

# Targeted Therapies for Lung Cancer: Molecular Drivers, Resistance Mechanisms, and Clinical Integration (2015–2025)

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**Abstract.** Lung cancer is a particularly serious form of cancer that garners significant attention worldwide. While there have been advancements in surgery, radiation, and chemotherapy, survival rates remain low, especially in advanced stages. Key genes, such as mutations in EGFR and gene fusions involving ALK, have transformed treatment through the development of targeted therapies. Mutations in EGFR activate signalling pathways that promote tumour growth, support the formation of new blood vessels, and help the tumour evade the immune system. Similarly, ALK fusions keep the kinase active, leading to rapid cell proliferation. However, resistance to treatment continues to pose a significant challenge. For example, the tumours will trigger secondary mutations, or there are some alternative signalling pathways activated. The target of the drug might be lost at this stage. A deeper understanding of how tumours grow and develop resistance at the molecular level is essential for creating more effective drugs and devising innovative combination therapy strategies.

## 1 Introduction

Lung cancer remains a prominent focus in global cancer research, mainly because of its high mortality rate (approximately 18%), which has attracted worldwide attention. The number of cases is different in each area. East Asia and Eastern Europe have the most cases. One notable aspect is that, from 2012 to 2020, there was an increase of over 400 thousand more people who got lung cancer within the age of technological development and the discovery of new cancer treatment. Also, the death cases caused by lung cancer were rising during the eight-year period. These differences happen because of changes in smoking habits, environmental exposure, and screening methods. According to the investigation report, more than four-fifths of patients with lung cancer have been smoking for a long time. Tobacco use continues to be one of the primary factors contributing to the development of lung cancer [1]. One of the two main types of lung cancer—non-small cell lung cancer (NSCLC)—will be the focus of this paper. The cases of NSCLC make up the majority of the cases of cancer. The other type of lung cancer is small-cell lung cancer (SCLC), which is also significant in the field of cancer treatment and research.

Despite advancements in diagnosis and treatment, the survival rate for lung cancer between 2015 and 2021 remains low, averaging around 28.1% globally. This figure, however, varies significantly based on the stage at which the cancer is diagnosed and the accessibility of innovative therapies. Early detection through low-dose CT screening and biomarker-driven treatments is beginning to improve outcomes, yet challenges continue to exist. Not only the clinical performance of the lung

cancers that patients might have, but also some tumour-associated syndromes would exist in those patients, such as hypercalcaemia and abnormal secretion of antidiuretic hormone (SIADH). These syndromes can significantly impact the overall clinical picture and management of the patients.

Traditionally, the primary treatment modalities for lung cancer have included surgery, radiotherapy, and platinum-based chemotherapy. These approaches demonstrate significant efficacy in managing localised disease; however, for advanced-stage lung cancer, the survival benefits associated with chemotherapy are limited and often come with severe adverse effects [2].

Over the past two decades, targeted therapies and immunotherapies have fundamentally reshaped the landscape of cancer treatment. Targeted therapies utilise oncogenic driver mutations—such as alterations in EGFR, ALK, ROS1, BRAF, MET, RET, KRAS, and HER2—through precision medicine approaches, leading to significant improvements in progression-free survival (PFS) and overall quality of life [3]. Additionally, immunotherapy has broadened the spectrum of treatment options, although only a subset of patients experiences a durable benefit [4].

Among the various innovative approaches in cancer treatment, targeted therapies hold a pivotal role in the realm of personalised medicine. It is crucial to gain a comprehensive understanding of their mechanisms of action, classification, and inherent limitations. This knowledge not only enhances the efficacy of treatment strategies but also informs clinical decisions, ultimately improving patient outcomes in the ever-evolving landscape of oncology.

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## 2 Pathogenesis of Lung Cancer-Related Targets

### 2.1 Epidermal Growth Factor (EGFR) Overexpression

EGFR is a protein that helps regulate how cells grow and divide. When there is an overproduction of certain substances within the body, or when these substances malfunction, it can interfere with the normal functions of cells. Such disruptions may contribute to the development of lung cancer. EGFR frequently becomes excessively active in many cases of NSCLC [5]. Studies show that about 10% to 15% of White patients with NSCLC and at least 30% of Asian patients have mutations in the EGFR gene. These mutations are often found in individuals with a type of lung cancer called adenocarcinoma and in those who have never smoked [6]. EGFR is situated on the cell surface and comprises parts that enable its function. One part is extracellular and binds to growth factors like EGF and TGF- $\alpha$ . Another segment traverses the cell membrane, anchoring the protein. The internal part transmits signals that instruct the cell to grow. The protein's end contains sites where other proteins can attach.

When EGFR is activated by its ligand, its conformation changes. This facilitates homodimerisation with other ErbB family members (forming dimers with EGFR itself or heterodimerisation with ErbB2/HER2, ErbB3 or ErbB4), followed by autophosphorylation of tyrosine residues [7]. The dimerisation triggers downstream signalling cascades via the RAS-RAF-MEK-ERK and PI3K-AKT-mTOR pathways, thereby promoting cell proliferation and survival. A significant quantity of somatic mutations in the TK domain has been discovered in lung cancer. In-frame deletions in exon 19 account for around 45% of mutations, whereas leucine-to-arginine substitutions at L858R in exon 21 account for about 40%.

There are many ways that lung cancer can cause EGFR to be overexpressed. One important factor is the amplification of the ERBB1 gene, which causes cells to have more copies of the receptor. Fluorescence in situ hybridisation (FISH) studies reveal that 22% of patients with surgically resected NSCLC at stage I-IIIa exhibit elevated levels of EGFR gene amplification, a correlation linked to a more aggressive tumour phenotype [8]. Moreover, the incidence of amplification is 40% to 50% elevated in patients with advanced NSCLC. It is also important to note that EGFR protein overexpression is much more noticeable in metastatic tumour sites than in the primary tumour [9].

Second, oncogenic transcription factors like AP-2, Sp1, and STAT proteins may increase EGFR expression by changing the way genes are transcribed. Certain NSCLC cells demonstrate aberrantly expedited CME, along with dysregulated initiation and maturation of CCPs. This phenotype is associated with the activation of the non-neuronal dynein subtype dyn1 and the overexpression of CLCb in non-neuronal cells, wherein the upregulation of CLCb modifies dynein-1-dependent EGFR transport. Additionally, extended exposure to

tobacco carcinogens and inflammatory cytokines significantly amplifies EGFR promoter activity.

Abnormal expression of microRNA can hinder the degradation of EGFR mRNA, resulting in enhanced protein synthesis. For instance, the loss of miR-7 or miR-34 is linked to unregulated EGFR expression. Specifically, miR-7 downregulates EGFR in cancer cells by directly binding to three seed sequences within the 3'-UTR of human EGFR mRNA or by targeting various downstream effector molecules in the EGFR signalling pathway, such as inhibiting the PI3K/Akt and ERK pathways. This action suppresses cancer cell migration, invasion and metastasis [10]. Additionally, miR-34 indirectly inhibits EGFR signalling by targeting c-Met, a pivotal compensatory pathway that enhances resistance to EGFR-TKIs, thus restoring tumour sensitivity to EGFR-targeted therapies [10].

Some lung cancers produce excess ligands for the EGFR, such as EGF and TGF- $\alpha$ . These ligands continue to activate the EGFR signalling pathway through autocrine and paracrine feedback. The EGFR pathway becomes self-sustaining by being continually stimulated by the large number of its ligands. The sustained downstream cascade reaction caused by the auto-active EGFR pathway will then promote the reproduction of cancer cells and inhibit the apoptosis of those cancer cells. For instance, the inflammatory cytokine interleukin-6 can activate the JAK/STAT pathway, which subsequently stimulates EGFR pathway signalling [11]. Persistent signal transduction gives tumour networks vitality, supporting the development of inflammation and cancer.

Overexpression of EGFR amplifies downstream signalling beyond normal physiological levels. It is a malignant transformation causing the uncontrolled reproduction of cells. The MAPK pathway is one of the most critical pathways affected by active EGFR. The phosphorylation of EGFR recruits adaptor proteins such as Grb2 and SOS. These proteins will activate the RAS GTPase. This activation initiates a cascade of RAF kinase activity. The ERK is then activated and translocates to the nucleus, promoting the transcription of genes associated with cell proliferation, including MYC, FOS, and JUN. Prolonged MAPK activity results in unchecked cell division and increases resistance to apoptosis, which is one of the keys to the growth and development of cancer [12].

Additionally, the PI3K/AKT pathway is important in the signalling cascade caused by activated EGFR. PI3K interacts with activated EGFR via the p85 subunit. This triggers the subsequent activation of the catalytic p110 subunit. The activation causes the conversion of PIP2 to PIP3, followed by the recruitment of AKT. AKT then phosphorylates various substrates, which include the inhibition of pro-apoptotic proteins like BAD and BAX. The activation of mTOR influenced by AKT boosts protein synthesis and metabolism, as well as enhances glucose uptake and survival signalling [13]. The PI3K/AKT pathway can help cancer patients resist treatment while it is constantly active.

EGFR can activate STAT proteins. It does this either directly or through JAK proteins in the JAK-STAT pathway. STAT3 and STAT5 activate genes that

promote cell growth, blood vessel formation, and survival. These genes include cyclin D1, VEGF and BCL-XL. [14].

Furthermore, in the SRC family kinase and FAK pathway, the overexpression of EGFR stimulates both SRC and FAK, subsequently facilitating cytoskeletal remodelling, migration, and invasion. This process makes it easier for tumour cells to spread and metastasise. The interaction among these pathways forms a redundant network that facilitates cancer cell proliferation, survival, angiogenesis and metastatic capability. SRC/FAK signalling also promotes EMT, increases cell mobility, and degrades the extracellular matrix, all of which facilitate cancer cell invasion and spread.

The molecular signalling effects seen in cancer cell traits are important. The hyperactive MAPK signalling propels continuous cell cycle progression and leads to uncontrolled proliferation. Also, the activation of AKT obstructs intrinsic apoptosis pathways, thereby enabling cells to endure genotoxic stress [12]. There is another key pathway, the EGFR-STAT3 signalling pathway, which enhances VEGF expression to maintain tumour angiogenesis. This pathway is responsible for supplying critical sustenance for tumour survival [14]. Moreover, the activation of mTOR drives anabolic processes that facilitate rapid biomass accumulation, whereas EGFR overexpression fosters resistance to apoptosis induced by chemotherapy and radiotherapy, ultimately resulting in adverse clinical outcomes.

The EGFR pathway is one of the main ways that causes cancer in NSCLC. When the EGFR-PI3K-AKT-STAT3 pathway turns on, it makes more PD-L1. This makes T cells weaker and causes less immune defence. Drugs that block PD-L1 work well in many NSCLC patients. The VEGF and HIF-1 $\alpha$  pathways also help new blood vessels grow. EGFR signals bring in CAFs, which make growth factors and other proteins. These make fibroblasts move and change how tissues are built.

EGFR has transformed how doctors treat lung cancer. Patients with NSCLC often undergo tests to determine their EGFR status. High EGFR levels usually indicate a poorer prognosis. However, some mutations in the EGFR gene, such as those in exon 19 or exon 21, assist doctors in selecting targeted drugs like gefitinib, erlotinib or osimertinib. Tumours with high EGFR levels but no gene mutations do not respond well to these drugs. This highlights the complexity of EGFR-related cancer. Additionally, cancer can develop resistance through other alterations, such as T790M or C797S mutations, or via MET gene amplification and epithelial-mesenchymal transition.

## **2.2 The Anaplastic Lymphoma Kinase (ALK) Fusion**

Lung cancer is a major public health issue, and ALK-rearranged lung cancer is a specific type of NSCLC, most commonly found in adenocarcinoma cases. A Japanese study revealed that out of 71 kinase-positive lung cancers, 44 exhibited ALK fusions, all categorised as adenocarcinomas. The discovery of ALK gene fusions has significantly improved our understanding of

the oncogenic mechanisms behind lung cancer development and has led to the development of highly effective targeted therapies. The subgroup affected by ALK fusions makes up roughly 3% to 7% of NSCLC cases, mainly impacting non-smokers, younger individuals, and those with adenocarcinoma histology. ALK fusions keep the ALK tyrosine kinase continuously active, causing cells to grow, survive, and spread uncontrollably.

The ALK gene is on chromosome 2 at the p23 spot. It makes a protein called a receptor enzyme. This protein is part of the insulin receptor group. In normal cases, ALK is mostly active in the growing nervous system. It helps nerve cells grow, stay alive, and make links with each other.

The proteins ALKAL1 and ALKAL2 stick to ALK at its glycine-rich part. They mainly connect through a loop on ALK and a charged area on the ALKAL proteins. This makes ALK turn and helps two ALK molecules join. They stay together through another loop that keeps them steady. When this happens, the inner parts of the proteins come close. This starts a chain of signals inside the cell, such as RAS–MAPK and PI3K–AKT, which help the cell live and grow.

In cancer, chromosomal rearrangements can cause the kinase domain of ALK to join with different partner genes. This leads to constant activation even when ligands are not present, which helps tumours grow. In the case of NSCLC, a fusion brings together the 5' region of EML4 and the 3' region of ALK. As a result, this rearrangement is in-frame and creates a chimeric oncogene capable of autonomous kinase signalling, known as the EML4–ALK fusion oncogene.

Various fusion protein partners, including KIF5B, TFG, HIP1, STRN, and KLC1, exhibit similar mechanisms of action, though they differ in promoter strength, dimerisation domains and intracellular localisation. These factors significantly impact oncogenic potential and sensitivity to therapeutics. Nevertheless, it is important to recognise that EML4-ALK remains the predominant variant, accounting for approximately 95% of ALK-positive NSCLC fusions.

The ALK gene was initially discovered in non-Hodgkin lymphoma due to a chromosomal change called t[24-25](p23;q35). This change fuses the ALK gene with another gene known as NPM. The fusion places ALK under the control of the NPM gene and produces a part that promotes dimerisation. This dimerisation activates ALK even without external signals. It keeps ALK permanently active and triggers strong cell signals that can lead to cancer. Later, additional ALK fusions, such as EML4–ALK in lung cancer, were identified. These fusions maintain ALK in an active state, while ALK provides a component that functions as a switch for cell signals. The signals typically travel through common cell growth pathways like MAPK, PI3K/Akt, and mtor. In neuroblastoma, ALK can also be activated by gene mutations or amplifications instead of fusions.

### 3 Conclusion

Lung cancer is very difficult to treat because it has many types of cells and can change to resist treatment. The reason is that each type of cell has its own characteristics and genetic makeup. New drugs that target specific genes have transformed how doctors treat non-small cell lung cancer. In recent years, major advances have been made with the development of targeted therapies—drugs designed to act on specific genetic changes that drive cancer growth. In NSCLC, drugs that target mutations in genes such as EGFR and ALK have significantly improved patient outcomes. These treatments can shrink tumours, relieve symptoms, and extend survival, offering new hope for many patients who once had very limited options. However, many patients still stop responding to treatment. This might occur when new genetic changes develop. For example, some genes mutate to resist the effects of medication, or they simply develop as oncogenes and disrupt the balance of cell reproduction and apoptosis. Additionally, activation of alternative cell signalling pathways is a potential factor that causes lung cancer, promoting the proliferation and metastasis of cancer cells. It is also possible that the cells themselves may alter their form and behaviour to evade treatment. During the mutation process, targets that the drug is targeting are very likely to be lost. In fact, there are many drugs targeting lung cancers that are effective at the very beginning of treatment; however, the effectiveness of these drugs is lost soon after. The explanations above address this phenomenon. Patients lose their response to targeted treatment. To overcome these challenges, scientists are exploring new strategies. Combining targeted drugs with immunotherapies—treatments that help the body’s immune system recognise and attack cancer cells—may offer a more powerful approach. In addition, monitoring patients’ genetic changes in real time through liquid biopsies or other advanced technologies can help doctors detect resistance early and adjust treatments accordingly. Continued research into how cancer cells grow, adapt and survive will be essential for improving treatment and ultimately saving more lives.

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