as the chosen therapeutic intervention for ALK fusions, which in turn other medications to participate in clinical trials with the objective of acquiring improved disease management and results.

The 2017 J-ALEX study, led by Hida et al., was an important phase 3 trial that played a significant role in the approval of ALK-targeted therapy. Patients from Japan who had one prior chemotherapy regimen or were chemotherapy-naive but had ALK-positive NSCLC were the primary participants in this study. Until disease progression, intolerable toxicity, death, or withdrawal, 207 patients were randomly assigned to receive oral alectinib or crizotinib.

PFS was the principal outcome measure utilized in this research. Patients who were administered alectinib had a significantly longer PFS than those who were administered crizotinib (hazard ratio [HR] 0.37, 95% confidence interval [CI] 0.26-0.52; median PFS 34.1 months versus 10.2 months with crizotinib), according to a subsequent analysis of the data. With the exception of the median OS, neither treatment arm achieved a superior overall survival (OS) rate than the other at the time of the final OS analysis in late 2020 (HR 1.03, 95% CI 0.67-1.58, P = 0.9105; median OS did not reach 0.67). A possible limitation of this study went beyond this demographic cohort, as the study's representation was almost exclusively of the Asian population.

Overall, additional research is required to determine the long-term efficacy and generalizability of alectinib beyond the J-ALEX trial, where it demonstrated a superior PFS in comparison to crizotinib.

Medication	Trials	Primary Endpoint
Alectinib vs Crizotinib	J- ALEX	PFS with alectinib (not estimable [NE] [95% CI 20·3–NE]) compared with crizotinib (10·2 months [8·2–12·0]; HR 0·34 [99·7% CI 0·17–0·71]; p<0·0001)
Brigatinib vs Crizotinib	ALTA-1L	PFS 67% [95% {CI}, 56 to 75] vs. 43% [95% CI, 32 to 53]; HR for disease progression or death, 0.49 [95% CI, 0.33 to 0.74]; P<0.001
Ensartinib vs Crizotinib	NCT02767804	PFS for patients without brain metastases was not reached with ensartinib vs 16.6 months with crizotinib (at 12 months: 4.2% with ensartinib vs 23.9% with crizotinib; cause-specific HR, 0.32; 95% CI, 0.16-0.63; P = .001)
Lorlatinib vs Crizotinib	CROWN	PFS 78% (95% [CI], 70 to 84) in the lorlatinib group and 39% (95% CI, 30 to 48) in the crizotinib group (HR for disease progression or death, 0.28; 95% CI, 0.19 to 0.41; P<0.001)

Table 2. ALK targeted therapy.

In the ongoing development of treatments for ALK-positive non-small cell lung cancer (NSCLC), another ALK inhibitor, brigatinib, has shown promise when compared to crizotinib. The ALTA-1L trial, led by Camidge et al., involved randomly assigning patients with advanced ALK-positive NSCLC who had not previously received any ALK inhibitors. The patients were given either brigatinib or crizotinib with the primary endpoint being progression-free survival (PFS).

The results demonstrated a higher rate of PFS with brigatinib compared to crizotinib. The estimated 12-month PFS for patients receiving brigatinib was 67% (95% confidence interval [CI], 56 to 75) versus 43% (95% CI, 32 to 53) for those receiving crizotinib, with a hazard ratio for disease progression or death of 0.49 (95% CI, 0.33 to 0.74; P<0.001). These findings led the authors to conclude that brigatinib significantly prolongs PFS compared to crizotinib among patients with ALK-positive NSCLC who have not previously received an ALK inhibitor. This study underscores the effectiveness of brigatinib as a valuable therapeutic option for patients with this specific genetic profile, potentially offering improved outcomes over the previously preferred crizotinib.

In a large multicenter, open-label, randomized phase 3 trial conducted across 120 centers in 21 countries, 290 patients with advanced, recurrent, or metastatic ALK-positive NSCLC were enrolled between July 25, 2016, and November 12, 2018. This study, led by Leora Horn et al., investigated the efficacy of ensartinib compared to crizotinib. Patients, aged 18 years or older (median age, 54 years; range, 25-90 years), were randomized in a 1:1 ratio. In the ITT (intention-to-treat) population, the median PFS was significantly longer with ensartinib than with crizotinib (25.8 [range, 0.03-44.0 months] vs 12.7 months [range, 0.03-38.6 months]; hazard ratio, 0.51 [95% CI, 0.35-0.72]; log-rank P < .001), with a median follow-up of 23.8 months (range, 0-44 months) for the ensartinib group and 20.2 months (range, 0-38 months) for the crizotinib group. In the mITT population, the median PFS in the ensartinib group was not reached, and the median PFS in the crizotinib group was 12.7 months (95% CI, 8.9-16.6 months; hazard ratio, 0.45; 95% CI, 0.30-0.66; log-rank P < .001). The intracranial response rate was 63.6% (7 of 11) with ensartinib vs 21.1% (4 of 19) with crizotinib for patients with target brain metastases at baseline. PFSl for patients without brain metastases was not reached with ensartinib vs 16.6 months with crizotinib as a result of a lower central nervous system progression rate (at 12 months: 4.2% with ensartinib vs 23.9% with crizotinib; cause-specific hazard ratio, 0.32; 95% CI, 0.16-0.63; P = .001). Frequencies of treatment-related serious adverse effectsvents (ensartinib: 11 [7.7%] vs crizotinib: 9 [6.1%]), dose reductions (ensartinib: 34 of 143 [23.8%] vs crizotinib: 29 of 146 [19.9%]), or drug discontinuations (ensartinib: 13 of 143 [9.1%] vs crizotinib: 10 of 146 [6.8%]) were similar, without any new safety signals. (254)

For patients with newly diagnosed, ALK-positive non-small cell lung cancer (NSCLC), the recommendation has shifted towards using a next-generation ALK inhibitor as the first-line treatment over crizotinib, due to the superior efficacy and safety profiles of these newer agents. Among the second-generation ALK inhibitors, alectinib is often suggested due to the availability of longer-term follow-up data from clinical trials, which has demonstrated its effectiveness and tolerability. However, it is important to note that direct comparisons between second-generation ALK inhibitors have not been extensively performed, making it challenging to definitively rank one over the others based solely on direct head-to-head data. As such, other second-generation inhibitors such as brigatinib and lorlatinib are also recognized as viable first-line options. Each of these medications has shown significant efficacy in clinical settings and can be considered depending on individual patient profiles, such as the presence of brain metastases, specific mutation patterns, and potential side effects. This approach allows for personalized treatment planning to optimize outcomes for patients with ALK-positive NSCLC.

The CROWN trial, a phase 3 study led by Shaw et al., evaluated lorlatinib against crizotinib in patients with previously untreated advanced ALK-positive NSCLC. Lorlatinib demonstrated a significantly higher overall response rate (ORR) of 76% (95% CI, 68 to 83) compared to 58% (95% CI, 49 to 66) in the crizotinib group. Notably, lorlatinib achieved 71% rate of intracranial complete response, highlighting its effectiveness in treating patients with CNS involvement-a common complication in NSCLC. The most frequent adverse events associated with lorlatinib were hyperlipidemia, edema, peripheral neuropathy, and cognitive effects. These findings underscore lorlatinib's potential as a superior first-line option for this patient population, particularly for those with a significant risk of or existing brain metastases.

Ceritinib was the first second-generation ALK inhibitor approved specifically for the treatment of NSCLC patients resistant to crizotinib. It effectively inhibits the L1196M and G1269A ALK mutations, which are among the most common mechanisms of resistance to crizotinib. This makes cells expressing ALK significantly more sensitive to ceritinib compared to crizotinib, providing a robust treatment option for patients who develop resistance. In current clinical studies, ALK-positive NSCLC, other second-generation ALK inhibitors such as alectinib, brigatinib, and PF-06463922 (lorlatinib) are currently under development. Each of these agents targets different crizotinib-resistant ALK mutations, enhancing the potential for tailored treatment strategies based on the genetic profile of the tumor. The genetic identification of crizotinib-resistant mutations is key for selecting the most effective treatment strategy to overcome resistance and improve

progression-free survival in NSCLC patients. This guidance emphasizes the importance of personalized medicine in the management of cancer, allowing for more targeted and effective interventions based on individual tumor genetics.

ROS 1

ROS1 gene fusions account for approximately 1-2% of all cases of non-small cell lung cancer (NSCLC). Similarly to ALK NSCLC, patients with ROS1+ NSCLC tend to have minimal smoking history and be of the female sex. In most cases, adenocarcinoma is the dominant histology [28]. There are currently fourthree target therapies for NSCLC with ROS-1 mutation. However, the resistance to current ROS1 inhibitors remains a significant clinical challenge. Focusing on the development of ROS-1 target therapy will serve a critical role in treating NSCLS with activating ROS1 gene mutations and improve the mortality.

Medication	Trials	Primary Endpoint
Crizotinib	PROFILE 1001	ORR) was 72% [95% (CI), 58% to 83%] in 53 patients
Entrectinib	ALKA-372-001 and STARTRK-1	ORR 86% in 14 patients [95% (CI), 60, 96]
Repotrectinib	TRIDENT-1	ORR was 91% in 11 patients
Ceritinib	ASCEND-5	PFS compared with chemotherapy (5·4 months [95% CI 4·1–6·9] for ceritinib *vs* 1·6 months [1·4–2·8] for chemotherapy; hazard ratio 0·49 [0·36–0·67]; p<0·0001)

Table 3: ROS1 targeted therapy.

The ROS1 tyrosine kinase is a critical therapeutic target in NSCLC, and it shows high sensitivity to several inhibitors including the ROS1/MET inhibitor crizotinib and the ROS1/tropomyosin receptor kinase (TRK) inhibitors entrectinib and repotrectinib. These agents have proven effective in addressing both primary and resistance mutations in ROS1 fusion-positive NSCLC.

A clinical analysis of three phase I or II trials involving 161 patients with ROS1 fusion-positive NSCLC, including those with CNS metastases, demonstrated significant efficacy of entrectinib. The objective response rate (ORR) to entrectinib was 67 percent, with a median progression-free survival (PFS) of 15.7 months and a 12-month overall survival (OS) rate of 81 percent. Notably, the median duration of response also stood at 15.7 months, indicating durable responses in a substantial portion of patients.

Further emphasizing the effectiveness of ROS1 inhibitors, the TRIDENT-1 trial, a phase I/II study, assessed repotrectinib in patients with ROS1-positive NSCLC. Among 71 TKI-naïve patients, the ORR was an impressive 79 percent, and the median PFS reached 36 months. However, in a subset of 56 patients who had received one prior TKI but no chemotherapy, the ORR decreased to 35 percent, and the median PFS was nine months. This difference highlights the challenges in treating TKI-pre-exposed patients but also underscores the potency of repotrectinib in a first-line setting. In recognition of these compelling outcomes, repotrectinib was FDA approved in November 2023 for the treatment of new patients with ROS1-positive tumors or for those who have failed previous therapy. This approval was particularly notable as repotrectinib has shown efficacy in overcoming specific ROS1 resistance mutations like G2032. The approval of repotrectinib, along with the success of other TKIs in this setting, represents a significant advance in the treatment of patients with ROS1-driven NSCLC, providing new hope and options for this subgroup of lung cancer patients.

Observational clinical data support the use of crizotinib for ROS1-positive NSCLC (31). In an open-label, (PROFILE 1001 trial), international study of crizotinib of 53 patients with ROS1-positive NSCLC, over 80 percent of whom had received one or more prior chemotherapy regimens, ORR was 72 percent (6 complete and 32 partial responses). The median duration of response was 25 months, and the median PFS and overall survival (OS) were 19.3 and 51 months, respectively (32,33). Crizotinib demonstrated a remarkable efficacy profile in a phase II trial involving 127 East Asian patients diagnosed with NSCLC positive for ROS1. These results are consistent with those observed in larger populations. A median progression-free survival (PFS) of 15.9 months was documented in the trial. In contrast to indirect comparisons to conventional chemotherapy or chemoimmunotherapy, where the median overall survival (OS) typically extends a duration of nine months to two years, these findings are especially significant. This comparison highlights the substantial benefit that targeted therapies offer in this particular subgroup of patients with NSCLC.

Nevertheless, it is also considered acceptable to save these specific agents for subsequent-line settings, following the patient's response to initial chemotherapy and/or immunotherapy. The

adaptability of treatment sequencing permits customized therapeutic approaches in accordance with the unique circumstances of each patient and their previous responses to treatments.

In the long term clinical experience that has been acquired through the prolonged use of crizotinib, entrectinib has emerged as the preferred option among numerous clinicians. The rationale behind this preference is entrectinib's superior intracranial efficacy and longer duration of response in comparison to crizotinib. Anticipated is repotrectinib to achieve a comparable standing in the future. Recent clinical trial outcomes and approvals indicate that repotrectinib might provide benefits comparable to or exceeding those of intracranial protection and duration of response.

Regarding resistance to ROS1 therapy, Lin et al. published a report on 55 patients who underwent a repeat biopsy after progression: 47 post-crizotinib and 32 post-lorlatinib. Mutations in ROS1 were detected in 38% and 46% of the cases, respectively. The ROS1 G2032R mutation was identified as the most prevalent in 33% of the cases. D2033N (2.4%), S1986F (2.4%), L2086F (3.6%), G2032R/L2086F (3.6%), G2032R/S1986F/L2086F (3.6%), and S1986F/L2000V (3.6%) were additional ROS1 mutations observed after crizotinib and L2086F, respectively. A patient whose disease progressed despite treatment with crizotinib, lorlatinib, and ROS1 L2086F was managed with cabozantinib for nearly eleven months. We also detected METamplification (4%), KRAS G12C (4%), KRAS amplification (4%), NRAS mutation (4%), and MAP2K1mutation (4%), among lorlatinib-resistant biopsies [35].

MET

Expansion and maintenance of cancer stem cells are dependent on MET signaling and expression [37]. MET overexpression, which is frequently associated with a poor prognosis and is observed in the majority of solid malignancies (including lung cancers), is the result of increased gene copies and transcriptional regulation [38]. Tumor development and MET activation are caused by mutations including D1228N, Y1235D, and M1250T [39]. MET amplification acquired in certain tumors results in the upregulation of kinases and the stimulation of survival signals that follow; these are referred to as acquired resistance mechanisms to various EGFR TKIs [40]. Lung cancer patients frequently harbor oncogenic mutations in the juxtamembrane domain (exon 14) and the Sema domain (exon 2) [41]. There have been reports of MET exon 14 (METex14) splice site mutations in NSCLC and other types of tumors [42]. In lung cancer, point mutations in the juxtamembrane domain of MET variants (R988C and T1010I, for example) were associated with increased tumorigenicity and metastatic potential [43]. A fusion of the MET domain with the kinesin family member 5B gene (KIF5B) was identified in a lung adenocarcinoma sample from a patient [44].

In recent times, additional MET fusion partner genes in patients with lung cancer have been identified via next-generation sequencing (NGS) technologies. Ataxin 7-like 1, human leukocyte antigen (HLA)-DRB1, StAR-related lipid transfer domain-3 N-terminal like (STARD3NL), and CD47 are some of these genes [45]. Although it has been demonstrated that the MET exon 14 mutation is mutually exclusive with EGFR, KRAS, BRAF, ALK, and ROS1 rearrangements, it can co-occur with MET, MDM2, CDK4, EGFR amplification, and PI3KCA [36] among others.

Crizotinib, a non-selective MET TKI, is authorized for the treatment of advanced NSCLC with ALK and ROS1 rearrangements [47]. It inhibits multiple kinases, including MET, ALK, ROS1, and RON. The PROFILE 1001 phase I trial, which included 69 patients with non-small cell lung cancer (NSCLC) and multiple genetic alterations, demonstrated the following: median progression-free survival (PFS) of 7.3 months (95% CI 5.4-9.1) and median duration response (DOR) of 9.1 months (95% CI 6.4-12.7) [48]. The objective response rate (ORR) was 32% (CI 21-45). Patients who had MET exon 14 mutations were enrolled in the METROS study, a phase II clinical trial. Skipping and amplification of these mutations led to an ORR of 27% (95% CI 11-47) and a median PFS of 4.4 months (95% CI 3.0-5.8) [49]. AcSe also demonstrated a PFS of 3.2 months and an ORR of 16% in the phase II clinical trial involving NSCLC patients with MET alterations [50]. Cabozantinib is an approved small-molecule, type II MET TKI for the treatment of multiple cancers; it targets multiple kinases, including VEGFR1-3, RET, TIE2, FLT-3, and KIT. In a Phase II trial involving advanced non-small cell lung cancer (NSCLC) patients with EGFR wild type who were treated with cabozantinib alone or in combination with erlotinib, PFS was improved (4.3 months, HR 0.39, 80% CI 0.27-0.55; 4.7 months, HR 0.37, 80% CI 0.25-0.53; cabozantinib and erlotinib alone; 1.8 months, 95% CI 1.7-2.2) [51].

Capmatinib, which was approved by the FDA in May 2020 for patients with metastatic NSCLC and MET exon 14 alterations, is one of the selective MET TKIs that is highly effective against MET activation, including MET exon 14 alterations [52]. The endorsement was granted on the grounds of a GEOMETRY mono-1 phase 2 trial involving patients with NSCLC who possessed EGFR wild type, ALK-negative, and MET exon 14 skipping mutation and amplification [53]. In contrast to treatment-naïve patients who had not undergone any prior treatment, the pretreated patients in this study exhibited a notable enhancement in ORR (68%), DoR (12.6 months), and ORR (41%), lasting 9.7 months [53].

Following the VISION trial phase II, the FDA approved potentinib as a second-line oral MET inhibitor of high selectivity, specifically for the treatment of patients with NSCLC who have a MET exon 14 skipping mutation [54]. The median PFS was 8.5

months (95% CI: 6.7-11) and the ORR was 46% (95% CI: 36-57) [54]. Savolitinib is a type Ib MET TKI that is oral and ATP-competitive. It was approved in China in 2021 for the treatment of patients with advanced NSCLC who have MET exon 14 skipping alterations and progressive disease [55]. In Chinese patients with metastatic pulmonary sarcomatoid carcinoma or unresectable or metastatic NSCLC with MET exon 14 altered NSCLC, a multi-cohort phase 2 trial established an ORR of 49.2% (95% CI 31.1-55.3) with a median PFS of 6.9 months and a median overall survival (OS) of 12.5 months [56].

Medication	Trials	Primary Endpoint	Secondary Endpoint
Capmatinib	GEOMETRY mono-1 (NCT02414139) (53)	ORR 41%	Median PFS in treatment naïve (12.4 months), prior treated patient (5.4 months)
Tepotinib	VISION (NCT02864992) (54)	ORR 46%	Median PFS 8.5 months, DOR 11.1 months
Savolitinib	NCT02897479 (56)	ORR 49.2%	Median PFS 6.9 months
Crizotinib	PROFILE-1001 (NCT00585195) (48)	ORR 32%	Median PFS 7.3 months, DOR 9.1 months
Cabozantinib	NCT01708954 (51)	ORR 3%	Median PFS 1.8 months, OS 5.1 months
		ORR 11%	Median PFS 4.3, OS 9.2 months

Table 4: MET targeted therapy.

Escape mechanism of EGFR

Presently, MET-targeted therapy mechanisms consist of neutralizing antibodies or kinase activity inhibitors to prevent the MET-HCF interaction extracellularly; small molecule inhibitors to impede kinase phosphorylation; and related signal transducers to obstruct MET signaling [9]. Additional research is required to determine the optimal sequential approach from the array of MET-TKIs that are currently available, in addition to the treatment method that can postpone resistance.

By inhibiting MET protein degradation, the MET exon-14-skipping mutation induces the protein to function as an oncogenic driver. Capmatinib and tepotinib, which are MET inhibitors, have received approval from the FDA for the treatment of adult patients who have a MET exon-14-skipping mutation. In lieu of immunotherapy and/or chemotherapy, their utilization is recommended in the front-line setting [36].

Discussion

Targeted therapy for lung cancer represents a paradigm shift in oncology, offering a more personalized and effective approach to treatment. By specifically targeting the AGA driving tumor growth, these therapies have demonstrated significant improvements in patient outcomes and hold promise for further enhancing survival rates in the future. Traditional treatments for lung cancer, such as chemotherapy and radiation therapy, have been limited by their non-specific nature and associated toxicities. In contrast, targeted therapies focus on exploiting the unique genetic alterations present within cancer cells. This approach has been particularly successful as shown in multiple phase 2 and 3 trials and now a days there are the treatments of choice for patients with genetic alterations that are actionable instead of palliative and toxic chemotherapy.

TKIs targeting EGFR, including erlotinib, gefitinib, and osimertinib, have revolutionized the therapeutic paradigm in the realm of EGFR-mutant lung cancer. These agents exhibit prolonged PFS and tumor regression in comparison to chemotherapy. In the same direction, crizotinib, alectinib, and brigatinib, which are ALK inhibitors, have exhibited remarkable effectiveness in patients with lung cancer who are ALK-positive. This has resulted in enhanced prognoses and quality of life. In addition, the advancement of next-generation sequencing (NGS) technologies has facilitated the identification of additional actionable mutations by enabling comprehensive genomic profiling of lung tumors. This has enabled the identification and clinical application of previously undiscovered targeted agents, including MET inhibitors (e.g., dabrafenib, trametinib) and ROS1 inhibitors (e.g., entrectinib), thereby increasing the range of treatment alternatives available to patients with these molecular modifications.

Furthermore, targeted therapy presents a challenge to immunotherapy, a field that continues to demonstrate positive results. It is possible that in the future, a viable combination of targeted therapy and immunotherapy, such as antiangiogenesis inhibitors, can be identified, as it currently suggests these two treatment modalities are incompatible. Immunocheck inhibitors do not provide any benefit to patients with AGA, including those who were previously discussed, despite elevated levels of PDL1 immunohistochemistry (IHC) staining. Furthermore, the concurrent or sequential use of these inhibitors has not been deemed safe, primarily due to the increased risk of toxicities such as interstitial lung disease. With the development of novel agents and the enhancement of treatment strategies via more

precise molecular profiling, the future of targeted therapy in lung cancer appears to be bright. The implementation of liquid biopsy techniques, which enable the detection of circulating tumor DNA in a non-invasive manner, will support the continuous monitoring of treatment response and the identification of resistance mechanisms in real time. As a result, clinicians will be able to modify treatment accordingly, thereby optimizing therapeutic effectiveness and reducing the advancement of the disease.

Conclusions

In conclusion, targeting pathways at the molecular level in NSCLC holds considerable potential as a means to enhance patient outcomes. Targeted therapies have significantly revolutionized the treatment paradigm, and further investigations are continually demonstrating novel molecular targets and therapeutic approaches. To optimize the efficacy of precision medicine in non-small cell lung cancer (NSCLC), obstacles including resistance and the requirement for reliable biomarkers must be overcome. The combination of state-of-the-art scientific advancements and clinical application will determine the trajectory of NSCLC treatment, ultimately fostering optimism among those who are resisting this serious condition.

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