REVIEW ARTICLE

Systemic Therapies for Non-Small Cell Lung Cancer Chemotherapy: Targeted Therapy and Immunotherapy

B. Lokeshwari[1], P. Gowtham Ganapathy[2], J. D. Preethi[3], P. Saranraj[1], K. Gayathri[1]

[1]Department of Microbiology, Sacred Heart College (Autonomous), Vellore, Tamil Nadu, India, [2]Department of General Medicine, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India, [3]Department of Paediatrics, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, India

Abstract

Non-small cell lung cancer (NSCLC) constitutes 85% of global lung cancer cases and is a predominant cause of cancer-related mortality. Personalized chemotherapy, targeted therapy, and immunotherapy have been employed to treat NSCLC. Traditional platinum-based chemotherapy increases survival rates, especially in advanced stages, but no specificity and toxicity require customized treatments. Molecularly targeted medicines have revolutionized NSCLC treatment for epidermal growth factor receptor, anaplastic lymphoma kinase, C-ros oncogene 1, B-raf proto-oncogene, mesenchymal-epithelial transition, and rearranged during transfection mutations. Tyrosine kinase inhibitors kill cancer cells without harming normal tissues, improving prognosis and survival in molecularly defined malignancies. Next-generation inhibitors and combination treatments are needed to treat targeted drug resistance. Immunotherapy with immune checkpoint inhibitors that target the programmed cell death protein 1/programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 pathways has revolutionized cancer treatment by harnessing the host immune system to fight cancer, especially in patients with high PD-L1 expression or a high tumor mutational load. Despite these advances, immunotherapy resistance and immune-related adverse effects remain difficult. Biomarkers, new targets like Kirsten rat sarcoma G12C, and immunotherapies including bispecific antibodies and cancer vaccines will be used to treat NSCLC. By adding AI and machine learning into immediate resistance pattern input, dynamic response evaluation will improve personalized treatment. This paper addresses all systemic medicines for NSCLC, including precision oncology and biomarker-driven treatments to enhance survival and quality of life.

Key words: Chemotherapy, immunotherapy, non-small cell lung cancer, personalized medicine, and targeted therapy

INTRODUCTION

The most common cause of death in worldwide cancer and tumors is non-small cell lung cancer (NSCLC). The smart molecular profile of NSCLC makes this condition inaccessible to a single therapy method, and as a result, immunotherapy, targeted therapy, and conventional chemotherapy are used together.[1] Over several years, chemotherapy was the main systemic approach which depended on cytotoxic compounds like platinum-based compounds to induce cell death and prevent cell proliferation. Nonetheless, the method usually led to a decreased survival rate particularly when the disease was at an advanced stage due to lack of specificity and high levels of toxicity. These weaknesses underscored the need to develop more accurate treatment approaches and eventually leading to the emerging of molecularly targeted therapies. It has been possible to treat certain genetic mutations such as epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) rearrangements, and C-ros oncogene 1 (*ROS1*) gene fusions using such drugs.[2] Specific cancer

Address for correspondence:
P. Saranraj, Department of Microbiology, Sacred Heart College (Autonomous), Tirupattur, Vellore, Tamil Nadu, India.
E-mail: microsaranraj@gmail.com

Received: 04-05-2026
Revised: 18-06-2026
Accepted: 25-06-2026

therapy has a less significant effect on other body tissues and, that is why, is more accurate treatment. Individualized therapies, such as administration of monoclonal antibodies and small-molecule tyrosine kinase inhibitors (TKIs), have demonstrated significant clinical advantages in patients with specific molecular mutations.

Immunotherapy – especially immune checkpoint inhibitors (ICIs) that can inhibit cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1) – has drastically redefined how NSCLC is treated by triggering impressive host anti-tumor immunity.[3] In spite of the long-term advantages and better survival provided by immune checkpoint blockage, the following issues remain, such as primary/secondary resistance, immune adverse events, particularly in patients with high PD-L1 expression, or high tumor mutational load. Chemotherapy combined with immunotherapy has also been used to advance treatment and overcome resistance mechanisms and increase effectiveness with dual checkpoint inhibition.[4] Among the systemic methods to promote the treatment of NSCLC, the development of both bispecific antibodies, antibody-drug conjugates (ADCs), and individual cancer vaccines can be identified. The role of their adaptive trial designs, liquid biopsy-based real-time monitoring of resistance pathways, and biomarker-oriented treatment options is becoming more and more crucial. The management of NSCLC remains dynamic in light of research on the molecular and immunological pathways that mediate tumor growth and resistance to therapeutic interventions in addition to the integration of established and emerging treatment modalities.

The future of systemic therapy is to improve patient selection using biomarkers, explore new molecular targets, including Kirsten rat sarcoma (KRAS) G12C mutations, mesenchymal-epithelial transition (MET) dysregulation, rearranged during transfection (RET) fusions or HER2 changes, and next-generation immunotherapy delivery platforms, like engineered T-cell therapies or custom neoantigen vaccines.[5] The tumor microenvironment is assessed by stomach interactions, immune evasion maneuvers, and metabolic remodeling. It is a key factor in identifying therapeutic response, as well as resistance to affect clinical management and treatment outcomes. Artificial intelligence (AI) and machine learning (ML) in the field of oncology may be used to treat NSCLC on an individual basis.[6] A combination of immunotherapy, targeted therapy, and chemotherapy is one of the examples of the further development of precision oncology in NSCLC, but the prognosis is difficult. The swift growth of molecular diagnostics, immunogenomics, and the forms of treatment will further enhance the systemic treatment approach to NSCLC, enhancing the treatment of the patient in this most complex and dynamic disease.

EPIDEMIOLOGY OF NSCLC

NSCLC develops because of smoking, exposure to the environment, access to health services, policies of the government regarding health, and the environment. The effects of most carcinogens and epigenetics point out that smoking is the most common risk factor for NSCLC. Individuals who are not smokers are more likely among women and younger people.[7] Other risk factors include radon, hereditariness, environmental contamination, workplace carcinogens, and carcinogenic viral infections. The patterns of oncogenic driver mutations in various populations are different as compared to those of NSCLC.[8] Unproportional effects are observed in persons who have been diagnosed with NSCLC at a median age. The epidemiology of NSCLC is determined by different factors, such as ethnicity, gender, and socioeconomic status. These parameters are affected because minorities and low-income groups have a greater rate of incidence, severity of the diagnosis, and poor survival rates. Smoking restrictions, lung cancer screening, and treatment innovations have led to the standardization of the mortality trends in a number of countries.[9]

PATHOLOGICAL CLASSIFICATION AND CHARACTERIZATION OF NSCLC

NSCLC is contingent upon variables such as smoking, environmental exposure, healthcare accessibility, and public health initiatives. Although smoking is the primary risk factor, women and younger individuals who have never smoked have a reduced incidence.[10] Oncogenic virus infections, air pollution, occupational carcinogens, genetic predispositions, and radiation exposure constitute additional risk factors. The molecular epidemiology of NSCLC is crucial due to the varying patterns of oncogenic mutations across different populations. Age is a key epidemiological determinant such as NSCLC primarily affects older adults. Despite advancements in early diagnosis, the majority of NSCLC diagnoses are at an advanced stage, rendering therapy ineffective. Prolonged diagnosis contributes to the worldwide burden of NSCLC. The epidemiology of NSCLC shows its advancement, screening, and prevention through systemic treatment.[11]

Histological classification

Histological sub-classification is used to inform clinical decisions, prognoses, and treatment plans for NSCLC, a large class of epithelial lung tumors. The most common adenocarcinoma subtype originates from distal airway epithelial cells, characterized by glandular development, mucus production, and expression of thyroid transcription factor-1 (TTF-1) and napsin A.[12] Tobacco use is more strongly linked to proximal bronchial epithelial squamous cell carcinoma. Undifferentiated large cell carcinoma typically

lacks the symptoms associated with adenocarcinoma or squamous cell carcinoma. Immunohistochemical and molecular tests eliminate other diseases.[13] Large cell neuroendocrine carcinoma (LCNEC), adenosquamous, sarcomatoid, and other rare pleomorphic carcinomas have distinct histological features and management issues. A few cytological or microscopic biopsies are needed to diagnose NSCLC due to its histological variation. Histology underpins most systematic therapy, but proper classification ensures accurate diagnosis.[9-12]

Molecular characterization

NSCLC, a diverse group of epithelial lung tumors, utilizes histological subclassification for clinical prognosis and treatments. The World Health Organization classifies adenocarcinoma, squamous cell carcinoma, and small-cell carcinoma as the primary histological subtypes of NSCLC. The most common adenocarcinoma subtype, originating from distal airway epithelial cells, exhibits glandular development, expresses mucin, TTF-1, and napsin A.[14] Squamous cell carcinoma, on the other hand, starts in proximal bronchial epithelial cells and is related to smoking. The less common forms of squamous carcinoma, sarcomatous carcinoma, LCNEC, and pleomorphic carcinoma are distinct. Due to the heterogeneity of NSCLC, cytologic or small biopsies are necessary for a precise pathological diagnosis.[15]

THERAPIES FOR NSCLC

PD-1 and PD-L1 ICIs have also revolutionized immunotherapy. Traditional therapy involves atezolizumab, durvalumab, nivolumab, and pembrolizumab.[16] Cisplatin-based neoadjuvant chemotherapy or chemo-immunotherapy decreases recurrence and increases survival in high-risk pathological features. NSCLC treatment is based on sequential systemic medicines, where molecular retesting during each stage is becoming a more crucial factor. One of the invasive methods to monitor diseases and detect curable anomalies is liquid biopsies. The treatment of NSCLC will be more dynamic and intricate, using real-time molecular and immunological platforms.[17] Figure 1 illustrates the major therapeutic strategies for NSCLC, including surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy. It highlights how treatment selection depends on cancer stage, genetic mutations, and patient-specific factors, often involving a combination of these approaches for improved outcomes.

Adjuvant chemotherapy

A groundbreaking meta-analysis by the Lung Adjuvant Cisplatin Evaluation Collaborative Group, which included the International Adjuvant Lung Trial, found that platinum-based adjuvant chemotherapy significantly improves survival, reducing the risk of death by 11% at 5 years.[18] Cisplatin-based doublets with vinorelbine, docetaxel, gemcitabine, or pemetrexed are the most prevalent treatment. Histologic subtype (e.g., pemetrexed with non-squamous carcinomas) and side effect tolerance may dictate patient regimens.[19] Despite showing a survival benefit compared to 5 years of treatment, it still has a major clinical impact on most patients and is an important part of multidisciplinary treatment.[20]

Neoadjuvant immunotherapy

The long-term outcomes for early-stage disease have caused a paradigm shift in NSCLC. This method often has a 5-year survival rate of <50% and high cancer recurrence. In metastatic cases, ICIs targeting the PD-1, PD-L1, and CTLA-4 pathways are efficacious.[21] These large pathogenic reactions improve survival, suggesting micrometastatic illness eradication.[22] The neoadjuvant strategy allows evaluation of the tumor sample for biological efficacy and predictive

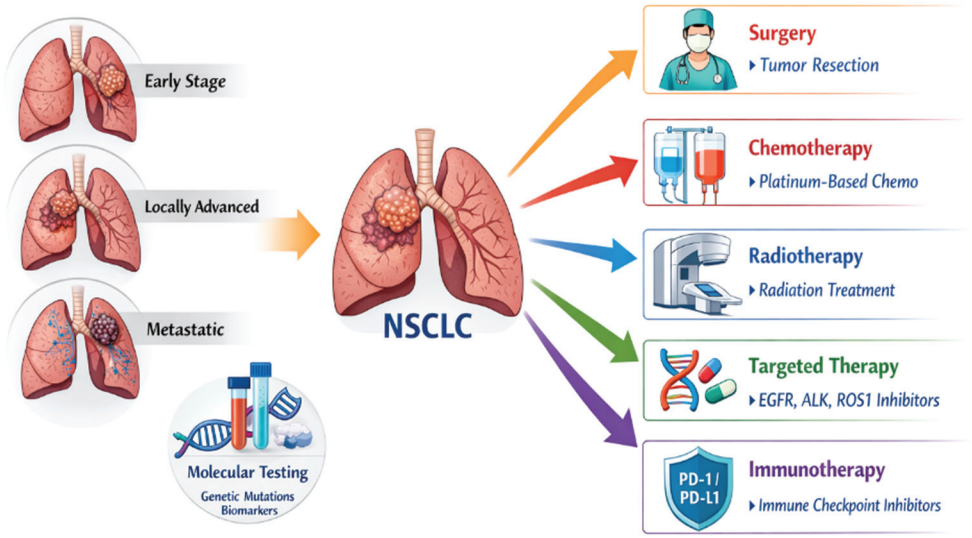

Figure 1: Therapies for non-small cell lung cancer

indicators such as tumor mutational burden (TMB), PD-L1 expression, and tumor-infiltrating lymphocyte composition. Despite optimizing neoadjuvant immunotherapy regimens, including length, chemotherapeutic combination, and patient selection, biomarker-guided techniques are predicted to maximize efficacy and minimize toxicity.[23]

Perioperative immunotherapy

Pre- and post-surgery immunotherapy is a successful treatment for resectable NSCLC. This method maximizes survival by combining immune stimulation and surgery. The procedure as an *in vivo* vaccine may boost the immune system and elicit a significant T-cell response that targets the primary tumor and diffused micro metastases.[24] The delivery of immunotherapy before resection allows real-time monitoring of biological and pathological responses, which helps identify prognostic biomarkers and provides invaluable insights into the tumor immune milieu.[25] The adjuvant phase strengthens this immune response, eliminates disease, and prevents recurrence. The adjuvant atezolizumab after chemotherapy improved disease-free survival (DFS) compared to chemotherapy alone, proving adjuvant immunotherapy's efficacy and validating perioperative procedures.[26]

Adjuvant targeted therapy

Adjuvant targeted treatments are a more feasible and effective alternative than conventional chemotherapy for the molecularly defined population of individuals with NSCLC. Nevertheless, it is a non-specific strategy that does not explicitly target the driving oncogenes that cause most patients' malignancies to develop. The identification of malfunctioning molecular circuits throughout the carcinogenesis process has enabled the creation of drugs that specifically target particular pathways, thereby improving efficacy while reducing the systemic side effects associated with cytotoxic treatment.[22] The target agent exhibited a significantly better toxicity profile and demonstrated a median DFS advantage of 28.7 months compared to 18.0 months.[23] Erlotinib has also shown a DFS benefit in the EVAN study. Adjuvant therapy is on the rise, and current trials, such as ALINA (for ALK-positive disease), continue to explore the use of targeted drugs in perioperative care.

Neoadjuvant targeted therapy

A potential and medically appropriate approach for treating active NSCLC with molecularly identifiable drivers is neoadjuvant targeting. TKIs are administered before surgery in an attempt to downstage the primary tumor, eliminate micrometastatic implants, and increase the probability of a complete (R_0) resection before surgery. Due to its superior efficacy, favorable resistance profile, and enhanced central nervous system (CNS) penetration compared with earlier-generation tyrosine kinase inhibitors (TKIs), third-generation osimertinib has emerged as a preferred therapeutic option for EGFR-mutated non-small cell lung cancer (NSCLC). Ongoing clinical studies, including NeoADAURA, are further evaluating its potential role in the neoadjuvant settings.[24] Due to its superior resistance profile and increased central nervous system (CNS) activity compared to first- and second-generation drugs, the third-generation agent osimertinib has been the subject of several ongoing neoadjuvant studies (e.g., NeoADAURA). Tolerability and the ability to administer a full dosage of treatment without causing incapacitating toxicities are the advantages of neoadjuvant targeting over chemotherapy delivery. This allows for a longer time before surgery and maintains the patient's performance level.[25]

Adjuvant molecular targeted therapy

One of the most notable examples of precision medicine in oncology is adjuvant molecular targeted therapy, which offers a tailored therapy regimen to patients with NSCLC and known to have certain molecular alterations in their excised tumors. The toxicity rate of adjuvant platinum-doublet chemotherapy is high although it remains the primary treatment. It marginally enhances survival, which means that less dangerous and more effective approaches are needed.[26] The identification of oncogenic drivers has resulted in drugs targeting these abnormal pathways, improving their effectiveness, and reducing collateral damage to normal tissues. Mortality or recurrence was lessened by 80%; the experiment recorded a new record DFS. Consequently, adjuvant osimertinib was approved worldwide.[27] The excised NSCLC has resulted in a new paradigm underlining the significance of comprehensive molecular testing in all patients to identify which ones will respond to these therapies.[28]

DIAGNOSIS OF NSCLC

NSCLC accounts for 85% of lung cancer cases. Histological subtypes include adenocarcinoma, squamous cell carcinoma, and giant cell carcinoma.[29] Diagnoses establish conditions and treatment options. Images such as chest X-rays and computed tomography (CT) scans are evaluated. Histological study is essential for separating the two most frequent forms, adenocarcinoma and squamous cell carcinoma.[30] NSCLC development and treatment increasingly use molecular testing. It enables targeted therapy by detecting tumor-level mutations, fusions, and amplifications. The optimum chemotherapy, targeted therapy, or immunotherapy depends on diagnosis and stage. Figure 2 depicts the diagnostic pathway for NSCLC, including imaging techniques such as CT/positron emission tomography (PET) scans, tissue biopsy, and molecular testing for genetic mutations. It emphasizes the importance of accurate staging and biomarker identification to guide personalized treatments.

Image test

NSCLC causes 85% of lung cancer occurrences. Initial clinical investigations focus on hemoptysis, dyspnea,

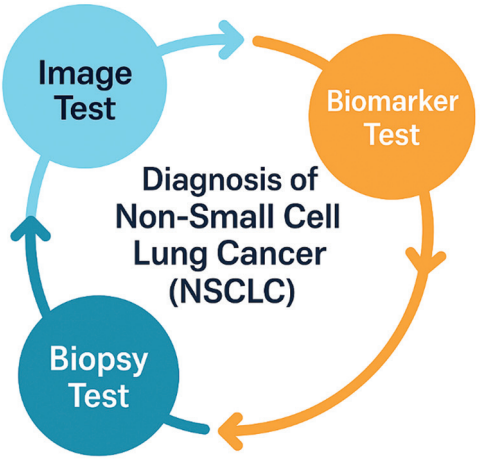

Figure 2: Diagnosis of non-small cell lung cancer

chronic cough, weight loss, and chest pain.[28] Imaging, CT, and PET are important for confirming and describing the condition. CT images show the lungs clearly, and PET scans show tumor metabolic activity and aggressive extension to remote sites in the illness phase.[31] Imaging is essential for diagnosing and staging NSCLC, but it cannot diagnose histology. Cell material must be obtained from tissue samples following imaging, which is essential to pathogenesis. Immunohistochemistry uses antibodies to protein markers to sort NSCLC into relevant subgroups. Modern oncology routinely uses molecular profiling to diagnose NSCLC, allowing personalized chemotherapy and targeted therapy. This genomics study allows patient-specific therapy.[32]

Biopsy test

Biopsy is essential for diagnosing and treating NSCLC. In precision medicine, histological and genetic data from biopsy samples decide treatment. Biopsy methods vary by tumor size, location, accessibility, and patient health and lung function.[33] Bronchoscopy is the main treatment for centrally situated airway tumors; however, endobronchial ultrasound-guided biopsy and electromagnetic navigation bronchoscopy are increasingly employed for peripheral lesions and lymph node sampling. CT-guided percutaneous needle biopsy is a common, less invasive peripheral lung mass diagnosis.[34]

Biomarker test

NSCLC has been a major breakthrough in diagnostics and treatment for prognostic and predictive as well as pharmacodynamic indicators of response to immunotherapies and drug resistance mechanisms. This type of testing is essential to patients who are planning to undergo chemotherapy, targeted therapy, or immunotherapy.[35] Next-generation sequencing has transformed this area by allowing many genes to be interrogated at the same time using limited tissue samples of tissue acquired by biopsy. The analysis of biomarkers has become standard practice as a patient with advanced disease or metastatic disease is subject to reflex testing in which the automatic analysis of biomarkers is triggered by diagnosis with a non-small cell. Although liquid biopsies are becoming more popular, the gold standard is a tissue-based test because it is sensitive and specific to the majority of changes.[36]

TREATMENTS FOR NSCLC

The stabilization of non-progressing patients is done with chemotherapy. Targeted therapy has been used to treat the cancerous molecular alterations to enhance response rates and minimize systemic toxicity.[37] Oral TKIs are useful in the management of EGFR-mutant tumors. The intracranial effect of the ALK inhibitors is greater than that of chemotherapy. One of the ICIs, inflammatory therapy based on the PD-1/PD-L1 pathway, has transformed treatment since the agent is effective even in the case of metastases.[38] Figure 3 summarizes the different modes of treatment of NSCLC such as surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy. It illustrates the customization of treatment plans in response to tumor stage, molecular characteristics, and patient health to achieve the best clinical outcomes.

Chemotherapy and chemoradiotherapy

Radiotherapy and chemotherapy are some of the basic therapies for this disease and for NSCLC that lacks targetable mutations. The most common one in advanced cases and also in surgery to eradicate the residual microscopic disease is platinum-based chemotherapy. One of the major advances is chemoradiotherapy, which involves both treatments simultaneously. This needs specific planning so as to be as effective as possible against the tumor with minimal damage to the tissue. The PACIFIC trial established a novel standard by showing that following chemoradiotherapy with the immunotherapy drug durvalumab greatly improves survival for patients with stage III disease. Radiation innovations such as intensity-modulated radiation therapy and stereotactic body radiation therapy have become more precise so that they can use more and more doses with fewer damages to the surrounding tissues.[39]

Chemotherapy

Advanced NSCLC patients who are not highly expressing PD-L1 or have certain genetic mutations do not receive high PD-L1 or specific mutation-targeted chemotherapy, but instead systemic chemotherapy is the main treatment. Although this method is effective in interfering with the growth of cancer cells, it is not selective and usually leads to serious side effects, such as tiredness, nausea, and bone marrow suppression.[40] Surgery is the preferred treatment of the disease at its early stages; in high-risk patients, chemotherapy is employed following adjuvant surgery. The

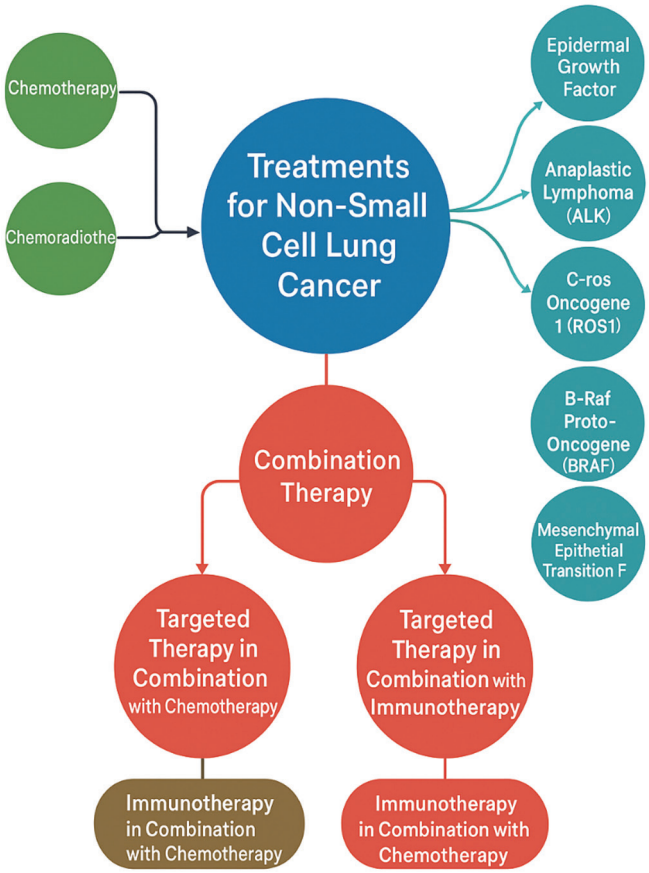

Figure 3: Treatments of non-small cell lung cancer

most common therapy for metastatic cancer is a two-drug, platinum-based regimen. Depending on the cancer subtype, the particular combination depends, and pemetrexed is typically used with non-squamous cancers, and agents such as gemcitabine with squamous cell carcinomas.[37]

Chemoradiotherapy

Concurrent chemoradiotherapy is a key, intensive treatment for patients with locally advanced, inoperable NSCLC. It is a standard, curative-intent strategy for those who are not candidates for other therapies.[38] In this approach, chemotherapy acts as a radiosensitizer, rendering the cancer cells more susceptible to radiation. This synergy provides superior tumor control and survival compared to giving the treatments separately. However, the combination also increases side effects, damaging both dividing cells and tissues in the radiation field, which can lead to esophagitis, pneumonitis, and reduced blood cell counts. The regimen typically uses a platinum-based drug combined with another agent.[39]

Targeted therapy

Targeted therapy has revolutionized the treatment of NSCLC, as it involves the use of drugs that target tumors due to their genetic mutations. These drugs are known as TKIs and target drivers such as EGFR, ALK, and ROS1, resulting in better response rates and disease control compared to conventional chemotherapy.[40] This requires comprehensive genetic testing during the initial diagnosis and, in the case of disease progression, to inform further treatments.

EGFR

EGFR mutations are typical, targetable oncolytic drivers of NSCLC, which often occur in specific patient groups. These mutations cause sustained cell signaling that facilitates tumor growth. Specific deletions are sensitive to EGFR inhibitors, including those in exon 19 and the L858R mutation.[41] This mutation-targeted therapeutic strategy inhibits downstream signaling pathways and provides an effective treatment approach for patients with BRAF V600E-mutated NSCLC. First- and second-generation targeted drugs were superior to chemotherapy, but they were frequently hampered by the development of resistance, typically due to the harmful T790M mutation. Third-generation inhibitors, including osimertinib, which appear to circumvent this resistance mechanism, are now a first-line therapeutic option due to improved outcomes and the ability to treat brain metastases.[42]

ALK

A small fraction of NSCLC patients has *ALK* gene rearrangements. The initial targeted drug, crizotinib, demonstrated a significant improvement over chemotherapy but lacked efficacy due to resistance and limited brain activity.[43] This prompted the emergence of new and more effective inhibitors (ceritinib, alectinib, brigatinib, lorlatinib). These new-generation drugs are resistant to invasion and very useful in the treatment and prophylaxis of brain metastases. Alectinib is commonly a first-line therapy medication because of its strong effects and tolerable side effects. The successive application of these agents has transformed ALK-positive NSCLC into a condition that is manageable in a chronic state.[44]

ROS1

A unique fusion of the *ROS1* gene occurs in a small %age of cases of NSCLC and is a rare driver mutation. These alterations are particularly effectively treated with targeted therapy using TKIs.[45] Crizotinib is the first approved drug to produce strong responses, but resistance may still occur. Entrectinib and lorlatinib are more powerful inhibitors designed to address this drawback. Entrectinib has one significant benefits and it is highly effective in treating CNS diseases. NSCLC emphasizes the crucial role of thorough molecular screening in identifying such rare changes, thereby enabling patients to receive more effective and less toxic targeted therapies rather than traditional chemotherapy.[46]

B-raf proto-oncogene (BRAF)

BRAF gene mutations are found in a small population of NSCLC, with the most frequent mutation being the V600E mutation. Such a mutation constantly activates an important cell growth pathway.[47] A combination of two medications

is the most effective: A BRAF inhibitor (dabrafenib) and a mitogen-activated extracellular kinase inhibitor (trametinib). This mutation-blocking strategy, which also inhibits a downstream protein of great importance, has become the new standard of care. It elicits potent and sustained effects, contributing to the delay of treatment resistance emergence.[48]

MET factor

Tumor growth in a minor fraction of NSCLC cases is associated with abnormal MET pathway signaling, which is typically caused by MET exon 14 skip mutations. These mutations have been previously associated with poor chemotherapy outcomes.[49] MET inhibitors have now become an important strategy to be used in targeted therapy of cancer. Although the multi-targeted agent crizotinib was used, more specific agents, including capmatinib and tepotinib, have been approved and have shown reasonable response rates and efficacy against brain metastases. As in other targeted therapies, resistance ultimately occurs.[47] Combination strategies that target downstream pathways or are used in combination with other agents are currently considered to overcome this resistance.[50]

Combination therapy

Combinations can be employed to manage cancer and overcome resistance to individual treatments. This treatment method implies combining chemotherapy, targeted therapy, and immunotherapy.[51] The combination of treatments is more potent than either therapy. A combination of chemotherapy with targeted agents may lead to deeper responses, and the addition of immunotherapy may modify the tumor microenvironment to stimulate the body's immune attack. The combination of ICIs has proven particularly revolutionary in the treatment of advanced NSCLC in the absence of driver mutations.[52]

Targeted therapy in combination with chemotherapy

Combination targeted therapy and chemotherapy can be effective in patients with actionable mutations.[53] The advantages of both are utilized in this strategy and the targeted drug will block the key cancer-driving pathway, while chemotherapy will be used to kill a wider variety of tumor cells, including those that may be resistant to the targeted agents. EGFR-mutant lung cancer, which involves the combination of an EGFR TKI and chemotherapy, has been reported to have a greater PFS in comparison to the utilization of the TKI solely.[54] It aims to maximize patient benefit to achieve a more rapid and more complete response and must be careful about the combined toxicity.

Targeted therapy in combination with immunotherapy

Individual therapy combined with immunotherapy is not a simple one. In theory, the killing of tumor cells by targeted drugs may release antigens and trigger an immune response. Nevertheless, mutation-driven cancers, such as those involving EGFR or ALK, tend to possess a cold tumor microenvironment with minimal immune cell function, so immune therapy alone cannot be used. Initial clinical trials involving these treatments have shown serious side effects (including hepatotoxicity and pulmonary inflammation).[55]

Immunotherapy in combination with chemotherapy

Immunotherapy of metastatic NSCLC without driver mutations using platinum-doublet chemotherapy plus immune checkpoints is an initial-line treatment. Chemotherapy supplements immunotherapy by triggering immunogenic cell death, which can be utilized to stimulate the immune system and modulate the tumor microenvironment. This paradigm of synergy is effective in patients with low PD-L1 expression, who typically respond less favorably to immunotherapy monotherapy. Pivotal clinical trials have validated this combination strategy, demonstrating improved survival outcomes.[56]

Immunotherapy

Immunotherapy is a novel technology in the treatment of lung cancer which involves the use of the immune system in the body to fight cancer. Such drugs are ICIs (e.g., pembrolizumab, nivolumab), by assisting to release the immune cells, permitting them to successfully attack a tumor and can often lead to long-term responses.[57] These methods of resistance and novel innovative technologies such as bispecific antibodies and cellular therapies can help more patients.

CLINICAL TRIALS FOR SYSTEMIC THERAPIES IN NSCLC

NSCLC treatment was dominated by targeted and immune-based medications in 2024 and early 2025, but endeavor persists to offer potent alternatives and improve treatment regimens. Individualized treatment simplifies second-line treatment and combats resistance outside initial approvals. The phase III LAURA found that osimertinib consolidation following chemoradiation significantly improved PFS in unresectable Stage III NSCLC.[58] Next-generation TKIs and the PAPILLON study of amivantamab plus chemotherapy give this subgroup, which is already treated, a good choice for EGFR exon 20 insertion mutations. The phase III ALINA trial made alectinib the standard of treatment for stage IB-IIIA ALK-rearranged NSCLC, prolonging DFS and reducing recurrence by almost 70%, equivalent to metastatic disease.[59]

In the KRYSTAL-12 phase III trial, adagrasib surpassed docetaxel in second-line PFS and overall survival (OS),

and innovative combos with KRAS G12C inhibitors and immunotherapy or SHP2 inhibitors are showing potential in overcoming therapeutic resistance. For MET exon 14 skipping mutations and RET fusions, long-term follow-up and real-world evidence suggest tepotinib, capmatinib, and selpercatinib, with an emphasis on next-generation medicines to address on-target resistance mechanisms.[60] Improved immunotherapy includes ICIs. Pembrolizumab plus chemotherapy in non-squamous cancer showed a 21.6% 5-year OS rate compared to 12.0% in the KEYNOTE for metastatic NSCLC without mutations.[61]

Nivolumab, ipilimumab, and limited-course chemotherapy safely improve squamous NSCLC long-term survival (9LA).[62] The landmark TROPION-Lung01 Phase III trial found that TROP2-targeted ADC datopotamab deruxtecan (Dato-DXd) improved PFS over docetaxel in advanced NSCLC patients with non-squamous hist. The HERTHENA-Lung01 trial showed patritumab deruxtecan (HER3-DXd), an anti-HER3-directed ADC, effective in EGFR-mutant NSCLC patients resistant to osimertinib and platinum.[63] Personalize and sequentially treat all stages using non-PD-L1 predictive biomarkers, blood-based TMB, circulating tumor DNA (ctDNA) to detect minimal residual disease (MRD) for perioperative use, and complex genomic signatures to better select patients for specific immunotherapies or combinations[64] [Table 1]. Summarizes the targeted, immunotherapeutic, and ADC systemic therapy for NSCLC that improves survival. Personalized therapy overcomes resistance and improves efficacy with molecular targets and predictive indicators.

LIMITATIONS OF NSCLC

NSCLC, the most common oncology issue with 85% of all lung cancer cases, is a significant barrier to patient care because of the ongoing and intertwined restrictions in patient care during the initial diagnosis and detection process and throughout the treatment process in managing the disease.

Table 1: Overview of novel drugs and clinical trials in NSCLC management

Trial name	Therapy/drug	Target/ mechanism	Outcomes	Clinical significance
LAURA (Phase III)	Osimertinib (consolidation)	EGFR TKI	Significant increases PFS	New standard consolidation therapy
PAPILLON (Phase III)	Amivantamab and chemotherapy	EGFR exon 20 insertion	Improved response and PFS	Effective for resistant EGFR mutations
ALINA (Phase III)	Alectinib	ALK inhibitor	>70% recurrence, increased DFS	New adjuvant standard of care
KRYSTAL-12 (Phase III)	Adagrasib versus docetaxel	KRAS G12C inhibitor	Improved PFS and OS	Better 2nd-line alternative
MET/RET studies	Tepotinib, Capmatinib, Selpercatinib	MET exon 14/RET fusion	Durable responses	Targeted therapy expansion
KEYNOTE trials	Pembrolizumab and Chemotherapy	PD-1 inhibitor	5-year OS: 21.6% versus 12%	Long-term survival benefit
CheckMate 9LA	Nivolumab and Ipilimumab and Chemo	Dual ICI and chemo	Improved OS	Effective combination regimen
AEGEAN (Phase III)	Perioperative Pembrolizumab	PD-1 inhibitor	Improved EFS and OS	Strong perioperative strategy
PACIFIC regimen	Durvalumab (consolidation)	PD-L1 inhibitor	Sustained survival benefit	Standard for locally advanced disease
SKYSCRAPER-01	Tiragolumab and Atezolizumab	TIGIT and PD-L1 inhibition	No OS benefit	Highlights immunotherapy resistance
TROPION-Lung01 (Phase III)	Datopotamab deruxtecan (Dato-DXd)	TROP2 ADC	Improved PFS versus Docetaxel	Promising ADC therapy
HERTHENA-Lung01	Patritumab deruxtecan (HER3-DXd)	HER3 ADC	Strong antitumor activity	Novel option after resistance
Biomarker studies	bTMB, ctDNA, MRD	Predictive biomarkers	Improved patient selection	Enables personalized therapy

NSCLC: Non-small cell lung cancer, EGFR: Epidermal growth factor receptor, TKI: Tyrosine kinase inhibitor, ICI: Immune checkpoint inhibitors, PFS: Progression-free survival, ALK: Anaplastic lymphoma kinase, DFS: Disease-free Survival, KRAS: Kirsten rat sarcoma, OS: Overall survival, MET: Mesenchymal-epithelial transition, RET: Rearranged during transfection, EFS: Event-free survival, PD-L1: Programmed death-ligand 1, ADC: Antibody-drug conjugates, bTMB: Based tumor mutational burden, ctDNA: Circulating tumor DNA, MRD: Minimal residual disease

Once it spreads locally or metastatically, the disease can lead to chronic cough, hemoptysis, chest pain, and dyspnea, which makes it less likely to be cured.[65] CT screening using low doses in the high-risk population (e.g., heavy smokers) reduces the death rate. Nevertheless, it is characterized by great false-positive rates, mental distress, overdiagnosis, and low availability in well-funded healthcare environments. In centrally located or microscopic lesions, bronchoscopy or CT-guided biopsy may result in pneumothorax and bleeding, which may slow down the treatment. Types of NSCLC include adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Nevertheless, they vary in genetic reasons, cellular pathogenesis, and clinical manifestations, complicating the choice of treatment and the universal therapy.

Targetable oncogenic agents include EGFR, ALK, ROS1, BRAF, MET, RET, and KRAS mutations found by genomic profiling. ICIs against PD-1/PD-L1 have revolutionized the way a set of patients are treated, with only 20–30% achieving long-term clinical response to treatment. CNS metastases in up to 40% of NSCLC patients are used to treat with many systemic chemotherapeutic and targeted medicines, which cannot cross the blood–brain barrier. Local treatment such as whole-brain or stereotactic radiosurgery (SRS) may exacerbate cognition and CNS. There is a long-standing underestimation of the needs of older people, low performance status, and people with significant in clinical studies. Such patients are treated with less strong therapies to minimize toxicity, which can slow down the healing process.[66] Novel targeted therapy and immunotherapy are costly, restricting access in developing nations, as well as in well-developed healthcare systems and NSCLC diagnosis and intense treatment significantly affect the quality of life.

FUTURE PERSPECTIVES

The management of NSCLC is likely to become radical in the future, shifting the paradigm of traditional approaches to a new era of personalized and therapeutic sophistications. Future in molecular profiling, immunotherapy, and novel modalities of treatment will transform the survival and quality of life of patients. The standard of care will be biomarker-driven therapy, including common drivers (EGFR, ALK, ROS1) and more infrequent but still targetable changes in cancer genes (KRAS G12C, MET, RET, and HER2).[67] It will develop an ever-expanding repertoire of high-efficacy TKIs that undergo effective first-line and subsequent targeted treatment. ICIs against PD-1/PD-L1 and CTLA-4 will be implemented in immunotherapy to overcome primary and acquired resistance by developing new agents such as TIGIT blockers, lymphocyte-activation gene 3 blockers, and personalized cancer vaccines to prime the immune system against tumor-specific neoantigens.

By combining AI and ML with the workflow in oncology, the field will have a more personalized approach to treatment through the analysis of intricate multimodal data sets and providing predictive analytics. The success of neoadjuvant and adjuvant immunotherapy and targeted therapy has shown that the management of early-stage disease will undergo a revolution with the confirmation of their efficacy, which has been demonstrated in trials such as CheckMate 816 and ADAURA.[68] The creation of ADCs is also a paradigm shift, which provides a specific method of delivering cytotoxic payloads to tumor cells with certain surface antigens. The issue of CNS metastases will be the intentional development of the next-generation TKIs with better CNS penetration as well as the tactical employment of SRS. Liquid biopsy based on ctDNA analysis will create a part of the diagnostic and monitoring cascade, allowing to assess the molecular response in a non-invasive and real-time manner, identify the existence of MRD after surgery, and the emergent resistance mechanisms at the earliest signs of clinical progression.[69]

CONCLUSION

In the past two decades, NSCLC treatment has changed from a generalized, chemotherapy-centric strategy to a highly personalized paradigm integrating targeted therapy and immunotherapy. Molecular and immunological causes of the disease are evolving. For biomarker-selected patients, medicines targeting EGFR, ALK, ROS1, BRAF, MET, and RET mutations have shown stronger efficacy and less systemic effects than conventional chemotherapy. ICIs targeting the PD-1/PD-L1 and CTLA-4 axes have revolutionized advanced disease treatment by harnessing the host's immune response to induce sustained anti-tumor effects, especially in tumors with high PD-L1 expression or mutational burden. These advances have been used in targeted therapies and primary and secondary resistance to immunotherapy, as well as immune-related adverse events. NSCLC management will involve the identification and treatment of novel oncogenic drivers such as KRAS G12C, next-generation inhibitors and combination therapies to overcome resistance, and novel modalities such as ADCs, bispecific antibodies, and cancer vaccines. Moreover, liquid biopsies will be integrated with AI and ML to monitor real-time resistance and MRD by using liquid biopsies, which will contribute to validating novel therapies by means of strict clinical trials. This will ensure better, biomarker-based treatments increase patient quality of life and survival rates.

AUTHORS' CONTRIBUTIONS

B. Lokeshwari, Akanksha Singh Chandel: Writing - review and editing, validation, visualization. P. Saranraj, K. Gayathri

and K. Kesavardhini: Data curation, formal analysis; investigation.

REFERENCES

1. Zhong WZ, Wang Q, Mao WM, Xu ST, Wu L, Shen Y, *et al*. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): A randomised, open-label, phase 3 study. Lancet Oncol 2018;19:139-48.
2. Rallis K.S, Lai Y, Sideris M. Tepotinib for the treatment of non-small cell lung cancer with MET exon 14 skipping mutations. Expert Rev Anticancer Ther 2021;21:917-24.
3. Garassino MC, Gadgeel S, Speranza G, Felip E, Esteban E, Dómine M, *et al*. Five-year outcomes from the KEYNOTE-189 study: Pembrolizumab plus pemetrexed and platinum versus placebo plus pemetrexed and platinum as first-line treatment for metastatic nonsquamous non–small-cell lung cancer. J Clin Oncol 2024;42:12-23.
4. Volpi CC, Grosso FR, Santini D. PD-L1 expression in non-small-cell lung cancer, including various adenocarcinoma subtypes. Ann Oncol 2018;29:741-2.
5. Zhou C, Ramalingam SS, Kim T.M, Felip E. Treatment outcomes and safety of osimertinib in EGFR-mutated non-small-cell lung cancer in real-world clinical practice. Ann Oncol 2021;32:638-46.
6. Spiro SG, Rudd RM, Souhami RL, Brown J, Fairlamb DJ, Gower NH, *et al*. Chemotherapy versus supportive care in advanced non-small cell lung cancer: Improved survival without detriment to quality of life. Thorax 2007;62:1-8.
7. Poels KE, Schoenmaekers J, Dingemans, AC. Brain metastases in non-small cell lung cancer: A review of old and new therapies. J Thorac Dis 2021;13:6504-24.
8. Zafar SY, Abernethy AP. Financial toxicity in cancer care: Prevalence causes consequences and reduction strategies. J Surg Oncol 2021;123:85-92.
9. Aggarwal, D, Yang J, Salam MA, Sengupta S, Al-Amin MY, Mustafa S, *et al*. Antibody-drug conjugates: The paradigm shifts in the targeted cancer therapy. Front Immunol 2023;14:1203073.
10. Travis WD, Brambilla E, Riely GJ. New pathologic classification of lung cancer: Relevance for clinical practice and clinical trials. J Clin Oncol 2013;31:992-1001.
11. Wang M, Herbst RS, Boshoff C. Toward personalized treatment approaches for non-small-cell lung cancer. Nat Med 2021;27:1345-56.
12. Duan J, Cui L, Zhao X, Bai H, Cai S, Wang G, *et al*. Use of immunotherapy with programmed cell death 1 vs programmed cell death ligand 1 inhibitors in patients with cancer: A systematic review and meta-analysis. JAMA Oncol 2021;7:375-84.
13. Kim Y, Kim HK, Kim J. Adjuvant chemotherapy for completely resected non-small-cell lung cancer. J Thorac Dis 2021;13:2595-614.
14. Mullard A. FDA approves 100th monoclonal antibody product. Nat Rev Drug Discov 2021;20:491-5.
15. Liam CK, Andarini S, Lee P, Ho JC. Lung cancer staging now and in the future. Respirology 2020;25:13-22.
16. Heymach JV, Harpole D, Mitsudomi T, Taube JM, Galffy G, Hochmair M, *et al*. Perioperative pembrolizumab for early-stage non-small-cell lung cancer. N England J Med 2024;390:987-99.
17. Reck M, Ciuleanu TE, Dols MC, Schenker M, Zurawski B, Menezes J, *et al*. Nivolumab + ipilimumab + 2 cycles of chemotherapy vs 4 cycles of chemotherapy as first-line treatment for stage IV/recurrent non-small-cell lung cancer: 5-year results from CheckMate 9LA. J Clin Oncol 2024;42:631-41.
18. Duma N, Santana-Davila R, Molina JR. Non-small cell lung cancer: Epidemiology, screening, diagnosis, and treatment. Mayo Clin Proc 2019;94:1623-40.
19. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, *et al*. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. N Engl J Med 2022;386:1973-85.
20. Leonetti A, Sharma S, Minari R, Perego P, Giovannetti E, Tiseo M. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. Br J Cancer 2019;121:725-37.
21. Hirsch FR, Scagliotti GV, Mulshine JL, Kwon R, Curran WJ, Wu, YL, *et al*. Lung cancer: Current therapies and new targeted treatments. The Lancet 2017;389(10066), 299-311.
22. Esagian SM, Grigoriadou GI, Nikas IP, Boikou V, Sadow PM, Won JK, *et al*. Comparison of liquid-based to tissue-based biopsy analysis by targeted next generation sequencing in advanced non-small cell lung cancer: A comprehensive systematic review. JCO Precis Oncol 2020;4:1008-19.
23. Han B, Tjulandin S, Hagiwara K, Normanno N. EGFR mutation prevalence in Asia-Pacific and Russian patients with advanced NSCLC of adenocarcinoma and non-adenocarcinoma histology: The IGNITE study. Lung Cancer 2015;87:143-50.
24. Nooreldeen R, Bach H. Current and future development in lung cancer diagnosis. Int J Mol Sci 2021;22:8661.
25. Abbosh C, Birkbak NJ, Swanton C. Early stage NSCLC - challenges to implementing ctDNA-based screening and MRD detection. Nat Rev Clin Oncol 2023;20:577-86.
26. Gow CH, Hsieh MS, Wu SG, Shih JY. A comprehensive analysis of clinical outcomes in lung cancer patients harboring a MET exon 14 skipping mutation compared to other driver mutations in an East Asian population. Lung Cancer 2017;103:82-9.
27. Rosell R, Cao M.G. Liquid biopsy in non-small cell lung cancer: Current status and future potential. Cancer Treat Rev 2022;102:102308.
28. Zhao BC, Zhao B, Wang J. The role of EGFR tyrosine

kinase inhibitors in the treatment of advanced non-small cell lung cancer. Curr Cancer Drug Targets 2005;5:455-63.
29. Vinod SK, Hau E. Radiotherapy treatment for lung cancer: Current status and future directions. Respirology 2020;25 Suppl 2:61-71.
30. Zhao J, Han Y, Li J. Combination of immune checkpoint inhibitors with chemotherapy in lung cancer. Onco Targets Ther 2021;14:2269-81.
31. Wang BY, Huang JY, Chen HC. The comparison between adenocarcinoma and squamous cell carcinoma in lung cancer patients. J Cancer Res Clin Oncol 2014;146:43-52.
32. Pennell NA, Arcila ME, Gandara DR, West H. Biomarker testing for patients with advanced non-small cell lung cancer: Real-world issues and tough choices. Am Soc Clin Oncol Educ Book 2019;39:531-42.
33. Tan AC, Tan DS. Targeted therapies for lung cancer patients with oncogenic driver molecular alterations. J Clin Oncol 2022;40:611-25.
34. Treglia G, Sadeghi R, Annunziata S, Caldarella C, Bertagna F, Giovanella L. Diagnostic performance of fluorine-18-fluorodeoxyglucose positron emission tomography in the postchemotherapy management of patients with seminoma: Systematic review and meta-analysis. Biomed Res Int 2014;2014:852681.
35. Bera K, Schalper KA, Rimm DL, Velcheti V, Madabhushi A. Artificial intelligence in digital pathology - new tools for diagnosis and precision oncology. Nat Rev Clin Oncol 2019;16:703-15.
36. Yang CJ, Chan DY, Shah SA. Lymph node evaluation in non-small cell lung cancer. J Thorac Dis 2022;14:2746-56.
37. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, *et al*. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): A randomised, phase 2, open-label trial. Lancet 2021;393:2051-8.
38. Hicks KC, Knudson KM, Lee KL. ERBB family fusions in solid tumors: A review of current diagnostic and therapeutic strategies. Cancer Treat Rev 2007;57:53-60.
39. Rikova K, Guo A, Zeng Q, Possemato A, Yu J, Haack H, *et al*. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. Cell 2007;131:1190-203.
40. Ibrahim M, Parry S, Wilkinson D. ALK immunohistochemistry in NSCLC: Comparison of antibodies and the effect of preanalytical factors. Appl Immunohistochem Mol Morphol 2016;24;296-302.
41. Couraud S, Zalcman G, Milleron B, Morin F, Souquet PJ. Lung cancer in never smokers--a review. Eur J Cancer 2012;48:1299-311.
42. Kong-Beltran M, Seshagiri S, Zha J, Zhu W, Bhawe K, Mendoza N, *et al*. Somatic mutations lead to an oncogenic deletion of met in lung cancer. Cancer Res 2006;66:283-9.
43. Drilon A, Clark JW, Weiss J, Ou SI, Camidge DR, Solomon BJ, *et al*. Antitumor activity of crizotinib in lung cancers harboring a MET exon 14 alteration. Nat Med 2020;26:47-51.
44. Husain H, Velculescu VE. Cell-free DNA beyond a biomarker in non-small cell lung cancer. Clin Cancer Res 2017;23:4140-2.
45. Hieggelke L, Schild SE, Vokes EE. Chemoradiotherapy in locally advanced non-small cell lung cancer. J Thorac Dis 2020;12:3371-8.
46. Li T, Kung HJ, Mack PC, Gandara DR. Genotyping and genomic profiling of non-small-cell lung cancer: Implications for current and future therapies. J Clin Oncol 2022;40:355-67.
47. Wu YL, Tsuboi M, He J, John T, Grohe C, Majem M, *et al*. Osimertinib in resected EGFR-mutated non-small-cell lung cancer. N Engl J Med 2023;389:1672-84.
48. Mazieres J, Drilon A, Lusque A, Mhanna L, Cortot AB, Mezquita L, *et al*. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: Results from the IMMUNOTARGET registry. Ann Oncol 2019;30:1321-8.
49. Mathieu L, Shah S, Pai-Scherf L. FDA approval summary: Atezolizumab plus carboplatin and nab-paclitaxel for advanced non-small-cell lung cancer. Clinl Cancer Res 2023;29:17-21.
50. Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. N Engl J Med 2017;377:62-70.
51. Revels SL, Lee JM. Racial and ethnic disparities in lung cancer screening. Ann Am Thorac Soc 2018;15:903-5.
52. Peters S, Gettinger S, Johnson ML, Jänne PA, Garassino MC, Christoph D, *et al*. Phase II trial of atezolizumab as first-line or subsequent therapy for patients with programmed death-ligand 1-selected advanced non-small-cell lung cancer (BIRCH). J Clin Oncol 2022;40:1301-11.
53. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, *et al*. Lung adjuvant cisplatin evaluation: A pooled analysis by the LACE collaborative group. J Clin Oncol 2008;26:3552-9.
54. Ramalingam SS, Belani CP. Systemic chemotherapy for advanced non-small cell lung cancer: Recent advances and future directions. Oncologist 2008;13 Suppl 1:5-13.
55. Khozin S, Blumenthal GM, Pazdur R. Real-world data for clinical evidence generation in oncology. J Natl Cancer Inst 2014;109:djx187.
56. Awad MM, Oxnard GR, Jackman DM, Savukoski DO, Hall D, Shivdasani P, *et al*. MET exon 14 mutations in non-small-cell lung cancer are associated with advanced age and stage-dependent MET genomic amplification and c-Met overexpression. J Clin Oncol 2016;34:721-30.
57. Faivre-Finn C, Vicente D, Kurata T, Planchard D, Paz-Ares L, Vansteenkiste JF, *et al*. Four-year survival with durvalumab after chemoradiotherapy in stage III NSCLC-an update from the PACIFIC trial. J Thorac Oncol 2017;16:860-7.
58. Wahidi MM, Herth FJ, Chen A. State of the art:

Interventional pulmonology. Chest 2021;159:2443-54.
59. Matsubara D, Kishaba Y, Ishikawa S. Lung cancer classification by histology and genomics: A concensus proposal. J Thorac Oncol 2022;17:1134-48.
60. Arighi E, Borrello MG, Sariola H. RET tyrosine kinase signaling in development and cancer. Cytokine Growth Factor Rev 2005;16:441-67.
61. Santini FC, Rudin CM. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med 2017;377:1290-1.
62. Kim ES. Chemotherapy resistance in lung cancer. Adv Exp Med Biol 2016;893:189-209.
63. Lim SM, Syn NL, Cho BC, Soo RA. Acquired resistance to EGFR targeted therapy in non-small cell lung cancer: Mechanisms and therapeutic strategies. Cancer Treat Rev 2018;65:1-10.
64. Herbst RS, Giaccone G, De Marinis F, Reinmuth N, Vergnenegre A, Barrios CH, *et al*. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. N Engl J Med 2020;383:1328-39.
65. Hung YP, Sholl LM. Diagnostic and predictive biomarkers in non-small cell lung cancer. Surg Pathol Clin 2018;11:57-72.
66. Trombetta D, Gravina S, Valerio M. Lung cancer in never smokers: A review of the literature and a case report. Lung Cancer: Targets Ther 2016;7:65-70.
67. Xiao D, Pan H, Li F. Analysis of the status and factors associated with EGFR-TKI primary resistance in patients with non-small cell lung cancer harboring EGFR mutations. J Thorac Dis 2021;13:2847-58.
68. Xie Y, Wu L, Wang M. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. N Engl J Med 2021;372:93-5.
69. Cainap C, Balacescu O, Cainap SS, Pop LA. Next generation sequencing technology in lung cancer diagnosis. Biology (Basel) 2021;10:864.

Source of Support: Nil. **Conflicts of Interest:** None declared.