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Review article

A concise review on advancement in molecular targeted therapy for lung cancer

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Abbreviations:
AKT – Ak strain transforming.
ALK – anaplastic lymphoma kinase
EGFR – epidermal growth factor receptor
EMA – European Medicines Agency
ERK – extracellular signal-regulated kinase
FDA – Food and Drug Administration
GCN – gene copy number
HER2&3 – human epidermal growth factor receptor 2&3
HGF – hepatocyte growth factor
KRAS – Kirsten rat sarcoma viral oncogene homolog
LC – lung cancer
MAPK – mitogen-activated protein kinase
MET – mesenchymal epithelial transition
MKIs – multi-kinase inhibitors
mTOR – mammalian target of rapamycin
NSCLC – non-small cell lung cancer
NTRK – neurotrophic receptor tyrosine kinase
PFS – progression-free survival
PI3K – phosphoinositide 3 kinase
POI – protein of interest
PROTAC – proteolysis targeting chimeras
PTM – post-translational modification
ROS1 – ROS proto-oncogene 1
RTK – receptor tyrosine kinases
SFMs – solvent front mutations
TCGA – The Cancer Genome Atlas
TKIs – tyrosine kinase inhibitors
VEGF – vascular endothelial growth factor

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Abstract

Lung cancer is one of the leading causes of cancer-related deaths worldwide, with non-small cell lung cancer (NSCLC) accounting for 84% of cases. Traditional treatments like surgery and chemotherapy have limited effectiveness and significant side effects. Despite combination chemotherapy being the preferred first-line therapy, the prognosis for advanced NSCLC remains poor, with a median survival of 8-11 months and a 1-year survival rate of 30%. There is a critical need for new treatments targeting the molecular mechanisms of NSCLC. Precision medicine, or targeted therapy, has emerged as a promising approach, focusing on genetic and epigenetic alterations. This method is more effective for advanced NSCLC. It involves drugs targeting specific genetic abnormalities such as ROS proto-oncogene 1 (ROS1), EGFR (Epidermal growth factor receptor), ALK (Anaplastic lymphoma kinase), BRAF (v-Raf murine sarcoma viral oncogene homolog B1, MET (Mesenchymal epithelial transcription factor), and RET (Rearranged during transfection) mutations, which are vital driver genes for lung cancer development and progression. With up to twenty treatments approved by the FDA, targeted medicines are still being developed, and targeted therapy and chemotherapy have dramatically improved patient outcomes. Despite progress, treating metastatic NSCLC remains challenging due to resistance to genetic changes. This narrative review provides a detailed description of the various classifications of molecular targeted therapeutic approaches employed in lung cancer management and its mechanisms of action in cancer prevention and its advantages and disadvantages.

INTRODUCTION

Lung cancer (LC) is the most frequent and prevalent cancer and the leading cause of cancer-associated death on a global scale *(1)*. In 2022, it was the most commonly diagnosed cancer, accounting for approximately 12.4% of all cancer cases *(2)*. LC has two major types, namely non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), distinguished by their histological characteristics. SCLCs are less common than NSCLCs, accounting for nearly 15% of all LC cases, whereas NSCLCs constitute around 85% *(3)*. Depending on its histopathological characteristics, NSCLC is classified into several subgroups, including squamous cell carcinoma, lung adenocarcinomas, and giant cell carcinoma *(4)*. Chemotherapy was the most conventional and primary therapeutic strategy for patients with stage III and IV NSCLC prior to the complete development and discovery of targeted therapy. After that, targeted therapy has yielded remarkable results in managing LC *(5)*. The standard treatment protocol consists of surgical excision,

chemotherapy utilizing platinum compounds, and radiotherapy, either as a standalone treatment or in combination. Unfortunately, the prognosis for persons suffering from LC, which has a 5-year survival rate of 15%, has shown limited progress over the past thirty years when employing conventional medical therapies *(6)*. Recent advancements in understanding its molecular genetics have facilitated the detection of key genetic anomalies in NSCLC. Driver mutations cause oncogene activation, which encodes signaling molecules critical for cell growth, proliferation, and survival. The concept of oncogene activation advances that tumors acquire a substantial dependence on the existence of particular oncogenes to secure their viability *(7)*. Several significant pathways that can be targeted in lung adenocarcinoma have been identified, including EGFR, VEGF, ALK, KRAS, BRAF, RET, MET, HER2 & 3, PI3K/AKT/mTOR, RAS–MAPK, and NTRK/ROS1 pathways. The clinical advantages of several pharmacological drugs targeting these pathways have been demonstrated via their development. Certain drugs, such as VEGF targeting antibody like Bevacizumab and Ramucirumab which can be used alone or in combination with chemotherapy against advanced NSCLC, EGFR inhibitors like erlotinib and gefitinib, PI3K/AKT/mTOR inhibitors like Everolimus, and NTRK/ROS1 inhibitors like entrectinib, have surpassed standard chemotherapy as the predominant therapeutic modality *(8)*. However, despite the progress made in targeting therapy for NSCLC, the development of drug resistance in tumors is still unavoidable. Understanding the underlying causes of resistance and developing combinational treatment strategies are crucial to optimize therapy effectiveness *(8)*. This review especially aims to provide a brief insight into the FDA and NCCN guidelines approved targeted therapy discovered in targeting EGFR, ROS1, ALK, MET, BRAF, and RET. It is crucial to understand the alterations that have occurred to these specific molecules, which promote abnormal cell proliferation and lead to lung cancer, and to develop novel drugs, in addition to established molecular targeted therapy, that specifically target these altered molecules to prevent cancer formation. Apart from this, several combinational therapeutic approaches, such as chemotherapy with targeted therapy and immunotherapy with targeted therapy, may be developed, showing greater effectiveness in preventing lung cancer. All the information regarding targeted therapy for lung cancer has been described critically and is up-to-date.

EPIDEMIOLOGY OF LUNG CANCER

The incidence rate of LC is high in developing countries where cigarette smoking is more common with a variance in incidence of over 20 times between regions. According to a report submitted by the US National Cancer Institute Surveillance, Epidemiology, and End Results Program from 2010 to 2019, localized lung cancer has been found in 20.1% of male patients and 24.9% of female patients. In contrast, distant LC has been found in 50.9% of male patients and 46.5% of female patients *(9)*. Based on GLOBOCAN's most recent estimates from 2020, only 60% (1,315,136 people) of newly diagnosed cases of lung cancer and 62% (1,112,517 people) of all LC-related fatalities occurred in Asia, with an age-standardized incidence rate of 34.4 per 100,000 in East Asia. In contrast to Western counterparts, a greater number of non-smokers in Asia have lung cancer. While over 70% of lung cancer patients in Europe and the US have never smoked, less than 40% of Asian women who have never smoked have lung cancer, suggesting that Asian women with lung cancer are more likely to be non-smokers than ever-smokers. Most of randomized screening studies were conducted on smokers or those who had just stopped. However, similar screening programs for non-smokers are necessary in Asia due to the high prevalence of lung cancer among non-smokers *(10, 11, 12)*.

According to the GLOBOCAN-Global Cancer Statistics 2020 reports, lung cancer cases increased to 2.2 million, with 1.4 million male and 0.8 million female lung cancer cases. There has been a gradual decline in lung cancer incidence rates in males in high-income countries like Oceania and European countries and a rapid increase in females *(13)*.

One recent study reported the projection of lung cancer incidence by 2035 in 40 countries worldwide, which is a population-based study. As per this study, global age-standardized incidence rates (ASRs) of the 40 nations under study were expected to rise by 2% (0.3/16.8) among females, from 16.8 in 2010 to 17.1 in 2035, and fall by 23% (8.2/35.8) among men, from 35.8 per 100,000 person-years in 2010 to 27.6 in 2035. By 2035 it is anticipated that the ASRs of lung cancer in females will have increased significantly in the majority of countries, peaking in most European, Eastern Asian, and Oceanian nations after the 2020s, while the ASRs in males will continue to drop in nearly all of the nations *(14)*.

According to the very recent estimates of GLOBOCAN-Global Cancer Statistics 2022, 2.5 million new incidences of lung cancer and around 1.8 million demises due to lung cancer have been observed worldwide. In 2022, lung cancer is expected to be the primary cause of morbidity and death worldwide, accounting for nearly one in eight (12.4%) new cases of cancer diagnoses and one in five (18.7%) demise from cancer. Lung cancer holds the first rank in men and the second rank in women for incidence and mortality, as well as an incidence-to-mortality ratio of 2 for male-to-female lung cancer *(2, 15)*.

MOLECULAR THERAPIES IN LUNG CANCER

Molecular targeted therapy is a significant therapeutic technique in cancer medicine, alongside hormone therapy

and cytotoxic chemotherapy *(16)*. The primary objective of most targeted therapies is to combat cancer by disrupting specific proteins that play a role in tumor formation and growth *(17, 18)*. In direct opposition to chemotherapy, which generally eliminates rapidly proliferating cells without specific targeting, molecular targeted therapy is a personalized therapeutic approach intended to combat cancer by inhibiting specific molecular anomalies that contribute to the advancement of cancer. Standard chemotherapy regimens typically have a success rate of approximately 30%. However, personalized therapy can have a success rate of up to 80% *(19)*.

The aforementioned therapeutic approach is extensively employed as an advanced technique for managing LC. Molecular targeted therapies are an innovative type of medical intervention that interrupts particular molecular pathways to hinder the growth, progression, and dissemination of malignant cells *(20)*. Various types of cancer, including breast, leukemia, colorectal, lung, and ovarian cancers, have demonstrated significant success in clinical settings through the use of molecularly targeted medicines that have received endorsement from the FDA *(21)*.

Despite initial positive responses, many targeted therapeutic interventions eventually face resistance due to spontaneous mutations or activation of alternative signaling pathways. This acquired resistance to molecular targeted therapies presents a significant challenge in lung cancer treatment. Therefore, it is crucial to understand the resistance mechanism to current medications and to develop innovative treatments to overcome this hurdle and improve outcomes for lung cancer patients *(22)*.

TARGETED THERAPY FOR LUNG CANCER

Targeted therapy is the deliberate targeting of specific genes, proteins, or microenvironments within tumors that facilitate the development and survival of tumor cells. Immunotherapy and targeted therapy have demonstrated efficacy in managing advanced LC, particularly NSCLC. In recent times, there has been a movement in therapy approaches towards targeting small molecular medicines to enhance outcomes in individuals with NSCLC. The research on the human genome facilitates the proficient identification of variations in the genome that are abnormal promote cancer development and have the potential to serve as therapeutic targets. Targeted therapy is recommended for patients with distant metastases and stage IV illness *(23)*. Targeted cancer therapy acts by leveraging a diverse array of specific genes and proteins that play a crucial role in the proliferation and viability of cancer cells. Restricting the proliferation and dissemination of cancer cells mitigates the potential damage to normal cells. Tailored therapy is commonly employed in situations of advanced lung cancer patients due to the unique adverse effects associated with regular drugs *(24)*. Targeted therapy is frequently seen as a therapeutic approach for individuals exhibiting specific tumor abnormalities that can be identified via biomarker testing *(25)*. The genetic analysis of LC enhanced the comprehension of the biology and carcinogenesis of the disease, as well as revealing various potential targets for treatment. Targeting tumor dependencies on certain genetic anomalies (oncogene addiction) has significantly augmented therapeutic breakthroughs and dramatically enhanced consequences, even in advanced stages of cancer *(26)*. The effectiveness of the "personalized treatment" technique is attributed to the finding of genetic alterations that can predict the efficacy of specifically targeted medicines. These therapies focus on specific molecular modifications of various types of tyrosine kinases, such as EGFR, ALK, RET, and MET, that drive cancer growth and progression, offering a more precise and personalized approach than conventional treatments like chemotherapy and radiation. It has been found that due to the oncogenic mutation of these tyrosine kinases, they become constitutively active and don't need any ligands to be active, which ultimately leads to the development of lung cancer. Recently, targeted therapy has played a crucial role in addressing these altered molecules. Mutations can now be suppressed with small-molecule tyrosine kinase inhibitors (TKIs) or receptor monoclonal antibodies (mAbs), thanks to advancements in translational research *(27)*. One recent study investigates modifications occurring within the DNA of the tumor, encompassing mutations, additions, deletions, or rearrangements. Specific therapies for lung cancer can specifically target these changes. By specifically targeting certain problems within the malignant cells, these treatments frequently lead to less adverse effects in comparison to conventional methods, as their objective is to eliminate the abnormalities without causing harm to good cells *(28)*. The selection of specific therapeutic strategies for NSCLC comprises the evaluation of various parameters, including the patient's overall health, tumor location, size and grade, lymph node status, and lung function. Before administering any treatments, cancer cells will undergo examination to detect stage IVB malignancies that have metastasized throughout the body, aiming to identify specific gene alterations such overexpression or lower expression that causes the development of NSCLC *(24)*. The genes examined in this study encompass VEGF, KRAS, ALK, ROS1, EGFR, BRAF, MET, RET, and NTRK. If there are mutations in any of these genes, the initial treatment will likely involve administering a targeted therapy medication *(23)*. Identifying altered gene function due to mutation or modified protein expressions in LC has significantly improved the survival rates of patients with advanced disease, hence facilitating the development of molecular targeted therapy *(24)*.

Targeted therapies are employed in advanced lung malignancies when conventional treatments fail to yield significant results. These therapies disrupt specific molecular pathways essential for cancer growth and survival. Several targeted agents, including inhibitors targeting pathways like EGFR, RAS-MAPK, ALK, PI3K/AKT/mTOR, RET, BRAF, and MET, have been developed to manage NSCLC. These inhibitors are tailored to patient subgroups based on molecular profiling, enabling a more precise and effective treatment approach. Personalized cancer therapy, which involves identifying and evaluating the expression of essential target genes and proteins in individual patients, is critical for optimizing therapeutic outcomes *(24)*.

Approximately 30 percent of individuals diagnosed with LC may possess molecular targets that positively respond to targeted therapy. Targeted therapy medications such as osimertinib, crizotinib, and bevacizumab are employed to manage LC. One study reported that empirical chemotherapy combined with a platinum doublet is the gold standard for treating advanced NSCLC without a confirmed driver mutation *(29)*. However, ongoing research into tailored therapies aims to improve patient outcomes and quality of life by addressing specific genetic mutations, insertions, deletions, or rearrangements in the tumor's DNA *(27)*. These personalized approaches enhance treatment effectiveness by selectively targeting cancer-related cellular abnormalities, which reduces harmful side effects. The ability to precisely target malignant cells while sparing healthy ones offers significant advantages, as the therapies are specifically designed to focus on molecules located on or within tumor cells, resulting in a more focused and effective treatment *(30)*. Currently, the FDA has approved targeted therapies for LC cases that exhibit specific genetic abnormalities, aligning with the personalized approaches that address mutations, insertions, deletions, or rearrangements in the tumor's DNA.

The key genetic targets include:

1. EGFR (Epidermal growth factor receptor)
2. ALK (Anaplastic lymphoma kinase)
3. ROS-1 (C-ros oncogene 1)
4. BRAF (v-raf murine sarcoma viral oncogene homolog B1)
5. MET (Mesenchymal epithelial transcription factor)
6. RET (Rearranged during transfection)

Targeted therapy for EGFR (Epidermal Growth Factor Receptor) driven NSCLC

EGFR is a transmembrane glycoprotein that belongs to the ErbB family of receptor tyrosine kinases (RTKs) *(27)*. Upon binding specific ligands, EGFR can stimulate various intracellular signaling pathways, such as PI3K/AkT/mTOR, MAPK, and STAT, via signal transduction. This promotes abnormal cell proliferation, differentiation, and migration, eventually leading to cancer development *(30)*. With over 60% of NSCLCs expressing elevated levels of EGFR protein, this has emerged as a potential therapeutic target for managing these cancers. Clinically effective inhibitors that target the structural domain of tyrosine kinase inhibitors (TKIs) have been created. Furthermore, patients with activating mutations in the EGFR tyrosine kinase structural domain respond particularly well to these TKIs *(31)*. Several lung tumors exhibit elevated levels of modified forms of EGFR, hence promoting the proliferation of these malignancies. The most often utilized and effective EGFR inhibitors are osimertinib (Tagrisso) *(32)*. According to recent research, EGFR has emerged as the primary driver gene in NSCLC across the Asia-Pacific and Russian regions, with an incidence rate of 49.3%. The range of genetic mutations fundamentally includes single nucleotide polymorphism (SNP), insertion or deletion mutation, and variation in copy number *(33)*. Most of these mutations are found in exons between 18 to 21 exon, and the effects of EGFR-TKIs are significantly more beneficial in exons 19 and 21 than in exons 18 and 20. The deletion of amino acids at locations 747-750 inside exon 21 is the most common mutation. This finding supports the use of first-generation EGFR-TKIs, which are reversible drugs such as gefitinib (Iresa), erlotinib (Trockai), and ecotinib (Kemet sodium) *(33)*. In 2015, the FDA approved gefitinib as a first-line drug for NSCLC. It is also reported that it prolongs the patient's progression-free survival (PFS) as reported by an ISEL study conducted in 2004 *(34)*. After that Japan conducted a study in 2015 named NEJ002 to find the efficacy of gefitinib in comparison with carboplatin and paclitaxel which is the conventional chemotherapy for NSCLC. They reported that gefitinib had a higher PFS of about 10.8 months compared to the chemotherapy group, about 5.4 months *(35)*. China conducted one study in 2011 to study the efficacy of erlotinib in comparison to carboplatin and gemcitabine and reported that erlotinib had a high PFS of around 13.1 months compared to the carboplatin and gemcitabine groups and a higher effective rate of around 83%. In contrast, the carboplatin and gemcitabine groups showed a 36% effective rate *(36)*. The CONVINCE, a phase 3 open-label, randomized study conducted in 2017 on patients who have been diagnosed with positive lung adenocarcinoma with an advanced EGFR mutation, reported for the first time that icotinib has shown better clinical benefits than standard chemotherapy. In this study, it was observed that icotinib had a higher PFS of around 11.2 months than the chemotherapy group's PFS of around 7.9 months and also had lowered side effects, which was 54.1%, lower than the chemotherapy group, which was 90.5% *(37)*. The first generation of EGFR-TKIs benefits many LC patients, but the major limitation of these TKIs is the resistance developed by the lung tumor cells. To combat the developed TKI resistance by lung tumor cells, second-generation EGFR-TKIs evolved, which are irre-

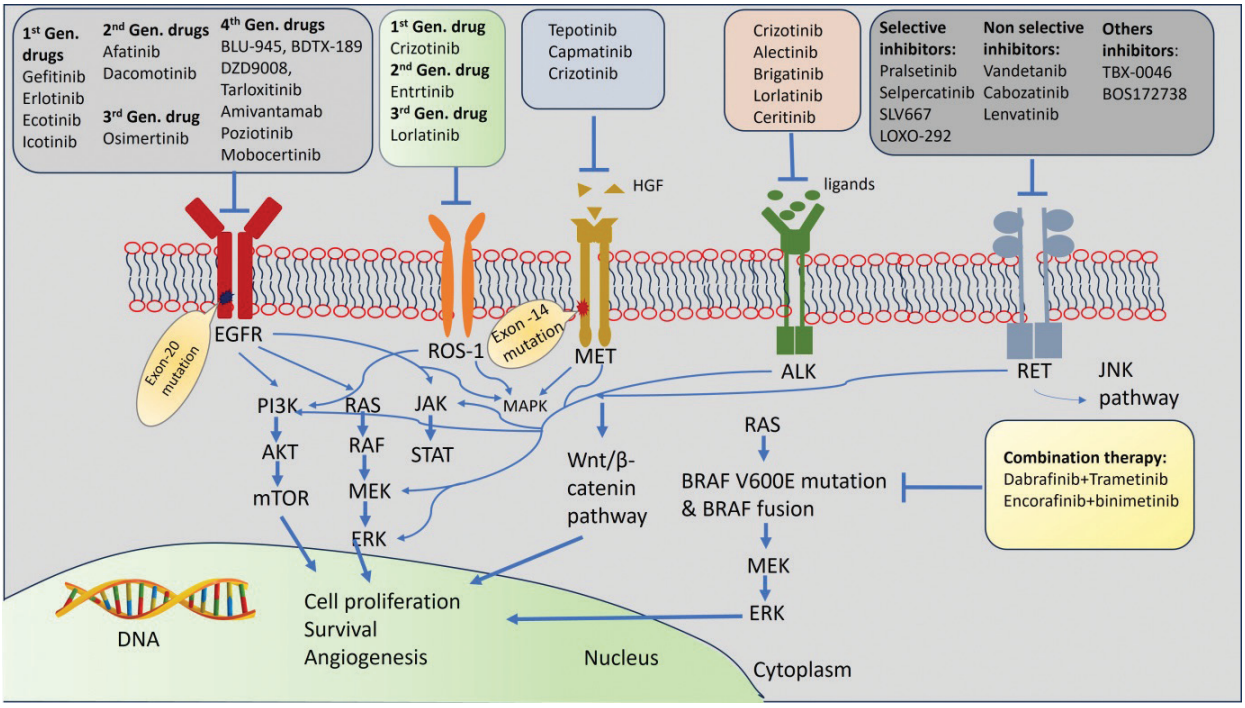

Figure 1. *Molecular targeted therapy in NSCLC: Targeting primary oncogenic signaling pathways.*

versible drugs that target the molecules more effectively than first-generation drugs, but their adverse effects are high. A well-known second generation of EGFR-TKI is afatinib (Giotrif), which acts as an irreversible inhibitor that specifically targets and covalently binds to EGFR and HER2. HER2 mutations cause EGFR-TKI resistance, and for patients who have developed this resistance, afatinib is more advantageous to them. Afatinib has exhibited effectiveness in targeting specific uncommon EGFR mutations and has obtained approval from the FDA for treating uncommon EGFR mutations, including L861Q, G719X, and S768I *(35)*. EGFR inhibitors hinder the function of the EGFR protein, and their modified versions are observed in elevated quantities in certain lung malignancies, leading to their accelerated proliferation *(33)*. The dacomotinib which is another second-generation EGFR-TKI, was utilized as first line drug in comparison with gefitib in the ARCHER-1050 clinical trial study and dacomotinib has shown higher PFS than gefitinib (14.7 months versus 9.2 months) *(38)*. First generation drugs (eroltinib and gefitinib) and second-generation drug afitinib both have shown significant improvement of PFS and more than 70% radiological response times compared to the platinum-based chemotherapy, when treated to the individuals with EGFR mutant NSCLC *(39)*.

Even after utilizing first-generation and second-generation EGFR-TKIs, drug resistance remains in most patients due to the mutation in exon 20 (exon T790 M mutation). Due to this EGFR T790 M resistance mutation in NSCLC patients, researchers aimed to develop second-line therapy. Then they discovered osimertinib, which is the first third-generation EGFR-TKI to irreversibly inhibit T790 mutant EGFR and also obtained approval from FDA (40). One clinical study was conducted on EGFR T790 M mutation-positive LC patients to study the efficacy of Osimertinib compared to cisplatin/pemetrexed. The PFS of osimertinib was 10.1 months, whereas the PFS of cisplatin/pemetrexed was 4.4 months, and the overall response rate (ORR) of osimertinib and cisplatin/pemetrexed was 71% and 31%, respectively. This study reported that osimertinib has the ability to prevent cancer metastasis (41). Osimertinib is a highly effective and extensively utilized inhibitor of EGFR. Adjuvant treatment is also utilized for resected EGFR-mutated stage Ib-IIIa NSCLC, as highlighted by Herbst RS *et al. (42)*. The study demonstrated a notable improvement in disease-free survival (DFS) compared to placebo, significantly reducing the risk of local and distant recurrence. Additionally, it showed enhanced central nervous system (CNS) DFS and maintained a consistent safety profile throughout *(42)*. To overcome the Osimertinib resistance to the most significant target C797S mutation, fourth-generation EGFR-TKIs, including EAI045 and BLU-945, are being explored *(43)*. The first allosteric inhibitor to target the EGFR mutations T790M and C797S is EAI045 *(44)*. It has shown efficacy in mouse studies when combined with cetuximab *(44)*. Another fourth-generation EGFR TKI, BLU-94, can effectively suppress triple-mutant EGFR, which is characterized by acquired T790M and C797S mutations in addition to either activated L858R or exon 19 deletion mutations *(43)*. Additionally, BDTX-189 is a small-mole-

cule inhibitor that irreversibly targets HER2, EGFR, and ErbB kinase, which play a potent role as oncogenic drivers after mutations *(45)*. One preclinical study conducted using CLN-081 (TAS6417) against NSCLC patients reported that it has the potential to inhibit the EGFR in a broad therapeutic way and target these mutations, such as T790M, EGFR exon 19 deletions, G719X L858R, S768I, L861Q, and exon 20 insertion mutations *(46)*. Apart from these, DZD9008 *(47)*, Tarloxotinib (a pan-ERBB kinase inhibitor) *(48)*, Amivantamab (JNJ-372) (a fully human anti-EGFR-MET bispecific antibody) *(49)*, Poziotinib (an irreversible TKI) *(50)*, and Mobocertinib (TAK-788) (an oral TKI) *(51)* are the critical fourth-generation EGFR TKIs against NSCLC *(52)*.

Various aberrant signalling pathways and cellular physiological processes are evident in lung cancer. Pharmacological interventions targeting these aberrations are outlined diagrammatically (Figure 1). These interventions encompass drugs that specifically block constituents of the EGFR pathway and related family members, as well as participants in the VEGFR pathways *(23)*. Additionally, on-going research involves the development of agents that target and inhibit JAK–STAT, RAS/BRAF/MAPK, and PI3K/AKT/mTOR signaling pathway *(4)*.

Targeted therapy for ALK (anaplastic lymphoma kinase) driven NSCLC

ALK is a transmembrane receptor; one type of tyrosine kinase, belongs to the insulin receptor superfamily, and is mostly found in the nervous system. These tyrosine kinases, consisting of 1620 amino acids, are synthesized by the proto-oncogene ALK. Alteration of the ALK gene happens due to chromosomal translocation, gene fusion, deregulation of the gene amplification, and point mutations that cause the activation of ALK signaling, which thereby induces the development of cancer and promotes its proliferation *(53)*. ALK inhibitors are specifically developed to target ALK protein rearrangements that directly contribute to the development of cancer.

The fusion of ALK is responsible for 3-5% of NSCLS, making it the second most common altered gene after EML4-ALK by inversion fusion. The EML4-ALK fusion demonstrates more than 21 unique shapes depending on the location of the fracture *(33)*. The diverse fusions exhibit sensitivity levels surpassing 21 distinct forms based on the fracture's location. Patients who had the fusion of exon 13 of the EML4 gene and exon 20 of the ALK gene exhibited significantly elevated rates of response and PFS when subjected to treatment with crizotinib (Xalkori) in comparison to individuals with alternative fusion variants *(33)*. It is also reported that EML4 and ALK oncogenic fusion genes have been found to be present in 2-7% NSCLC of stage III or IV patients as well as, more frequently, younger people who never smoke or who smoke very little. These patients are more likely to develop brain metastases *(54, 55)*. Crizotinib is the first FDA-approved ALK inhibitor that efficiently targets ALK fusion in NSCLC *(56)*. Then the other FDA-authorised drugs, alectinib (Alecensa), brigatinib (Alunbrig), erlotinib (Lorbrena), and ceritinib (Zykadia) *(20)* also showed potent efficacy in ALK-fusion-positive NSCLC *(57)*. In NSCLC, the ALK gene was found to undergo alterations and resulting in tumor growth, proliferation and differentiation of tumor cells. The tyrosine kinase is inhibited by a tiny pharmacological agent known as crizotinib, demonstrating enhanced PFS in both first and subsequent treatment regimens *(58)*.

Ceritinib, which is a second-generation inhibitor, has shown effectiveness in the treatment of advanced and metastatic ALK-positive crizotinib resistance in NSCLC and also has a potent inhibitory effect on I1171T, G1269A, L1196 M, and S1206Y mutations *(59)*. Effective targeted drugs encompass developing therapeutic alternatives and enhancing survival rates in response to certain molecular subtypes, such as ALK and EGFR. Alectinib has also been very effective in ALK fusion cizotinib resistance NSCLC and can target the L1196 M, F1174 L, and C1156Y mutations. In contrast to crizotinib, alectinib had a very high PFS of around 34.1 months, whereas crizotinib had a PFS of around 10.2 months *(60)*. Additionally, alectinib is very effective in preventing brain metastasis due to its high ability to cross the blood-brain barrier *(61)*. Brigatinib, a well-known second-generation ALK inhibitor, also can inhibit EGFR and ALK tyrosine kinase. It can overcome the T790 M and L119 M mutations of EGFR and ALK, respectively. In contrast to crizotinib, briagatinib has a longer PFS than crizotinib, and is effective against the cizotinib resistance of NCSLC *(62)*. Lorlatinib, which is a third-generation ALK inhibitor and can target both the ALK and ROS1 pathways, is effective against multiple drug resistance of first- and second-generation ALK-TKIs and overcomes the G1202R in ALK-positive NSCLC patients *(63)*. Apart from these ALK-TKIs inhibitors, SAF-189, TQ-B3101, TPX-0131, and Ensartinib (X-396) *(64)* are newly developed ALK inhibitors and also very effective to advanced ALK-positive NSCLC *(52)*. A prior misunderstanding existed regarding the dichotomy between ALK fusion and EGFR-activating mutations, which has been elucidated. EGFR and ALK are highly influential driver genes, and the presence of each gene is sufficient for the development of tumors *(33)*.

Targeted therapy for C-ROS oncogene 1 (ROS1)-positive NSCLC

The protein ROS1 is a proto-oncogene, a member of the insulin receptor family, has a structural similarity to ALK, and plays a crucial role in cellular signaling and cellular proliferation. A minority of individuals with NSCLC exhibit modified variants of the ROS1 gene, around 1-2% *(65)*. Two approved therapies for patients with these changes are Crizotinib (Xalkori) and entrec-

tinib (Rozlytrek) *(66)*. The protein known as ROS1 is of paramount importance in facilitating cellular signaling pathways and controlling nuclear proliferation. A group of persons diagnosed with NSCLC have been found to exhibit alterations in the ROS1 gene. Crizotinib (Xalkori) and entrectinib (Rozlytrek) have been approved as therapeutic approaches for the management of NSCLC patients who possess these genetic alterations *(24)*. The primary function of the ROS1 protein is to facilitate cell signaling and promote cell proliferation. It is reported that some individuals with NSCLC have rearranged variants of this gene (ROS1 gene). The rearrangement above was first identified in the year 2007 *(66)*.

Crizotinib (1st generation drug for ROS1-positive NSCLC)

The kinase areas of ALK and ROS1 demonstrate a 77% similarity in their amino acid composition. Crizotinib has shown improved efficacy to the NSCLCs patients who have been diagnosed positive for ALK, as well as the similarity in structures between ALK and ROS1, which further have generated interest in considering ROS1 as a key therapeutic target for crizotinib. In 2016, the European Medicines Agency (EMA) and FDA of the United States approved the use of crizotinib (Xalkori, PF-02341066) to manage of NSCLCs with ROS1 rearrangements. Nevertheless, resistance to crizotinib has been linked to the recurrence of tumours. The primary cause of resistance to crizotinib is the accumulation of additional point mutations, particularly G2032R mutation in the ROS1 gene *(67)*. This demonstrated how urgent it is to develop novel, highly effective ROS1-rearranged NSCLC-targeted therapies *(24)*.

Entrectinib (2nd generation drug for ROS1-positive NSCLC)

Entrectinib is an oral TKI that not only targets ROS1 but also has the potential to target TRK (receptor tyrosine kinase) and ALK. The FDA approves it for the treatment of ROS1-positive NSCLC *(68)*. Furthermore, reports have indicated that entrectinib had good penetration through the blood-brain barrier and generated intracranial activity. This suggests that entrectinib may have some efficacy in treating brain metastases. Several cohort studies were conducted to study the treatment efficacy of entrectinib for ROS1-positive NSCLC, such as ALKA-372-001, STARTRK-1, and STARTRK-2, and 77% of the overall objective response rate (ORR) and 24.6 months of median duration of response were observed from these studies *(69)*.

Lorlatinib (3rd generation drug for ROS1-positive NSCLC)

Lorlatinib (PF-06463922) is a third-generation TKI that can inhibit ROS1 and ALK tyrosine kinase. It is very effective in inhibiting the G2032R mutation of the ROS1 gene, which causes the development of crizotinib resistance in NSCLC, and very effective in treating glioblastoma *(70)*. In patients with NSCLC who had their ALK and ROS1 rearranged lorlatinib's efficacy was examined in phase I and II clinical trials conducted between 2017 and 2019 by assessing the overall response rate (ORR) and median PFS *(71, 72)*. In patients with advanced ROS1-positive NSCLC, the clinical trials demonstrated significant activity. Regarding CNS metastases or crizotinib resistance, lorlatinib demonstrated a potential impact. Furthermore, lorlatinib was easily tolerated and there was no discernible toxicity *(71, 72)*. Notably, lorlatinib demonstrated anti-tumor effectiveness in vitro against additional mutations that are resistant to crizotinib, including S1986Y/F, 66, L2026M, 66, 83, and D2033N mutations. However, lorlatinib may offer an alternative for treating metastatic non-small cell lung cancers with advanced crizotinib resistance.

Targeted therapy for BRAF (v-RAF murine sarcoma viral oncogene homolog B) driven NSCLC

BRAF is a member of the serine-threonine kinase family and plays a pivotal role in the regulation of the mitogen-activated protein kinase (MAPK)/ extracellular signal-regulated kinase (ERK) signaling pathway. In 2–4% of NSCLC cases, BRAF mutations are found, and the V600E mutation is observed chiefly *(73)*. The B-Raf protein is involved in the transmission of signals and the growth of cells. Genetic modifications in the B-Raf gene can augment the growth and spread of NSCLC cells. The authorization has been given by FDA for the use of a combination therapy consisting of dabrafenib (Tafinlar) and trametinib (Mekinist), which specifically targets the MEK protein, to treat patients with NSCLC with a certain mutation in the BRAF gene *(74)*. The combination of encorafenib (Braftovi) and binimetinib (Mektovi) has been approved for persons with metastatic NSCLC who have a BRAF V600E mutation. The BRAF gene mutation potentially confers resistance to EGFR-TKI, while also serving as a critical driving gene and therapeutic target (Table 1) *(33)*. Significantly, the mutation V600E is the most commonly seen and plays a crucial role in activating downstream signaling pathways. The National Council of Clinical Nurses (NCCN) guidelines have given approval to use dabrafenib (Tafinlar) and trametinib (Mekinist) as BRAF inhibitors in both first and subsequent management strategies for advanced NSCLC. The monotherapy of dabrafenib demonstrates 33% ORR (95% confidence interval 23-45%) in patients with NSCLC who have V600E mutations in the BRAF serine/threonine kinase and have not undergone previous treatment. Remarkably, the concurrent administration of dabrafenib and trametinib against BRAF-V600E mutated metastatic NSCLC patients who had not received treatment before

demonstrates an ORR of 64% (95% CI, 46-79%). Among these patients, a subgroup of 2 (6%) achieved an ORR of 63.2% (95% CI, 49.3-75.6%) *(75)*. Similarly, among these patients who have received prior treatment, the ORR is 63.2% (95% CI, 49.3-75.6%). The altered BRAF gene is the main contributor to the development and proliferation of NSCLC cells. Dabrafenib and trametinib are pharmacological agents specifically targeting the MEK protein, specifically the B-Raf pathway. Based on these observed results FDA approved these drugs for the treatment of NSCLC patients with specific mutations in the BRAF gene (Table 1) *(75)*.

Targeted therapy for MET (Mesenchymal Epithelial Transition) driven NSCLC

The c-MET is a transmembrane receptor, one type of proto-oncogene, and a member of the tyrosine kinase family. It gets autophosphorylated upon binding of hepatocyte growth factor (HGF), leading to the activation of several downstream signaling pathways such as Wnt/β-catenin, STAT, PI3K-AKT, and RAS/ERK/MAPK *(76, 77)*; undergoes several changes due to mutation, gain or amplification of MET gene copy number (GCN), and overexpression of MET protein, which promote cell survival and proliferation and ultimately lead to cancer development *(78)*. It has been found that in 20% of NSCLC patients, MET is overexpressed, and Met gene amplification was observed in 1-5% of NSCLC patients *(79)*. MET gene amplification and Met protein overexpression may develop resistance to the first or second-generation EGFR-TKI in NSCLC patients, representing roughly 5% of resistances *(80)*. As a result, a proposition among specific academics exists that a prospective resolution to this issue of medication resistance may entail an innovative strategy that integrates a c-MET inhibitor with an EGFR-TKI. Another notable variation of the MET genes is the presence of a mutation known as exon 14 skipping. Significantly, the data obtained from The Cancer Genome Atlas (TCGA) revealed that approximately 4% (10/230) of lung adenocarcinoma cases exhibited MET exon 14-skipping mutations. These mutations led to the partial or total deletion of MET exon 14 at the mRNA level. The NCCN guidelines recommend using crizotinib in treating individuals with NSCLC who have c-MET protein overexpression, MET gene amplification, and MET exon 14-skipping mutation (Table 1) *(33)*. After that, the FDA also approved tepotinib and capmatinib for the treatment of MET exon 14 skipping mutation-positive NSCLC (Table 1) *(81)*.

Targeted therapy for RET (Rearranged During Transfection)- positive NSCLC

RET proto-oncogene is a tyrosine kinase, a transmembrane glycoprotein, and about 1-2% of NSCLC patients exhibit RET fusion, fused with various upstream molecules such as CCDC6, KIF5B, TRIM33, and NCOA4, and has a strong association with the risk of brain metastasis *(82)*. In 2011, the RET fusion mutation was first identified in NSCLC by Ju *et al. (83)*. Upon activation of RET tyrosine kinase via autophosphorylation, it can stimulate several downstream pathways such as RAS/MAPK, PI3K/AKT, and the JNK-RAS/ERK pathway, which are found to play a crucial role in cell growth, proliferation, and differentiation *(84)*. Two types of RET inhibitors, selective and non-selective, have been studied clinically. The FDA has recently approved two selective RET inhibitors (pralsetinib and selpercatinib) as therapeutic options for metastatic NSCLC patients harboring RET fusions *(85, 86)*. Pralsetinib, also known as BLU-667, is the first oral RET-TKI. It was investigated to find its potential activity in the phase 1/2 ARROW clinical study. It demonestrtated its efficacy in RET fusion NSCLC patients with or without any prior therapy (Table 1) *(87, 88)*. Six percent of patients who had previously platinum-based chemotherapy had a full response, with an ORR of 61%. Patients who had never received treatment had an ORR of 70% and an overall response rate of 11%. Although previously treated patients demonstrated a higher median response duration in 6 and 12 months, these findings suggested a greater ORR in treatment-naïve patients *(89)*. While there were no documented treatment-related deaths, several side effects, such as anemia, hypertension, and neutropenia, were noted.

Selpercatinib, also known as LOXO-292, is orally administrable and can suppress both activating and resistant RET mutations. Selpercatinib has demonstrated a notable inhibitory effect on RET tyrosine kinase and shown significantly reduced toxicity in vitro and in vivo compared to the multi-kinase inhibitors (MKIs) *(90)*. A recent phase 1/2 study (LIBRETTO-001, NCT03157128) was conducted to investigate the effectiveness and toxicity of selpercatinib independently in two distinct cohort study populations in advanced RET fusion-positive NSCLC patients who had received prior treatment and those who were naïve to treatment (Table 1) *(91)*. 85% of patients new to treatment have shown an accurate response, compared to 64% of patients who had received prior treatment. Selpercatinib significantly inhibited brain metastases by intracranial actions, consistent with earlier findings. According to reports, the objective intracranial response was 91%, and the median CNS response length was 10.1 months *(91)*. Non-selective RET inhibitors are multiple kinase inhibitors and have been demonstrated to have low efficacy and generate off-target toxicity. Vandetanib, cabozantinib, and lenvatinib are very well-known nonslective inhibitors (Table 1). It was reported that these were the first MKIs studied in RET-fusion-positive NSCLC patients *(92)*. NCCN guidelines recommend cabozantinib and vandetanib for RET-fusion NSCLC patients, which are known as non-selective RET inhibitors *(93, 94)*. A novel RET inhibitor called TPX-0046 is effective against drug-resistant cancer models, including

Table 1. *Target molecules, signaling Pathways, and therapeutic drug mechanisms in NSCLC management.*

Sl. No.	Target molecule	Regulating pathways	Drugs name	Mechanism action	Reference
	EGFR	Regulate PI3K/AkT/mTOR, MAPK, and STAT signaling pathway	**1st Generation drugs** Gefitinib Erlotinib Ecotinib Icotinib.	These drugs are EGFR tyrosine kinase inhibitors (EGFR-TKIs) known as reversible inhibitors and exhibit effectiveness against NSCLC.	32, 33, 35
			2nd Generation drugs Afatinib Dacomotinib	These drugs are EGFR-TKIs, known as irreversible inhibitors. **Afatinib** exhibits effectiveness in targeting specific uncommon EGFR mutations such as L861Q, G719X, and S768I in NSCLC.	34
			3rd Generation drug- Osimertinib	**Osimertinib** EGFR-TKI irreversibly inhibits T790 mutant EGFR in NSCLC.	39
			4th Generation drugs- BLU-945, BDTX-189 DZD9008, Tarloxitinib Amivantamab Poziotinib Mobocertinib	**EAI045,** as the first allosteric inhibitor, targets the T790M and C797S EGFR mutations in NSCLC.	43
				BLU-945 has the ability to effectively suppress triple-mutant EGFR such as T790M, C797S, and L858R or exon 19 deletion mutations in NSCLC.	42
				BDTX-189 irreversibly targets HER2, EGFR, and ErbB kinase in NSCLC.	44
				TAS6417 targets these mutations, such as T790M, EGFR exon 19 deletions, G719X L858R, S768I, L861Q, and exon 20 insertion mutations in NSCLC.	45
	ALK	Regulate JAK-STAT, MEK/ERK, and PI3K/AkT/mTOR signaling pathway	Crizotinib Alectinib Brigatinib Lorlatinib Ceritinib	**Crizotinib** (the first FDA-approved ALK inhibitor) targets the fusion of exon 13 of the EML4 gene and exon 20 of the ALK gene in NSCLC.	55
				Ceritinib, as a second-generation ALK inhibitor, has shown effectiveness in the treatment of advanced and metastatic ALK-positive NSCLC and also has a potent inhibitory effect on l1171T, G1269A, L1196 M, and S1206Y mutations in NSCLC.	57
				Alectinib is very effective in ALK fusion cizotinib resistance NSCLC and can target the L1196 M, F1174 L, and C1156Y mutations.	58
				Brigatinib is a well-known second-generation ALK inhibitor that can stop EGFR and ALK tyrosine kinase from working. It can also get around the T790 M and L119 M mutations of EGFR and ALK.	60
				Lorlatinib, a third-generation ALK inhibitor, can target both the ALK and ROS1 pathways, is effective against multiple drug resistance of first- and second-generation ALK-TKIs, and overcomes the G1202R in ALK-positive NSCLC patients.	61
	ROS-1	Regulate PI3K/AkT/mTOR, and MAPK signaling pathway	**1st Gen. drug** Crizotinib **2nd Gen. drug** Entrtinib **3rd Gen. drug** Lorlatinib	**Crizotinib** can manage NSCLCs with ROS1 rearrangements.	64
				Entrectinib shows treatment efficacy against ROS1-positive NSCLC.	65, 66
				Lorlatinib can target both the ALK and ROS1 pathways and shows potential impact against mutations that are resistant to crizotinib, including S1986Y/F, 66, L2026M, 66, 83, and D2033N mutations**.**	68, 69
	BRAF	Regulate MEK/ERK signaling pathway	Dabrafinib, Trametinib Encorafinib, binimetinib	**Dabrafenib and trametinib** as BRAF inhibitors, in combination, treat NSCLC with BRAF-V600E mutation.	72
				Encorafenib and binimetinib in combination treat metastatic NSCLC.	32

MET	Regulate PI3K/AkT/mTOR, MAPK, MEK/ERK, and Wnt/β-catenin signaling pathway	Tepotinib Capmatinib Crizotinib	**Crizotinib** treats NSCLC with c-MET protein overexpression, MET gene amplification, and MET exon 14-skipping mutation. **Tepotinib and capmatinib** can treat MET exon 14 skipping mutation-positive NSCLC.	32 78
RET	Regulate PI3K/AkT/mTOR, JAK-STAT, MEK/ERK, and JNK-RAS/ERK signaling pathway	**Selective inhibitors:** Pralsetinib Selpercatinib SLV667 **Nonselective inhibitors:** Vandetanib Cabozatinib Lenvatinib **Others inhibitors:** TBX-0046 BOS172738	**Pralsetinib,** a RET-TKI, treats metastatic NSCLC with RET fusions. **Selpercatinib** can suppress both activating and resistant RET mutations. **Vandetanib, Cabozantinib, and Lenvatinib,** which are multi-kinase inhibitors (MKIs), exhibit effectiveness against RET-fusion-positive NSCLC.	84, 85 87, 88 89

those with solvent front mutations (SFMs)-mediated resistance *(95)*. RET inhibitor-resistant and naïve RET-driven malignancies are being studied in a phase I/II clinical trial (NCT04161391). Recently, BOS172738 was also reported to be a potent and very effective selective RET inhibitor and orally administrable, which has been found to show a wide range of anti-cancer activity with an ORR of 33% *(96)*.

Limitations of targeted therapy in NSCLC

Many variations have been observed in NSCLC patients during targeted therapy, such as few patients showing complete response, few partial responses, and few showing no response to the targeted therapy. Even with the most effective agents, the optimal initial response rate was observed to be around 70-80% *(97)*. Despite widespread advancements in targeted therapy to cure NSCLC, the management of NSCLC is still challenging and complicated. The most important limitations are resistance to the therapeutic agents, toxicity, and the high expense of treatment agents, which might hinder certain NSCLC patients from accessing them *(98)*.

Resistance to the therapeutic agents

Resistance is a critical challenge in targeted therapy for the management of NSCLC. Patients may respond to certain agents initially, but resistance often develops over time. This resistance develops in such a way that a cancer patient who initially responds to a particular therapy eventually becomes resistant to further consecutive treatment with the same agents, ultimately promoting the growth and proliferation of cancer cells *(97)*. Various mechanisms contribute to the development of resistance, such as mutational alterations in gene expression and changes in the tumor microenvironment. Sometimes, mutations can cause the amplification of specific target genes, allowing cancer cells to grow continuously, even in the presence of an inhibitor *(99)*. The driver oncogene activates due to mutation-induced genetic aberrations in the target gene, which are generated by the selective pressure of targeted therapy. For example, after osimertinib-targeted therapy, secondary mutations such as EGFR C797S have been observed, while resistance to erlotinib or gefitinib is often due to the EGFR T790M mutation *(99, 100, 101)*. Additionally, crizotinib is found to be resistant to ALK and ROS1-positive NSCLC patients due to L1196M and L2026M mutations, respectively *(102)*. These mutational alterations of the target gene subsequently develop resistance over time, creating significant challenges to the effectiveness of targeted therapy in NSCLC.

Tumor heterogeneity and lack of reliable biomarkers

Due to tumor heterogeneity, it is sometimes impossible to find reliable biomarkers to predict response to the targeted therapy, which is another major limitation of NSCLC targeted therapy *(94)*. Even though molecular testing is performed to identify the patients who can benefit from the targeted therapy, not every patient responds to the treatment with the particular abnormalities. Furthermore, only a small number of the cancer cells inside a tumor microenvironment may have specific molecular abnormalities, which could result in inadequate targeting and generate possible resistance *(103)*. After identifying particular molecular abnormalities in NSCLC patients, most targeted therapies have been discovered by targeting those molecules. Nonetheless, patients with early-stage NSCLC sometimes might not exhibit these molecular aberrations, which make targeted therapy inaccessible for their particular subtype of the disease *(104)*. This can make it difficult to decide which individuals need targeted therapy and other forms of care *(97, 105)*. Furthermore, even in cases where molecular aberrations are identified, there is sometimes insufficient information

available to determine the best course of treatment, including the best way to sequence drugs and which targeted therapy should be used.

Toxicity

Toxicity often develops in cases of long-term exposure and may have significant adverse effects, whereas exposure to targeted therapy for a short period is nontoxic and manageable. Targeted therapies particularly target cancer cells, and that's the reason it is considered less toxic. Although some targeted therapies may create severe adverse effects such as hepatotoxicity, nephrotoxicity, gastrointestinal problems, and blood clots *(97)*, due to these adverse effects, the effectiveness of targeted therapy is reduced, and the dose and periods of treatment are limited *(97)*. When a targeted therapy is intended to block cancer-specific targets, it may also block a specific set of proteins in normal cells; this is known as on-target toxicity, and thereby, it causes harm by blocking the signaling cascade. Numerous harmful side effects may arise, such as skin rash caused by EGFR inhibition, hyperglycemia caused by PI3K inhibition, and hypertension caused by vascular endothelial growth factor inhibition *(106, 107)*. When a drug inhibits a non-target protein, that toxicity is known as off-target toxicity, which can have detrimental side effects. In contrast to on-target toxicity, off-target toxicity is unique to a single drug and does not show class effects. For instance, osimertinib can cause cardiotoxicity, including heart failure, myocardial damage, dysfunction of the left ventricle, and conduction abnormalities, whereas gefitinib does not exhibit any cardiac toxicity *(108, 109)*.

TUMOR SUPPRESSOR GENE THERAPY

The p53 is one of the potential tumor suppressor molecules that regulate cellular proliferation and is activated by various stress stimuli such as hypoxia, oncogenes, and DNA. Consequently, the activation of subsequent genes implicated in cell-cycle arrest occurs, enabling either DNA repair or the induction of apoptosis if not repaired. 50% of NSCLCs and 90% of SCLCs often have a mutation that makes p53 inactive. The identification of apoptosis in LC cells with altered or deleted p53, which leads to restoration of p53 activity, has stimulated the advancement of pharmacological approaches to reactivate p53, for example, gene replacement therapy. Several clinical studies have been conducted by using a retroviral p53 expression vector, further demonstrating the safety, feasibility, and potential therapeutic effectiveness of p53 gene therapy in individuals diagnosed with NSCLC. Based on initial findings derived from investigations conducted on individuals diagnosed with LC, it has been found that a p53 adenoviral vector (INGN 201; Ad5CMV-p53, Advexin) exhibits both safety and efficacy *(23)*.

The FUS1 gene is a newly discovered tumour suppressor molecule found on chromosome 3p21.3, and this region is reported mostly to be deleted in cases of lung cancer. Most NSCLCs and SCLCs have been observed to often exhibit a reduced expression of FUS1 protein or a lack of post-translational modification (PTM) of the protein. The introduction of exogenous FUS1 overexpression has been found to impede tumour cell proliferation and promotes death in LC cells that lack the 3p21.3 gene. A nanoparticle delivery system has been devised for FUS1 gene therapy. Initial results from a phase I study conducted on individuals diagnosed with lung cancer indicate that the utilization of FUS1 nanoparticles is deemed safe. Further research is required to determine the therapeutic efficacy of these gene therapies in the context of LC *(23)*.

PROTEOLYSIS TARGETING CHIMERAS (PROTACS)

Drug development techniques that utilize intracellular ubiquitin-proteasome systems to induce targeted protein degradation can potentially advance the field of personalized therapy for individuals diagnosed with lung cancer *(110)*. Proteolysis targeting chimaeras (PROTACs), which are tiny molecules, have been created to address cancer targets that present promising prospects for the treatment of advanced lung cancer (111). PROTACs are composed of a pair of ligands linked together by a connector capable of binding to a specific target protein, together with an E3 ubiquitin ligase *(112)*. The initial introduction and demonstration of PROTACs occurred in 2001, wherein a proof-of-concept study showcased utilizing an endogenous ubiquitin-proteasome system for the degradation of pathogenic proteins *(111)*. This revolutionary technique in small-molecule drug discovery has spurred remarkable advancements in drug development in recent years *(110)*. This technique facilitates the development of innovative and precise cancer treatments. PROTACs are a class of hybrid molecules that integrate the inherent ubiquitin-proteasome system to specifically eliminate the proteins implicated in cancer and various other pathological conditions. The system comprises two ligands, one binding to the Protein of Interest (POI) and the second ligand binding to E3 ubiquitin ligase *(110)*.

In the field of PROTAC development, it is possible to employ tiny compounds that can attach to various surfaces of target proteins. The creation of PROTACs involved the use of ALK and EGFR inhibitors. Lung cancer exhibits a diverse array of tumors, and PROTAC can eliminate cancer-causing proteins with minimal intracellular concentration needs. This is achieved by targeting individual molecules that can undergo several rounds of degradation. Molecular oncology therapies have garnered significant attention as a prominent area of research in lung cancer. Given the novelty of PROTAC, it is impera-

tive to employ diverse biomarker tests to monitor their efficacy in both *in vitro* and *in vivo* settings. To summarize, PROTACs can overcome the current obstacles in lung cancer treatment and achieve the potential of tailored therapy *(110)*. Therefore, this review aims to provide a comprehensive analysis of the current research, highlighting recent advancements in molecular targeted therapy for the management of lung cancer, specifically non-small cell lung cancer with the goal of identifying potential avenues for further investigation and clinical application.

FUTURE PERSPECTIVE

The future of lung cancer research and therapy holds the potential for numerous innovations that can significantly transform the field of patient care and improve overall outcomes. The advent of molecular targeted therapy in lung cancer has shown promise in personalized diagnostic methods, surpassing conventional methods of early disease diagnosis. Further investigation into emerging therapeutic targets and pathways, modifications to the tumor microenvironment and regulators of epigenetics have the potential to reveal innovative approaches for intervention. By identifying and specifically addressing these pathways, improving outcomes for people with lung disease by overcoming resistance mechanisms. It is essential to recognize the limitations of current approaches, as this can help enhance existing information and create effective treatment solutions.

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