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Drug Resistance Mechanisms and Strategies of EGFR/ALK Targeted Therapy in Non-Small Cell Lung Cancer

Yanwei Wang

Immersion Academy, Irvine, USA
counselor@immersionacad.com

Abstract. Non-small cell lung cancer (NSCLC) remains a leading cause of global cancer-related mortality. Epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) targeted therapies have revolutionized the treatment of patients with corresponding mutations or fusions. However, the emergence of drug resistance—including primary resistance (e.g., EGFR exon 20 insertions, ALK fusion variant heterogeneity) and acquired resistance (e.g., EGFR T790M, ALK L1196M mutations)—severely limits long-term efficacy. This review systematically synthesizes the molecular mechanisms underlying EGFR/ALK resistance, highlighting both commonalities (e.g., target mutations) and specificities (e.g., small cell transformation in EGFR resistance). It further summarizes current coping strategies, including the development of next-generation inhibitors (osimertinib, lorlatinib), combination therapies (targeted therapy combined with chemotherapy, immunotherapy, or dual-target inhibition), and personalized regimens guided by liquid biopsy. Additionally, the review discusses recent research advances, ongoing challenges (complex resistance, toxicity management), and future directions (single-cell sequencing, multi-target drug design), aiming to provide insights for optimizing clinical practice and accelerating therapeutic innovation in NSCLC.

Keywords: Non-small cell lung cancer, EGFR, ALK, targeted therapy, drug resistance, therapeutic strategies.

1. Introduction

Non-small cell lung cancer (NSCLC), accounting for approximately 85% of all lung cancer cases, ranks among the leading causes of cancer-related morbidity and mortality globally, with over 2 million new cases and 1.8 million deaths reported annually in recent epidemiological data [1]. This high mortality burden stems not only from the aggressive biological behavior of NSCLC but also from challenges in early detection, as most patients present with advanced-stage disease (stage IIIB or IV) at diagnosis, limiting curative treatment options [2]. In the clinical management of NSCLC, traditional chemotherapy and radiotherapy, while partially effective in inhibiting tumor growth, lack specificity—often damaging normal tissues and inducing adverse reactions such as myelosuppression and gastrointestinal toxicity. Moreover, their efficacy is constrained by tumor heterogeneity, where subpopulations of cancer cells within a single tumor exhibit distinct genetic and phenotypic characteristics, resulting in suboptimal patient prognosis; median overall survival

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(OS) for advanced-stage NSCLC treated with conventional therapies remains less than 12 months [2]. Driven by breakthroughs in genomic sequencing, molecular diagnostics, and personalized therapeutic design, the advancement of precision medicine has revolutionized NSCLC treatment by introducing targeted therapy as a pivotal and transformative approach. Unlike traditional treatments relying on broad cytotoxic effects, targeted therapy acts by specifically recognizing and engaging tumor-specific molecular targets—abnormal proteins or genetic alterations that drive cancer initiation, growth, and progression—thereby minimizing damage to surrounding healthy tissues [1]. Among the complex network of oncogenic drivers implicated in NSCLC, two targets have emerged as the most extensively studied and clinically validated: epidermal growth factor receptor (EGFR), a transmembrane tyrosine kinase receptor whose mutations (e.g., exon 19 deletions, L858R substitutions) hyperactivate downstream proliferation-signaling pathways; and anaplastic lymphoma kinase (ALK), a receptor tyrosine kinase that, when fused with partner genes (e.g., EML4), generates chimeric proteins triggering uncontrolled tumor growth [1]. EGFR-sensitive mutations occur in 15%-30% of NSCLC patients globally—with rates as high as 50% in some Asian populations—while ALK fusions are observed in 2%-7% of cases, predominantly in younger, non-smoking patients [1]. Inhibitors targeting these pathways (EGFR-TKIs and ALK-TKIs) have significantly improved key clinical outcomes: they markedly boost objective response rates (ORR), with more patients experiencing measurable tumor shrinkage, and prolong progression-free survival (PFS), the duration of stable disease without worsening. These consistent benefits have established them as first-line treatments for eligible patients—those with tumors harboring corresponding EGFR mutations or ALK fusions [2]. However, drug resistance has emerged as a critical barrier to the long-term efficacy of EGFR/ALK targeted therapy. Primary resistance, characterized by an absence of initial treatment response, affects a subset of patients and is often driven by mechanisms such as EGFR exon 20 insertions or ALK fusion variant differences that inherently reduce drug sensitivity [1]. Acquired resistance, by contrast, develops over time in initially responsive patients—typically 10-14 months after treatment initiation—leading to disease progression, recurrence, or metastasis and ultimately shortening survival [1]. Currently, research on EGFR/ALK resistance mechanisms and coping strategies in NSCLC has accumulated substantial preclinical and clinical data. This review synthesizes current knowledge on these mechanisms, summarizes therapeutic strategies and research progress, analyzes existing challenges, and outlines future directions, aiming to inform both clinical practice and research by providing actionable insights and highlighting critical gaps in the field.

2. Mechanisms of drug resistance to EGFR/ALK targeted rherapy in NSCLC

2.1. EGFR target resistance mechanisms

Primary resistance: This form of resistance is mediated through two primary mechanisms. First, target-specific mutations—such as EGFR exon 20 insertions—induce conformational perturbations in the EGFR protein, abrogating molecular interactions between EGFR-TKIs and their cognate binding pocket and impairing inhibitory efficacy. EGFR exon 20 insertions, accounting for ~10% of all EGFR mutations, are particularly problematic: they sterically hinder binding of first- and second-generation EGFR-TKIs, resulting in ORRs of <10% with these agents [2]. Second, aberrant activation of compensatory alternative signaling pathways—exemplified by MET amplification—enables tumor cells to bypass EGFR-mediated cascades entirely, maintaining proliferative and survival signaling through these alternative molecular circuits even under EGFR inhibition [1].

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Acquired resistance: A more common clinical challenge, acquired resistance to EGFR-TKIs arises through diverse mechanisms evolving under prolonged treatment pressure. The most well-characterized is the T790M mutation, occurring in the EGFR kinase domain, which reduces drug binding affinity by increasing EGFR's affinity for ATP (the natural ligand), thereby outcompeting TKIs [1]. This mutation is detected in 50%-60% of patients with acquired resistance to first- and second-generation EGFR-TKIs (e.g., gefitinib, afatinib). Another critical mechanism is the C797S mutation, which disrupts covalent binding of third-generation EGFR-TKIs (e.g., osimertinib), rendering these agents ineffective and presenting a significant clinical challenge [2]. Beyond target gene mutations, phenotypic shifts contribute to resistance: small cell transformation—where NSCLC cells transdifferentiate into a small cell lung cancer (SCLC)-like phenotype—occurs in 5%-10% of cases, associated with loss of retinoblastoma (RB1) and TP53 function, making tumors unresponsive to EGFR-TKIs [1]. Additionally, epithelial-mesenchymal transition (EMT)—a process where cancer cells lose epithelial traits and gain mesenchymal characteristics—enhances invasiveness and drug insensitivity by altering cell morphology and upregulating drug efflux pumps [2]

2.2. ALK target resistance mechanisms

Primary resistance: This form of resistance is intimately linked to two pivotal determinants. First, heterogeneity of ALK fusion variants—where distinct isoforms of the ALK fusion protein exhibit conformational divergences that reduce binding avidity for ALK-TKIs, impairing drug engagement and target inhibition. For example, the EML4-ALK variant 3a/b fusion confers lower crizotinib sensitivity than variant 1, with preclinical studies demonstrating a 3- to 5-fold higher half-maximal inhibitory concentration (IC50) [2]. Second, co-occurring mutations (e.g., TP53 aberrations) perturb cellular signaling networks governing drug responsiveness and tumor suppressor function, ultimately reducing ALK-TKI efficacy in constraining neoplastic proliferation [1].

Acquired resistance: This mechanism is characterized by two principal modalities. First, secondary ALK mutations (e.g., L1196M, G1202R) induce conformational changes in the ALK kinase domain, abrogating molecular interactions with ALK-TKIs and diminishing inhibitory efficacy. The L1196M "gatekeeper" mutation, analogous to EGFR T790M, is frequently detected in crizotinib-resistant patients, while G1202R is a recalcitrant mutation conferring resistance to most first- and second-generation ALK-TKIs [1]. Second, aberrant activation of bypass signaling cascades—typified by EGFR pathway upregulation—enables tumor cells to compensate for inhibited ALK-mediated signaling by hijacking alternative transduction networks to sustain proliferative signals essential for neoplastic progression [2].

2.3. Commonalities and specificities in resistance mechanisms

Both EGFR and ALK resistance share "target mutation" as a core mechanism, where secondary mutations (e.g., EGFR T790M, ALK L1196M) reduce drug-target affinity by altering kinase domain structure. This highlights the evolutionary pressure exerted by TKIs, which select for subclones harboring such mutations to survive and proliferate [1]. Additionally, both pathways exhibit bypass signaling activation as a resistance strategy—with MET amplification (EGFR) and EGFR upregulation (ALK) representing common examples of how tumor cells rewire signaling to evade inhibition [2]. Notable differences exist, however: "small cell transformation" is specific to EGFR resistance, reflecting the plasticity of EGFR-mutant NSCLC and its ability to transdifferentiate into a more aggressive phenotype [1]. In contrast, ALK resistance more frequently involves complex

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fusion variant heterogeneity, with certain variants (e.g., EML4-ALK variant 3) inherently predisposing tumors to early resistance [2]. Furthermore, ALK fusion-positive NSCLCs often exhibit higher intra-tumoral genetic diversity, leading to coexisting multiple resistance mechanisms (e.g., concurrent ALK mutations and bypass signaling) in a single patient, complicating therapeutic decision-making [1].

3. Strategies to overcome EGFR/ALK resistance in NSCLC

3.1. Development of novel targeted agents

The pursuit of next-generation TKIs designed to overcome known resistance mechanisms has been a major focus of therapeutic development. Third-generation EGFR-TKIs: Osimertinib, an irreversible inhibitor, was engineered to target the T790M mutation while sparing wild-type EGFR, reducing off-target toxicity. Clinical trials (e.g., AURA3) show it significantly extends PFS in patients with acquired T790M mutations (median 10.1 months vs. 4.4 months with chemotherapy) [1]. Fourth-generation EGFR-TKIs (e.g., BLU-945) are now in preclinical and early clinical evaluation for inhibiting EGFR with C797S mutations—alone or in combination with osimertinib—offering promise for this challenging resistance mechanism [2].

Next-generation ALK-TKIs: Lorlatinib, a third-generation ALK-TKI, exhibits broad activity against diverse ALK secondary mutations (e.g., L1196M, G1202R) and efficacy in patients progressing on prior ALK-TKIs. The CROWN trial demonstrated a median PFS of 36.7 months with lorlatinib in treatment-naive ALK-positive NSCLC—significantly outperforming crizotinib (9.3 months)—with durable responses in patients with baseline resistance mutations [2]. Other agents (e.g., entrectinib, brigatinib) have expanded the armamentarium; brigatinib, for example, shows activity against ALK mutations and central nervous system (CNS) metastases—a common progression site in ALK-positive disease [1].

3.2. Conbination therapy strategies

Given the complexity of resistance mechanisms, combination therapies targeting multiple pathways simultaneously have emerged as a rational approach to prevent or delay resistance.

Targeted therapy plus chemotherapy: Combining EGFR-TKIs with pemetrexed (a folate antimetabolite) shows synergistic effects in preclinical models, complementing EGFR inhibition with cytotoxicity against non-mutated subclones. Trials such as NEJ009 demonstrate that first-line gefitinib plus pemetrexed/platinum chemotherapy significantly improves median PFS (20.9 months vs. 11.2 months with gefitinib alone) in EGFR-mutant NSCLC, with benefits extending to patients with early resistance signs [3]. Dual-target inhibition: Co-targeting EGFR and MET addresses MET amplification—a common bypass mechanism in EGFR-TKI-resistant tumors. Phase II trials of combinations (e.g., osimertinib plus savolitinib, a MET inhibitor) report ORRs of 36%-52% in MET-amplified, EGFR-TKI-resistant NSCLC, highlighting this approach's potential [1]. Similarly, for ALK-positive NSCLC, combinations of ALK-TKIs with EGFR inhibitors (e.g., lorlatinib plus cetuximab) are being tested to counteract EGFR-mediated bypass signaling [2].

Targeted therapy plus immunotherapy: While oncogene-driven NSCLCs were historically thought less responsive to immune checkpoint inhibitors (ICIs), recent studies suggest combining EGFR/ALK-TKIs with ICIs may enhance efficacy by modifying the tumor microenvironment. The KEYNOTE-189 trial, evaluating pembrolizumab plus chemotherapy in non-squamous NSCLC, included EGFR/ALK-mutant subsets and demonstrated improved OS with combination therapy vs.

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chemotherapy alone, supporting this strategy in resistant settings [3, 4]. Preclinical studies further indicate EGFR-TKIs may reduce immunosuppressive myeloid cells in the tumor microenvironment, enhancing ICI activity [5].

3.3. Resistance monitoring and personalized therapy

Real-time detection of resistance mechanisms and tailored therapy are critical for optimizing outcomes. Liquid biopsy: Circulating tumor DNA (ctDNA) analysis—a non-invasive method for detecting genetic alterations in cell-free DNA—enables real-time monitoring of resistance mutations (e.g., T790M, L1196M) with high sensitivity. Studies show ctDNA can detect T790M up to 3-6 months before radiological progression, allowing timely treatment adjustments [2]. Serial liquid biopsy also tracks clonal evolution of resistant subpopulations, providing insights into resistance dynamics and guiding sequential therapy decisions [1].

Personalized regimens: Tailoring therapy to specific resistance mechanisms has become a cornerstone of precision oncology. For example, osimertinib is recommended for T790M mutations, while dual EGFR-MET inhibition is preferred for MET amplification [1]. In ALK-positive NSCLC, patients with G1202R mutations may benefit from lorlatinib, whereas those with EGFR bypass activation may respond to ALK-TKI/EGFR inhibitor combinations [2]. This personalized approach improves ORRs and PFS compared to empiric therapy changes.

4. Research progress and challenges

4.1. Recent advances in resistance mechanisms

Recent years have seen significant strides in understanding EGFR/ALK resistance molecular bases, driven by technologies like single-cell sequencing and spatial transcriptomics. These tools reveal resistant tumors comprise heterogeneous subclones with distinct resistance mechanisms—a phenomenon termed "clonal mosaicism" [3]. For example, single-cell analysis of EGFR-TKI-resistant tumors identifies coexisting subclones with T790M mutations, MET amplification, and EMT, highlighting resistance network complexity. Additionally, cross-regulation of the PI3K/Akt/mTOR pathway has emerged as a key resistance mediator, with pathway activation observed in both EGFR and ALK resistant tumors, making it a potential combination therapy target [2]. Another notable advance is recognition of the tumor microenvironment (TME) as a resistance contributor. The TME—including immune cells, fibroblasts, and extracellular matrix components—promotes resistance by secreting growth factors (e.g., hepatocyte growth factor, HGF) that activate bypass signaling or creating physical barriers to drug penetration [4]. For instance, cancer-associated fibroblasts (CAFs) in EGFR-mutant NSCLC secrete HGF, leading to MET activation and EGFR-TKI resistance, underscoring the need to target stromal-tumor interactions [5].

4.2. Clinical translation of strategies

Several resistance-directed strategies have transitioned from preclinical research to clinical practice. Osimertinib, for example, is now standard for T790M-positive NSCLC, with long-term follow-up showing a 5-year OS rate of 28%—a significant improvement over historical chemotherapy outcomes [1]. Combination therapies have also advanced: the CHOICE-01 trial demonstrated toripalimab (a PD-1 inhibitor) plus chemotherapy significantly improved PFS and OS in treatment-naive advanced NSCLC, including EGFR/ALK-mutant subsets, supporting immunotherapy integration into resistance management [6]. In ALK-positive NSCLC, the CheckMate 9LA trial

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provided evidence for dual immunotherapy (nivolumab plus ipilimumab) with short-course chemotherapy in advanced disease—including patients with prior ALK-TKI resistance—with a 4-year OS rate of 37% in the combination arm [7, 8]. These data highlight immunotherapy-based combinations' potential to complement targeted therapy in resistant settings.

4.3. Current limitations

Despite these advances, significant challenges remain, eg. complex resistance: Multi-mechanism resistance—where tumors simultaneously exploit multiple pathways (e.g., concurrent T790M mutations and MET amplification in EGFR-resistant NSCLC)—is increasingly recognized and poses challenges for single-agent or dual-agent strategies. Detecting such complexity requires comprehensive genomic profiling, which is not universally accessible and may be cost-prohibitive in resource-limited settings [2]. Toxicity management: Combination therapies, while effective, often increase adverse event risks. For example, EGFR-TKI plus MET inhibitor combinations are associated with higher rates of rash, diarrhea, and interstitial lung disease, while immunotherapy combinations may cause immune-related toxicities (e.g., pneumonitis, colitis) requiring corticosteroids—potentially compromising anti-tumor immunity [9]. These toxicities can reduce adherence and limit optimal dosing.

Emerging resistance: Long-term use of novel agents has led to new resistance mechanisms. For example, osimertinib resistance may involve C797S mutations or activation of alternative pathways (e.g., FGFR1 amplification), requiring further mechanistic studies to develop next-generation strategies [10]. Similarly, lorlatinib resistance has been linked to ALK G1202R compound mutations, highlighting the need for continuous monitoring and drug development [11].

5. Conclusion

The development of epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) targeted therapies has marked a pivotal shift in the treatment of non-small cell lung cancer (NSCLC), substantially improving clinical outcomes for patients harboring actionable mutations or fusions. Nevertheless, the emergence of drug resistance—driven by diverse mechanisms including on-target secondary mutations, activation of bypass signaling pathways, and phenotypic transformations such as epithelial-to-mesenchymal transition—remains a major barrier to achieving long-term disease control. Over the past decade, significant strides have been made in deciphering these resistance mechanisms, catalyzing the development of next-generation inhibitors (e.g., osimertinib for EGFR T790M resistance, lorlatinib for ALK-resistant variants), rational combination therapies, and personalized treatment strategies guided by advances in liquid biopsy and comprehensive genomic profiling.

Despite these achievements, considerable challenges persist. These include the complexity of polyclonal and co-occurring resistance mechanisms, managing cumulative toxicities associated with combination regimens, and the continual evolution of new resistance mutations to novel agents. Future progress will hinge on the integration of cutting-edge technologies such as single-cell sequencing and multi-omics analyses, which provide unprecedented resolution into the dynamics of resistance evolution and the role of the tumor microenvironment. Furthermore, the design of innovative therapeutic modalities—including multi-specific inhibitors, smart drug delivery systems, and adaptive treatment strategies aligned with real-time monitoring—will be essential to address the heterogeneous and adaptive nature of resistant NSCLC.

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Moving forward, the convergence of mechanistic research, technological innovation, and multidisciplinary collaboration will pave the way for the next generation of therapeutic approaches. By shifting toward proactive, highly personalized, and multi-dimensional management frameworks, we can anticipate meaningful improvements in survival and quality of life for patients, ultimately transforming EGFR/ALK-positive NSCLC into a chronically controlled condition.

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