Chapter 10
Therapeutic Approaches in NSCLC:
Navigating Side Effects and Outcomes

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ABSTRACT

Non-small-cell lung cancer (NSCLC) stands as a predominant and complex malignancy, constituting approximately 85% of all lung cancer diagnoses. The etiology of NSCLC is multifactorial, with tobacco use emerging as the primary risk factor, while air pollution and radon exposure also significantly contribute to its development. The therapeutic landscape for NSCLC has undergone a paradigm shift with the advent of targeted therapies, facilitated by advancements in genetic and biomarker testing. These innovations have enabled the identification of specific mutations, thereby informing personalized treatment strategies tailored to individual patient profiles. This chapter aims to elucidate the current state of NSCLC management, with a particular focus on multimodal treatment approaches for locally advanced disease. It will also explore the role of innovative surgical techniques and contemporary pharmacological interventions in the context of early-stage NSCLC.This chapter aims to provide a nuanced understanding of the current therapeutic options and future directions in NSCLC management.

1. INTRODUCTION

Among the cancers, the deadliest malignancy is lung cancer, which strikes both men and women. Its mortality rate exceeds the sum of the mortality rates of three of the most frequently diagnosed cancers: colon, breast, and pancreatic. More than fifty percent of patients with lung cancer passed away in less than a year of receiving a diagnosis, and the five-year survival rate is approximately 17.8% (Zappa & Mousa, 2016). The lung tumor may spread to nearby tissues or other body regions if treatment is not received. Malignancy that starts in cells of the epithelium accounts for the bulk of lung cancers, commonly known as primary lung malignancies (Akhtar & Bansal, 2017). Around twelve million new instances of lung tumors were reported in 2000, making them one of the most prevalent cancer types worldwide, making up approximately 12 percent of all cancers (Minna et al., 2002). Many behavioral and environmental variables have been linked to lung cancer development. Cigarettes and tobacco usage account for between 85 and 90 percent of cases of lung cancer (Alduais et al., 2023). Lung cancer increased as cigarettes emerged as the main tobacco product produced in the 1900s.The risk of lung cancer varies with the number of periods or packets of cigarettes smoked daily (Zappa & Mousa, 2016). Tobacco usage significantly increases the risk of lung cancer and also genetic ancestry, hazardous chemicals, heavy metals such as asbestos, arsenic, chromium, beryllium, radon gas, and nickel, as well as passive smoking.Furthermore, the carcinogenesis

of lung cancer is also caused by alcohol consumption, HIV infection, and pulmonary fibrosis (Alduais et al., 2023).

2. EPIDEMIOLOGY OF LUNG CANCER

According to the International Agency for Research on Cancer's (IARC) most recent estimates, the following are the global cancer statistics by world region for 2022. Nearly 20 million new instances of cancer and 9.7 million cancer-related deaths occurred in 2022. It is estimated that one in five women and men may develop cancer at some point in their life. One in nine men and one in twelve women die from cancer. Lung cancer was the most common cancer diagnosed in 2022. The disease affected 2.5 million new cases, or one in eight malignancies worldwide.

More than 80% of all lung malignancies are NSCLC, which is also one of the leading causes of death worldwide.SCLC is the diagnosis for the twenty percent that is left of patients with lung tumors. For the restricted stage, they often live 12–16 for a period of time, while for the extensive stage, they typically live 7–11 months (Smolarz et al., 2025).

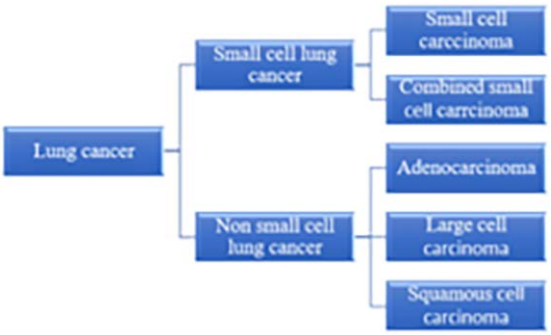
3. CLASSIFICATION OF LUNG CANCER

Histology has traditionally separated lung malignancies into two types.

1. Small-cell lung cancer
2. Non-small-cell lung cancers (NSCLCs).

Squamous cell carcinoma (SCC), adenocarcinoma, and large-cell carcinoma are subtypes of non-small cell lung cancer.Adenocarcinomas account for over 50 percent of all lung cancers. Figure 1 depicts the classification of lung cancer. (Shames & Wistuba, 2014)

Figure 1. Classification of lung cancer



I. **Adenocarcinoma:** The most prevalent histopathological kind of NSCLC is adenocarcinoma. Lung adenocarcinoma typically occurs by cigarette smoking; however, as rates of smoking decline, a substantially higher number of instances arise in never-smokers, who smoke fewer than 100 cigarettes in their lifetime (Cancer Genome Atlas Research Network, 2014).

II. **Large-cell carcinoma:** Having a relatively low prevalence, it has emerged as one of the rarest subtypes of NSCLC. LCC is characterized as "indistinguishable non-small cell carcinoma that exhibits secretory or epithelial differentiation, as well as the morphological and structural attributes" (Rekhtman & Travis, 2019).

III. **Squamous cell carcinoma:** Lung squamous cell carcinoma (SCC) is the most prevalent histologic subtype of non-small cell lung cancer. Thirty percent of NSCLC cases are squamous cell carcinoma (SCC), making it the most common histologic subtype. Although modifications in tobacco use practices are reducing the incidence of lung SCC, SCC remains a serious health concern.

4. TUMOR MICROENVIRONMENT OF NSCLC

Tumor growth, metastasis, and the response to therapeutic interventions are all significantly influenced by the TME, a complex microenvironment. The stromal cells, immune cells, signaling molecules, extracellular matrix, and other cellular and non-cellular components that make up TME interact with one another to control the behavior of tumors. The degree of immune cell infiltration in NSCLC varies according to the stage of the disease, indicating that the lung TME affects carcinogenesis and could be a predictor of outcome. Accordingly, several TME profiles are being researched as possible biomarkers for determining the stage and subtype

of the disease, forecasting clinical results, and directing treatment approaches (Edirisinghe et al., 2025).

5. THERAPIES

Chemotherapy, radiation, and surgery are the most often used cancer treatments. Although these techniques are frequently employed in hospitals, their efficacy is constrained by a number of serious issues. For instance, chemotherapy frequently lacks accuracy and has a number of negative consequences. However, surgery and radiation therapy might not always be successful in stopping cancers from growing or coming back. The majority of cancer patients receive treatment with a mix of chemotherapy, radiation, and/or surgery medicines (Schuster et al., 2006).

6. IMMUNOTHERAPY

By strengthening and rebuilding the immune system of the body by managing and eliminating tumor cells, immunotherapy for tumors combats them. The innate capacity of the immune system to combat cancer can be strengthened (active immunity) or given extra support (passive immunity) by this treatment. Immunotherapy in several forms, such as adoptive cell treatment, immune checkpoint inhibitors, and cancer vaccines, has shown encouraging outcomes in the treatment of cancer by influencing distinct immune system components. Further, a number of immunotherapy medications were approved by the U.S. Food and Drug Administration for clinical therapies in cancer treatment (Yuan et al., 2024).

A healthy immune system is essential for preventing the onset and spread of cancer because it recognizes and eliminates tumor antigens. The immune system may use immunoediting to fight against emerging malignancies that have escaped natural tumor suppressors like apoptosis (Forde et al., 2014). One such medication that has impacted lung cancer patients' survival, particularly for those with non-small cell lung cancer, is immunotherapy. Due to the increasing amount of information that is collected regarding the immune mechanisms, driver mutations, neoantigens, and oncogenic pathways involved in non-small cell lung cancer (NSCLC), new immunotherapeutic tools for targetable mutations have been designed with greater understanding of the tumor's microenvironment (TME), mutational load, and heterogeneity (Lahiri et al., 2023).

Immunotherapy is currently widely used to treat NSCLC at various stages (Wang, Li, et al., 2022). Non-Small Cell Lung Cancer (NSCLC) is a very diverse illness with a high mutational burden that codes for numerous potential neoantigens (Malhotra et

al., 2017). The adaptive immune response requires two signals between the effector T cells and the antigen-presenting cells (APCs). The first signal is mediated by the major histocompatibility complex classes I or II antigenic peptide and the T-cell receptor. In order to generate the second signal, which is a co-activation signal, the B7 family members on APCs interact with CD28 on the surface of T cells. These signals cause T lymphocytes to become activated and proliferate clonally in response to interleukin-2 (IL-2). Autoimmunity can be avoided by controlling this proliferation. CTLA-4, a homologue of CD28 that was initially identified in 1987 and belongs to the immunoglobulin superfamily, is expressed by T cells after activation (Tomasini et al., 2012). Both single-agent and combination ICI treatments have been studied in numerous cases to dramatically improve clinical efficacy endpoints in patients with extensive-stage small-cell lung carcinoma and locally progressed, metastatic NSCLC patients without mutations in the ALK and EGFR genes (Xiang et al., 2024). According to recent studies, checkpoint inhibitors may particularly reactivate self-antigen-mediated cellular immunity and T cells in healthy tissues, potentially leading to immune-related adverse events (irAE) (Lin et al., 2024).

Different roles in immune regulation are played by PD-1 and CTLA-4. These two checkpoint receptors have been the subject of the most research in the context of clinical cancer immunotherapy (Topalian et al., 2012).

In order to treat patients without a driver mutation, immunotherapy in the form of immune checkpoint inhibitors (ICIs) is a crucial component. One of the prognostic biomarkers that responds to checkpoint inhibitors is programmed cell death ligand-1 (PD-L1). Although PD-L1 expression is the most reliable clinical biomarker, it is not flawless (Mamdani et al., 2022). PD-L1, also known as B7-H1, and PD-L2, also known as B7-DC, are two recognized ligands of the PD-1 receptor. T-cell inhibition and downregulation of the T-cell response arise from PD1 binding to its ligands. On oncogenic cells, both PD-L1 and PD-L2 have been detected. PD-L1 is expressed by tumors on their surface and by cells within the tumor microenvironment; malignancies specifically co-opt this pathway, enabling the tumor to directly suppress anti-tumor cytolytic T-cell activity. In fact, tumor cells' adaptive immune resistance strategy in response to endogenous anti-tumor activity is the activation of the PD1/PD-L1 pathway (Villaruz et al., 2014). CTLA-4, a CD28 homolog, is only expressed by T cells. Through a number of mechanisms, including outcompeting CD28 for the binding of B7 molecules and inhibiting the production of interleukin-2 (IL2), CTLA-4 acts as a negative regulator of T-cell response, causing T-cell responses to be downregulated and stopping cell cycle progression (Malhotra et al., 2017). Through the disruption of inhibitory checkpoints that tumors use to avoid immunological attack, immunotherapy activates the immune system. Monoclonal antibodies in NSCLC target the PD-1/PD-L1 interactions, in which PD-L1 on tumor or antigen-presenting cells binds PD-1 on T cells to suppress cytotoxic activity,

rebuilding T-cell proliferation and function. CTLA-4 on T cells also weakens the co-stimulatory signal by competing with CD28 for CD80/CD86 binding; inhibiting CTLA-4 increases early T-cell activation. Checkpoint inhibitors work together to restore anti-tumor T-cell responses and facilitate strong immune-mediated destruction of cancer cells (Stanley et al., 2023). When treating non-small cell lung cancer (NSCLC), immunotherapy mostly consists of immune checkpoint inhibitors like pembrolizumab, nivolumab, atezolizumab, durvalumab, and ipilimumab. These can be administered either alone or in combination with radiation therapy or chemotherapy (Burke & Rashdan, 2021). These substances work by inhibiting the PD-1/PD-L1 or CTLA-4 pathways, which unlocks antitumor immunity. Although usually tolerated, immune-related adverse drug events (irAEs) are often observed; skin and endocrine irAEs are common. These include dermatitis, colitis, hepatitis, thyroid dysfunction, and pneumonitis (Zhou et al., 2022).

Many preclinical studies have demonstrated that blocking the CTLA-4 and PD-1 pathways improves intratumoral immunological responses, and blocking immunological checkpoints has been implemented in the current era of cancer treatment. Fully humanized, ipilimumab is an IgG1 anti-CTLA-4 mAb that inhibits CTLA-4 from binding to its ligand. When ipilimumab was administered after chemotherapy, a randomized phase II clinical study of paclitaxel and carboplatin with or without it in treatment-naïve stage IV NSCLC showed an improvement in immune-related progression-free survival (irPFS) (Anagnostou & Brahmer, 2015). According to preclinical evidence, simultaneous CTLA-4 and PD-1 inhibition markedly boosted tumor-specific immune response (Curran et al., 2010). In melanoma, a phase I trial of nivolumab with ipilimumab showed an ORR of approximately 40% (Wolchok et a., 2013). Immunotherapy has emerged as a viable treatment option for non-small cell lung cancer (NSCLC) after PD-1 and PD-L1 inhibitors were authorized as the current standard of care for the disease's second-line treatment. Pembrolizumab, a PD-1 inhibitor, is also used as a first-line treatment for patients with metastatic non-small cell lung cancer whose tumors express PD-L1.

A total of 191,802 patients were included in this study: 90,807 prior to immunotherapy and 100,995 following it. Overall survival increased and the OS improved dramatically throughout the immunotherapy era (1-year survival, 44.0% vs. 36.8%; 3-year survival, 21.7% vs. 14.4%; 5-year survival, 14.3% vs. 9.0%; median OS, 10 vs. 8 months; $p < .001$ by log-rank test). After taking age, sex, race, wealth, and geographic location into account, multivariate analysis using a Cox proportional hazards model indicated that survival rates were significantly higher during the immunotherapy era (adjusted hazard ratio, 0.830; 95% CI, 0.821–0.840; $p < .001$) (Wang, Kondrat, et al., 2025).

Despite the enormous potential of these medicines, response rates are still low, with the exception of cancers that exhibit high levels of PD-L1 expression (Malhotra

et al., 2017). The immune system can be reactivated against oncogenic cells with immunotherapy; however, it also results in a variety of autoimmune side effects, or immune-related adverse events (irAEs), including endocrine dysfunction. One of the most often reported endocrinopathies is pituitary dysfunction, which is significantly more prevalent following anti-CTLA-4 therapy than following other immune-based therapies. The occurrence of hypophysitis due to ipilimumab is above 10% on average. This ipilimumab led to hypophysitis, which is more common in men. Fatigue and headaches are the most common signs of ipilimumab-induced hypophysitis (Cukier et al., 2017).

7. CHEMOTHERAPY

Chemotherapy is a well-known method of treating cancer that uses cytotoxic medications to treat different types of cancer. In order to stop the cancer cell from growing and spreading further, these medications often aim to kill the cancer cell and stop it from reproducing. The majority of chemotherapy medications are either taken orally or intravenously. Numerous chemotherapeutic agents exist, and they are typically categorized into a number of groups, such as plant alkaloids, alkylating agents, anthracycline antibiotics, and antimetabolites. The renowned German chemist Paul Ehrlich began working on the development of drugs to treat infectious diseases in the early 1900s. He was the first to define the term "chemotherapy" as the use of chemicals to treat disease and was the first to document the efficacy of using animal models to screen a number of chemicals for their potential activity against diseases, a feat that had significant implications for the development of cancer drugs (DeVita & Chu, 2008).

In the 1960s, the two cornerstones of cancer treatment were surgery and radiotherapy. When micrometastases and cancer recurrence following surgery and radiation therapy became apparent, combination chemotherapy began to acquire importance (Amjad et al., 2020). Chemotherapy in combination is frequently used to achieve satisfactory results. They seem to encourage cytotoxicity in both resting and dividing cells, which inhibits the formation of resistant clones (Baserga, 1981). The complex cellular processes that either stimulate or inhibit cell division and proliferation involve several genes, receptors, and signal transmissions. The mechanisms of apoptosis, angiogenesis, metastasis, cell signal transmission, differentiation, and growth factor modulation have all been greatly illuminated by research in cancer cell biology (Adjei & Hidalgo, 2005). The role of cytotoxic chemotherapy in treating non-small cell lung cancer is still up for debate, despite the fact that it is frequently used to treat small cell lung cancer. A recent worldwide consensus report came to the conclusion that postoperative chemotherapy should be regarded as experimental because it has

not been shown to be beneficial (Non-small Cell Lung Cancer Collaborative Group, 1995). Chemotherapy for non-small cell lung cancer is a remarkable development in cancer treatment. The first chemotherapy drugs were introduced in the 1970s, and their clinical benefits were moderate. In the 1980s and 1990s, treatment was revolutionized with the development of platinum compounds and new-generation agents. A seminal meta-analysis conducted in 1995 showed that, when compared to supportive treatment alone, platinum-based chemotherapy increased survival rates from 5% to 15% at one year. In the treatment of non-small cell lung cancer (NSCLC), chemotherapy is still a vital component that must be used in conjunction with more recent therapeutic modalities. Even with developments in immunotherapy and molecular targeted therapy, chemotherapy is still essential for managing both early-stage and late-stage cancer (Lee, 2019).

8. OUTCOME

The survival rate for advanced non-small cell lung cancer is greatly increased when immunotherapies such as toripalimab are added to conventional platinum-based treatment. A median progression-free survival (PFS) of 8.4 months was achieved with toripalimab plus chemotherapy in the phase III CHOICE-01 study, compared to 5.6 months with chemotherapy alone (HR 0.49; $P < .0001$). Furthermore, the combination showed a hazard ratio of 0.69 ($P = .0099$), indicating an overall survival (OS) benefit. In the toripalimab arm, the median OS was not reached, while in the control group it was almost 17 months (Zhong et al., 2024).

The clinical treatment of lung cancer was dominated by chemotherapy prior to the identification of the gene types of NSCLC. Targeted therapy gradually replaced chemotherapy, but chemotherapy also includes cisplatin combination therapy. Today, chemotherapy for NSCLC primarily consists of cisplatin and carboplatin plus gemcitabine, taxanes, and pemetrexed, along with some targeted therapy medications (Guo et al., 2022). Chemotherapy has a variety of mechanisms, such as cisplatin, carboplatin, and gemcitabine, that may cause DNA damage, interfere with the DNA repair pathway, and cause the cancer cell to undergo apoptosis (Dasari & Tchounwou, 2014; Mini et al., 2006).

9. TYPES OF CHEMOTHERAPY

Chemotherapy for non-small cell lung cancer usually uses platinum-based doublets. Together with pemetrexed (particularly in non-squamous histology), docetaxel, paclitaxel, gemcitabine, or vinorelbine, cisplatin and carboplatin form

the backbone of the treatment. According to meta-analyses, pemetrexed-platinum combinations significantly increase overall survival when compared to alternative regimens, especially in non-squamous non-small cell lung cancer (Li et al., 2012). Different medication types and therapeutic modalities, each with unique mechanisms and uses, are included in chemotherapy.

Platinum-based (first-line)

Platinum-based chemotherapy continues to be the most widely used treatment for individuals with non-small cell lung cancer (NSCLC). These days, the platinum compounds employed in NSCLC are carboplatin and cisplatin. Cisplatin should remain the standard reference for treating some patients with non-small cell lung cancer due to several findings showing that third-generation regimens based on cisplatin are slightly more effective than carboplatin-based chemotherapy and have a different safety profile (Rossi & Di Maio, 2016).

In patients with metastatic non-small cell lung cancer (NSCLC), cisplatin-based regimens have demonstrated a slight benefit in extending survival in contrast to the most effective supportive care, but because of its toxicity, cisplatin is still a challenging medication to use. Later, another platinum analogue with fewer adverse effects, carboplatin, was created (Pujol et al., 2006; Rosell et al., 2002). The treatment of solid tumors frequently involves the use of platinum compounds. Platinum medications have transformed the treatment of germ cell cancers, and they are now considered standard therapy because of their remarkable cure rates (Decatris et al., 2004). While researching how electric currents affect microorganisms in 1965, Rosenberg made the coincidental discovery of cisplatin. These have a high frequency of toxicities, namely nephrotoxicity, nausea, and vomiting. First to be used widely in cancer chemotherapy, cisplatin (cis-dichlorodiammineplatinum II) belongs to a new class of powerful anticancer medications called metal coordination complexes. It has been demonstrated that the medication works well either by itself or in combination to treat a wide range of solid tumors in humans (Rosenberg, 1980). An analogue of cisplatin, carboplatin was created in the late 1970s when researchers were actively looking for a substance that had cisplatin's antitumor properties but also showed less toxicity. The initial carboplatin clinical trials were conducted by Calvert and colleagues (de Castria et al., 2013). Tests on a variety of malignancies have demonstrated that carboplatin is just as effective as cisplatin in treating extensive-stage small cell lung cancer (Vasconcellos et al., 2020).

According to extensive clinical studies, oxaliplatin shows promise in treating non-small cell lung cancer (NSCLC) and provides clear benefits for specific patient groups. More effective than conventional platinum-based treatments, with comparable cytotoxic effects while requiring fewer DNA adducts. demonstrates

less toxicity and better tolerance than traditional platinum chemical compounds. While stable disease indicates that the tumor did not considerably grow or shrink, partial response shows that the tumor has diminished. exhibits encouraging results in squamous cell NSCLC (Ban et al., 2014).

Non-platinum agents

Expanding on our consideration of platinum-based treatments, a number of non-platinum substances are essential for the treatment of non-small cell lung cancer (NSCLC) due to their varied toxicity profiles and modes of action. Modern chemotherapy regimens require these drugs, especially for certain patient demographics and illness stages.

Pemetrexed

A novel antifolate medication called Pemetrexed has been licensed for advanced non-squamous, non-small cell lung cancer (NSCLC) both in conjunction with cisplatin and as a stand-alone treatment for NSCLC that has relapsed or is chemotherapy-refractory following platinum-containing chemotherapy. It is activated intracellularly by poly-γ-glutamylation, which inhibits important intracellular folate metabolism enzymes. Pemetrexed shows no benefit in squamous-cell histology, while it works well in non-squamous cell non-small cell lung cancer. This makes it possible to treat advanced non-small cell lung cancer with tailored anticancer therapy (Joerger et al., 2010).

Docetaxel

A semisynthetic taxane that was first created to treat breast cancer, docetaxel exhibits considerable activity in lung cancer because of its twice increased binding affinity for beta tubulin. It is the most effective first-line treatment for advanced non-small-cell lung cancer (NSCLC) and the gold standard for second-line therapy (Belani & Eckardt, 2004). Compared to vinorelbine or ifosfamide, docetaxel has shown higher response rates and better 1-year survival rates in individuals who have already undergone treatment. In patients who had never had chemotherapy, docetaxel monotherapy also produced survival rates comparable to the majority of typical combinations involving platinum. The combination of docetaxel with other anticancer medications has also been shown to provide high response rates. Overall, the tolerability profile is acceptable. However, neutropenia is the primary dose-limiting side effect. Docetaxel is more effective at improving survival and patient tolerance than vinorelbine, ifosfamide, or optimal supportive care. Patients with

non-small cell lung cancer who received docetaxel 75 or 100 mg/ml as a first-line or second-line monotherapy experienced objective response rates of 20 to 38% and 14 to 25%, respectively, in noncomparative trials (Comer & Goa, 2000).

Paclitaxel

Non-small cell lung cancer (NSCLC) is treated with a platinum compound combination that includes the tubulin-binding drug paclitaxel. Short infusions are more likely to cause neuropathy, and myelosuppression is its dose-limiting hazard. Weekly versus 3-weekly paclitaxel regimens with carboplatin for advanced non-small cell lung cancer are now being compared in a randomized clinical trial. It has been demonstrated that paclitaxel and molecularly targeted medicines interact synergistically (Ramalingam & Belani, 2004). In a research study, patients with stage IV or relapsed non-small-cell lung cancer were evaluated for the toxicity and effectiveness of paclitaxel given by 1-hour infusion. Each dose was given to the patients by 1-hour infusion, and they were either given a single-day or three-day dose. A 3-year actuarial survival rate was observed, with a median survival period of 8 months. Patients receiving 200 mg/m^2 exhibited a higher response rate than those getting 135 mg/m^2. Both dosages and schedules of paclitaxel were well tolerated, and there were no serious hypersensitivity events. The study indicates that patients who have had cisplatin-based regimens in the past may respond to a paclitaxel dose of 200 mg/m^2, which is more effective than 135 mg/m^2 (Hainsworth et al., 1995).

Gemcitabine

The antimetabolite gemcitabine has demonstrated encouraging outcomes in Phase II trials with more than 400 patients, with more than 20% demonstrating response rates. Because of its distinct mode of action and advantageous toxicity profile, it is a perfect fit for combination therapy. With median survival times ranging from 8.4 to 15.4 months, gemcitabine-cisplatin combo response rates vary from 31% to 54%. Several double and triple combinations of gemcitabine with ifosfamide, carboplatin, paclitaxel, docetaxel, and vinorelbine have also been studied, in addition to clinical trials including gemcitabine-cisplatin combinations. (Manegold et al., 2000). Considering that gemcitabine is an active ingredient, its adverse effect profile is rather minimal. Gemcitabine-induced nausea and vomiting are minor and usually manageable with common antiemetics. Gemcitabine does not result in severe baldness, and its hematologic toxicity is mild and unlikely to necessitate hospitalization. For individuals with inoperable non-small cell lung cancer, gemcitabine may be useful as a monotherapy (Abratt et al., 1994).

Vinorelbine

Vinorelbine offers an effective and manageable therapy for both early-stage and advanced non-small cell lung cancer. The most frequent hazard is neutropenia, and patient survival is improved when platinum is administered in combination with other drugs. When used with cisplatin in adjuvant settings, vinorelbine regularly increases survival and is more well-tolerated than other third-generation drugs (Piccirillo et al., 2010). Vinorelbine is known to encourage cancer cells to undergo apoptosis. Numerous specifics remain unclear, and the exact mechanisms underlying this process are intricate. Activation or inactivation of several protein kinases implicated in important signaling pathways, such as p21 WAF1/CIP1 and Ras/Raf, PKC/PKA, and the expression of the tumor suppressor gene p53, are among the impacts of microtubule structural disarray (Wang, Liu, et al., 1999). The phosphorylation and subsequent deactivation of the apoptosis inhibitor Bcl2 are caused by these molecular alterations (Haldar et al., 1995). In non-small cell lung cancer (NSCLC), vinorelbine has been thoroughly investigated in conjunction with cisplatin; cisplatin-navelbine is the most successful combination. A multicenter European trial revealed a higher response rate of 14% for vinorelbine alone and 30% for cisplatin-vindesine. The most successful vinorelbine and cisplatin regimen resulted in significant benefit and cost-effectiveness, according to a pharmaco-economic analysis. Additionally, vinorelbine has been investigated in conjunction with other medications; in advanced non-small cell lung cancer, two-drug combos of cisplatin-vinorelbine have shown promising results (Gregory & Smith, 2000).

10. SIDE EFFECTS AND MANAGEMENT

Chemotherapy is associated with several key toxicities, which can be anticipated and effectively managed with supportive measures.

Hematologic Toxicity

Anemia, thrombocytopenia, and neutropenia are frequent symptoms of myelosuppression. Granulocyte colony-stimulating factor (G-CSF) primary prophylaxis is advised when the risk of febrile neutropenia is ≥20% or 10–20% with other risk factors, including age >65 or comorbidities. In actual use, long-acting G-CSFs have demonstrated a significant decrease in hospitalizations and febrile neutropenia. While platelet transfusions are recommended for severe thrombocytopenia, anemia can be treated palliatively with red blood cell transfusions or erythropoiesis-stimulating drugs (Estcourt et al., 2016).

Gastrointestinal Toxicity

An NK1 receptor antagonist, a 5-HT3 antagonist, dexamethasone, and olanzapine are the four medications needed for antiemetic prophylaxis while using cisplatin and other highly emetogenic regimens. Early loperamide treatment for chemotherapy-induced diarrhea, which is seen with pemetrexed-based combinations, is followed by escalation to octreotide in instances that are not responsive. Oral mucositis is still a common side effect. Preventative measures such as dental care, topical pain relievers, and photobiomodulation treatment are recommended (Venkateswaramurthy, 2024).

Renal and Ototoxicity

Hydration is necessary both before and after therapy since cisplatin is still the most nephrotoxic drug. Supplementing with magnesium has been demonstrated to dramatically lower nephrotoxicity. Baseline audiometry and cumulative dose monitoring are advised since cisplatin can also cause tinnitus and irreversible hearing loss. According to recent studies, sodium thiosulphate has shown promise as an otoprotectant (Lalla et al., 2014; Li et al., 2024).

Neurologic Toxicity

Chemotherapy-induced peripheral neuropathy is often caused by platinum compounds and taxanes (CIPN). For grade ≥ 2 neuropathy, dosage adjustments and routine screening are necessary. Duloxetine is still the only medication that consistently helps those with painful CIPN (Meijer et al., 2024).

Dermatologic Toxicity

Pemetrexed is linked to redness and other dermatological side effects. Premedication with dexamethasone, vitamin B12, and folic acid is required to reduce this. Extended low-dose dexamethasone successfully lowers the frequency and severity of rash (Desforges et al., 2022).

11. TARGETED THERAPIES

Targeted therapy treats patients with specific mistakes, or abnormalities, in their tumors. If you think of DNA as a book, then errors are like typos in the DNA, and mistakes in the DNA can cause cancer or unchecked cell growth. Targeted therapeutic release at the illness site with minimal off-target adverse effects to

healthy tissues is the key to the therapy's effectiveness. It is frequently used with other cancer treatments, such as chemotherapy. Drugs that inhibit the tumor cell proliferation, regulate the cellular cycle, or trigger programmed cell death or autophagy are developed as part of targeted therapy. Toxic compounds are delivered to cancer cells selectively to kill them. Oral tiny medicines or monoclonal antibodies are used in targeted therapy (Gerber, 2008). Targeted therapy works by addressing these "typos," or errors in the DNA, and halting the growth of the cells. For lung cancer tumors exhibiting mistakes or anomalies in the following areas, the FDA presently approves targeted therapies such as EGFR, including exon 20 of EGFR, NTRK, BRAF V600E, ALK, and ROS-1 (Dempke et al., 2010). Targeted therapy has first-line and second-line treatments.

EGFR BLOCKER

EGFR is a promising target in NSCLC because it is frequently overexpressed and because its stimulation results in the downstream activation of important signaling pathways, which increases cell viability, proliferation, blood vessel creation, and metastasis (Barr Kumarakulasinghe et al., 2015). The most significant subcategory of the genetic abnormalities found in lung malignancies is EGFR mutations. The two foremost variations of EGFR are a point replacement in codon 21 (L858R) and an elimination in codon 19 (del E746_A750). Tyrosine-rich cytoplasmic areas are homo/heterodimerized and autophosphorylated by the EGFR tyrosine kinase to auto-activate the receptor after ligand contact (Antonicelli et al., 2013).

Tyrosine kinase (TK) blockers are a group of small chemical drugs that inhibit the tyrosine kinase domain of EGFR. Gefitinib and erlotinib were the first generation of TK blockers to demonstrate therapeutic benefit. These two blockers, which bind to this kinase domain reversibly, are regarded as first generation. In patients with the most prevalent activating EGFR mutations, initially developed EGFR blockers have demonstrated exceptional treatment efficacy (Stewart et al., 2015).

EGFR mutations only show up in mixed adeno-squamous carcinomas; they are not found in pure squamous cell carcinomas (SCCs) (Rekhtman et al., 2012). In response to internal and external stimuli, In many biological processes, such as growth, differentiation, metabolism, and death. They play a crucial role in mediating the signaling cascade as well. It has been demonstrated that a major factor in the pathogenesis of human malignancies is the dysregulation of protein kinase activity. In targeted therapies, one of the first cancer treatments to demonstrate the possibility of such a tailored effect was imatinib. Oral targeted treatment imatinib inhibits tyrosine kinases. Because of its anti-PDGFR action, imatinib has also been shown to include platelet-derived growth factor receptor alpha gene PDGFRA, c-KIT, and BCR-ABL. In addition to its impressive efficacy in CML and GIST, imatinib

also helps a number of other cancers brought on by aberrant PDGFR and c-KIT expression. Because it is beneficial in steroid-refractory chronic graft-versus-host disease (Iqbal & Iqbal, 2014).

About 20 years ago, in April 1998, humans were initially given ZD1839, an EGFR-TK blocker that subsequently became gefitinib. The pharmacokinetics, antitumor efficacy, and tolerability of this oral EGFR-TKI were investigated in patients with solid malignant tumors during that phase I investigation. The individuals who were initially selected received fifty milligrams of ZD1839 blocker once a day for 14 days.

They then went another 14 days without taking their prescription. Following the administration of dosages ranging from 300 to 700 milligrams daily, four of sixteen patients with NSCLC were able to demonstrate verifiable partial therapeutic outcomes. Following treatment for advanced non-small cell lung cancer, these results led to 2 dose-finding, randomized clinical studies comparing 250 mg and 500 mg daily in patients (Vansteenkiste & Wauters, 2018; Jänne et al., 2015).

Even with early reactions to EGFR TK blockers (acquired resistance), most of the individuals will experience disease recurrence within 1 to 2 years of beginning treatment. The emergence of a second EGFR variation, EGFR T790M, causes developed resistance in approximately sixty percent of patients (Yun et al., 2008). The T790M mutation accounts for almost half of all resistance to the reversible inhibitors erlotinib and gefitinib. Threonine 790 is referred to as the facilitator domain in EGFR due to its critical location at the entrance to the nonpolar region at the back of the ATP-binding cleft, which influences the blocking selectivity of protein kinases. When this residue in EGFR is swapped out for a big methionine, it was once thought that steric interference with the attachment of TKIs, including gefitinib and erlotinib, causes drug resistance. This allows them to block EGFR kinase activity even when EGFR T790M is present (Jänne et al., 2015; Yun et al., 2008; Engelman et al., 2007).

In patients with EGFR-sensitizing mutations, the second-generation TK blockers dacomitinib and afatinib improved clinical outcomes in comparison to the initial-generation TK blocker and platinum-based chemotherapy. Afatinib also showed promise in treating cancer with uncommon EGFR deletions in a pooled analysis of the LUX-Lung studies; however, patients with exon-20 translocation mutations and de novo T790M saw a diminished therapeutic response (Yang et al., 2015). Under the presence of the T790M variation, fewer EGFR-TK blockers of the first or second generation bind to the nucleotide binding site of EGFR. This may accelerate the course of the disease by lessening the suppression of signaling downstream by EGFR-TKI.

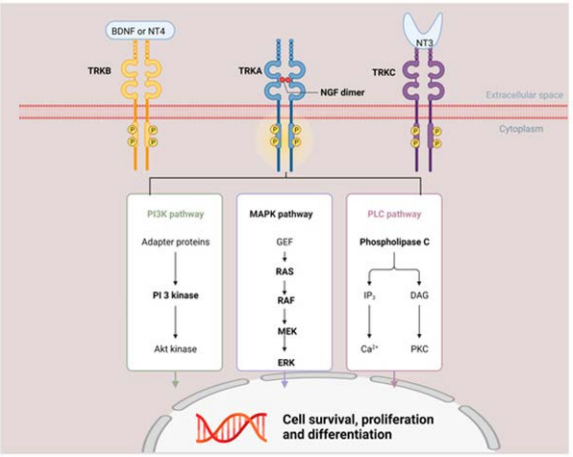
Osimertinib, a third-generation inhibitor, was significantly more successful than platinum treatment with pemetrexed for patients with T790M-positive metastatic

NSCLC (including those with CNS metastases) whose condition worsened after first-line EGFR-targeted therapy (Mok et al., 2017).

NTRK BLOCKER

As a part of the tyrosine receptor kinase family, which also includes NTRK1, NTRK2, and NTRK3, neurotrophic tropomyosin receptor kinase (NTRK) encodes for TRKC, TRKA, and TRKB, respectively. Each of the three NTRKs is essential for the formation of the central nervous system, involving cellular death, division, movement, and growth of cells. The downstream signal pathway and function of NTRK are shown in Figure 2. An internal kinase site, a membrane-spanning site, and external interacting ligand motifs are the typical components of NTRK. NTRK stimulates the subsequent pathway, which supports cellular division and proliferation, when it binds to its ligand. Phospholipase C (PLC), mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K), neurotrophin number four (NT4), neurotrophin nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF) (Qin & Patel, 2022).

Figure 2. The downstream signal pathway and function of NTRK



The NTRK1 gene, which is located on chromosomes 1q21–q22, codes for the specific protein TRKA, which interacts with NGF to stimulate the phosphorylation of tyrosine and tyrosine kinase activation. The protein TRKB has a unique interaction with BDNF, and the NTRK2 gene is found on the 9q22.1 allele. Moreover, the 15q5.2 allele contains the NTRK3 gene.

Oncogenic drivers, such as fusion or gene rearrangement involving NTRK1, NTRK2, or NTRK3, are present in a range of tumor forms in both adults and children, including less than one percent of NSCLCs. These gene rearrangements are functionally recognized by a 3′ terminus end that contains an upstream partner gene at the 5′ position and one of the three NTRK genes, which together comprise the whole kinase region (Drilon et al., 2022). Different chromosomal reorganizations can constitutively excite the TRK receptors. This leads to intra-frame gene rearrangement of the NTRK genes' C-terminal TK domain with an N-terminal hybrid target. When the gene rearrangement normally removes the ligand interaction site, cellular receptors dimerize and get phosphorylated without the ligand (Ekman, 2020).

In rare tumors, these fusions might be very common, whereas in more common cancers, they might be far less common (Harada et al., 2021; Hagopian & Nagasaka, 2024). It is undetermined whether gene rearrangement in NTRK returns in NSCLC. Adolescent patients with adenocarcinoma histopathology and little tobacco usage are more likely to have NTRK-mutated NSCLC. In an investigation of 91 lung tumor patients, an NTRK gene fusion was detected in three percent of patients who did not have any other carcinogenic alterations. TPM3-NTRK1, SQSTM1, and ETV6-NTRK3 are frequently detected amalgamation partners in NSCLC with an NTRK mutation (Hagopian & Nagasaka, 2024; Haratake & Seto, 2021).

The US FDA has just authorized larotrectinib and entrectinib, first-generation tropomyosin receptor kinase (TRK) inhibitors, for use in individuals who have solid tumors that have NTRK fusion, including NSCLC. Larotrectinib and entrectinib were approved according to a comprehensive analysis of sequentially registered patients with TRK fusion-positive malignancies throughout numerous clinical trials. Only 0.2 percent to three percent of NSCLCs had NTRK mutations (Doebele et al., 2020).

Larotrectinib

In November 2018, the US FDA expedited the acceptance of it for the therapy of solid malignancies with an NTRK hybrid gene in children and adults who do not have a known mutation that causes resistance (Sartore-Bianchi et al., 2020). The highly efficient pan-Trk inhibitor larotrectinib has been examined in a range of different kinds of tumors in both adult and pediatric patients, and it has shown an ORR of 73% in persons. With a dose reduction of 9% and a cessation of less than 1%, the bulk of the toxicity was grade 1-2. The US, Brazil, and Canada have all authorized larotrectinib. In addition, larotrectinib was recently recommended for approval for solid malignancies with NTRK fusion by the European Medicines Agency (EMA).

Entrectinib

The nucleotide triphosphate-competitive blocker entrectinib is effective and selective; it inhibits ROS1, ALK, TRKB, TRKC, and TRKA in vitro. Tumor cell lines and Ba/f3 cells with changes in the NTRK1 kinase region that made them resistant to another TRK inhibitor, such as the replacement of the key residue F589L and the xDFG motif G667C, were inhibited in their ability to proliferate by entrectinib (Frampton, 2021).

BRAFv600 BLOCKER

Current research has demonstrated that the replacement of a glutamine for a valine at position 600 (V600E) is the most frequent variation in BRAF in a malignant tumor (Khunger et al., 2018; Robinson et al., 2014). Along with ARAF and CRAF, BRAF belongs to the threonine kinase RAF group. The signaling through the MAPK cascade, which regulates the development of cells, growth, and their existence, depends heavily on RAF kinases. It has been found that there are about 300 different BRAF variants in tumor specimens and cancer cell lines from skin cancer, colon, and non-small cell lung cancer (NSCLC) (Tabbò et al., 2022).

BRAFV600 class I mutations show up as monomers that either contain or do not contain activated RAS. When RAS is activated, class II BRAF non-V600 mutations transmit as two molecules of monomers, but class III mutations have increased MAPK pathway signaling but lower kinase activity. This new classification can help anticipate how cancers will respond to targeted treatment (Mazieres et al., 2020). The first BRAF blocker, vemurafenib, was approved for the treatment of advanced BRAF V600E-variant skin cancer. Vemurafenib exhibited a superior progression-free survival (PFS) and a longer overall survival (OS) compared to the PFS and OS of dacarbazine (Khunger et al., 2018).

Initially studied and approved as stand-alone treatments for metastatic melanoma caused by the BRAF V600E mutation, dabrafenib inhibits multiple mutant forms of BRAF, while trametinib is a non-permanently inactivated inhibitor for kinase activity. When compared to dacarbazine, dabrafenib considerably increased PFS for a BRAF V600E or V600K mutation, and when compared to chemotherapy, trametinib significantly increased PFS ("Adverse Event Management in Patients with BRAF V600E-Mutant NSCLC Treated with Dabrafenib plus Trametinib," n.d.).

In line with adenosine triphosphate-competitive blocking, dabrafenib (GSK2118436) is a potent, non-permanently inactivated, and specific antagonist for BRAF V600E kinase activity. The phase I study did not achieve its highest permissible dose. A dose of 150 milligrams oral twice daily was selected depending on the drug kinetics, the impact of dabrafenib on a molecular biological marker

target (tumor pERK inhibition), the metabolic processes uptake of FDG-PET, the assessment of the illness as indicated by response according to RECIST criteria at initial restaging, and the safety profile. By day 15, exposure (Cmax and AUC) from 200 milligrams twice daily was no greater than that from 150 mg twice daily (Sánchez-Torres et al., 2013).

According to the National Comprehensive Cancer Network (NCCN) recommendations, individuals suffering from advanced non-squamous NSCLC should be tested for BRAF variants. If the results are positive, dabrafenib plus trametinib should be administered in the first line or later. Trametinib and Dabrafenib together were named a Breakthrough Therapy Designation by the US Food and Drug Administration in 2015 for the treatment of patients with non-small cell lung cancer who had a BRAF V600E alteration and received prior treatment (Anguera & Majem, 2018).

ALK blockers

ALK on the 2p23 allele can express the insulin receptor TK group's anaplastic lymphoma kinase (ALK). The NPM-ALK carcinogenic fusion protein, which is linked to anaplastic large cell lymphoma and is produced by a locational shift between alleles 2 and 5, was first found to contain it (Sullivan & Planchard, 2016). The recurrent deletion and flip of chromosome 2p causes a rare subset of non-small cell lung cancers (NSCLCs) to combine the N-terminus region of the protein expressed by the echinoderm microtubule-associated protein-like 4 (EML4) gene with the signal-regulated section of the ALK receptor TK. Although ALK-related genetic modifications have been found in other tumors, the EML4-ALK recombinant gene seems to be specific to NSCLC. In NSCLCs, a variety of EML4-ALK variants have been found, and they all seem to provide gain-of-function characteristics (Gerber & Minna, 2010).

For advanced NSCLC with ALK rearrangements, the initial choice drug therapy is crizotinib, an oral ALK blocker.

Additionally, more powerful and selective second-generation ALK inhibitors are beginning to be used in clinical settings. Ceritinib (also known as LDK378), the second-generation drug blocker, has shown exceptional efficacy in patients with ALK-driven lung cancer, including those who have developed resistance to crizotinib. The U.S. Food and Drug Administration recently approved crizotinib for use in patients who had previously received crizotinib treatment for advanced ALK-rearranged non-small cell lung cancer. Nevertheless, durability typically manifests within a year, and ALK blocker effectiveness is transient (Wilson et al., 2015).

Most people develop resistance to crizotinib within a year or two of beginning treatment.The ALK blocker resistance is both primary and secondary. Primary resistance occurs when the malignancy is judged unresponsive to the agent at the

start of the therapy itself. The primary resistance in ALK+ NSCLC is caused by the many fusion variants of ALK or other partner genes. It has been demonstrated that the ALK variant or fusion gene partner affects the sensitivity to crizotinib. The golden method for detecting ALK mutations in NSCLC at the moment is FISH (Wu et al., 2016).

Developed mechanisms known as secondary resistances emerge following the administration of an ALK antagonist to the malignancy. Secondary resistances are developed responses that emerge after the cancer has been approached with an ALK inhibitor. They can be classified as either ALK-driven or ALK-non-driven. The target ALK gene is mutated in the ALK-driven type, making it impossible to stop the expression of tyrosine kinase (Toyokawa & Seto, 2015).

A multicenter, randomly allocated, stage I/II clinical trial demonstrated that brentinib, another second-generation ALK blocker, can overcome resistance to crizotinib and other first- and second-generation ALK inhibitors in preclinical models, despite the fact that it is not yet approved for use as a first-line treatment (Toyokawa & Seto, 2015). In this study, a dosage of 180 milligrams daily with a 7-day lead-in of 90 milligrams daily produced an excellent outcome for brigatinib with a tolerable safety profile. In evaluable patients with brain metastases, this dose resulted in an overall treatment response rate of 67% (twelve out of eighteen patients) and a total response rate of 54%, including four complete responses. Following the FDA's approval of brigatinib early in the fourth quarter of 2017 for the treatment of crizotinib-resistant, ALK-driven NSCLC, there are now four drugs available to treat ALK-driven NSCLC (Golding et al., 2018).

ROS-1 BLOCKER

ROS1 is an initial oncogene that encodes a tyrosine protein kinase (RTK) receptor that is identical to the Ros sequence of the University of Manchester Tumors virus 2 (UR2) sarcoma virus. Current research is being conducted to identify the virus's ligands. Numerous types of tumors contain ROS1 fusion genes. It functions as an oncoprotein that promotes the growth of cells, stimulation, and progression through the cell cycle by initiating downstream signaling pathways, hence hastening the initiation and spread of non-small cell lung cancer (NSCLC). The first line of treatment for patients with non-small cell lung cancer that is ROS1-positive is ROS1 inhibitors. These tiny molecules provide a reasonable therapeutic option for those who have ROS1 positivity. Sometimes mutations that result in resistance to ROS1 inhibitors inevitably arise, which might cause tumors to develop or reoccur (Yu et al., 2022). The first ROS1 gene fusions were seen in a human glioma cell line (Birchmeier et al., 1987). It was discovered that the 5′ portion of the fused in glioblastoma gene (FIG), also referred to as Golgi-associated PDZ and coiled coil

motif including ROS1, was fused to the 3′ area of ROS1 [GOPC] in this cell line through the removal of 240 kilobases on chromosome 6q21, resulting in a constitutively active fusion kinase (Lin & Shaw, 2017). First discovered in 2007, ROS1 rearrangements account for 1-2 percent of NSCLC patients and cause 10,000-15,000 new cases annually worldwide (Rikova et al., 2007). Patients are usually young and either light smokers or non-smokers (D'Angelo et al., 2020). Currently, it is uncertain how ROS1 fusion proteins become constitutively active. For other RTK fusions related to cancer, including ALK, also known as anaplastic lymphoma kinase, the dimerization domain provided by the fusion partner causes constitutive oligomerization, which in turn activates the kinase (Camidge & Doebele, 2012). Whether dimerization plays a role in WT receptor activation for ROS1 is unknown, though. Additionally, it has been revealed that the UR2 avian sarcoma virus's v-ros product and the FIG–ROS1 fusion protein only exist as monomers (Charest et al., 2003). Accordingly, dimerization domains are absent from a large number of the known ROS1 fusion partners (Takeuchi et al., 2012).

12. COMBINATION THERAPIES

The TME's complexity and heterogeneity, the various immune evasion strategies employed by tumor cells, and the drawbacks of mono-immunotherapy provide the justification for combination immunotherapeutic approaches in NSCLC. The goal of combining several immunotherapeutic strategies or other anticancer drugs is to increase the range of antitumor activity, boost antitumor immune responses, and maybe circumvent resistance mechanisms in order to improve treatment results for patients with non-small cell lung cancer. Immune checkpoint inhibitors (ICI) are useful in the treatment of patients with non-small cell lung cancer (NSCLC); nevertheless, because of their limitations when used alone, these medicines are frequently combined with other therapy techniques. Given the limited effectiveness of ICI monotherapy, preclinical studies have shown that neoadjuvant ICIs are more effective than adjuvant ICIs at eradicating distant metastases because they produce a stronger and longer-lasting tumor-specific immune response (Wu et al., 2024). The KEYNOTE-189 study was a double-blind phase III research that assessed the efficacy of pemetrexed in conjunction with platinum-based drugs or a placebo for the treatment of non-squamous metastatic non-small cell lung cancer. The objective response rate (ORR) for the pembrolizumab plus pemetrexed-platinum arm was 48.3%, while the ORR for the placebo plus pemetrexed-platinum arm was only 19.9%. The 5-year overall survival (OS) rate was 19.4% in the pembrolizumab-combination group and 11.3% in the placebo-combination group. The PFS rates for the next five years were 7.5% and 0.6%, respectively (Ma et al., 2025).

13. CONCLUSION

Non-small cell lung cancer (NSCLC) treatment has advanced significantly over the last 20 years, enhancing multimodal therapy and early detection while expanding our knowledge of the illness and the mechanisms behind tumor formation. The use of therapies including immunotherapy, molecularly targeted medications, and chemotherapy, has led to unprecedented increases in survival in some patients. However, overall survival and cure rates for NSCLC remain low, particularly when the disease has progressed. Therefore, additional research into new drugs and combination therapy is required to improve outcomes in NSCLC and increase the clinical benefit to a larger patient group.

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