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Advancements in NSCLC
From Pathophysiological Insights to Targeted Treatments

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Abstract: With the global incidence of non-small cell lung cancer (NSCLC) on the rise, the development of innovative treatment strategies is increasingly vital. This review underscores the pivotal role of precision medicine in transforming NSCLC management, particularly through the integration of genomic and epigenomic insights to enhance treatment outcomes for patients. We focus on the identification of key gene mutations and examine the evolution and impact of targeted therapies. These therapies have shown encouraging results in improving survival rates and quality of life. Despite numerous gene mutations being identified in association with NSCLC, targeted treatments are available for only a select few. This paper offers an exhaustive analysis of the pathogenesis of NSCLC and reviews the latest advancements in targeted therapeutic approaches. It emphasizes the ongoing necessity for research and development in this domain. In addition, we discuss the current challenges faced in the clinical application of these therapies and the potential directions for future research, including the identification of novel targets and the development of new treatment modalities.

Key Words: NSCLC, targeted therapy, molecular mechanisms, targeted drugs

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Lung cancer persistently ranks atop global oncological mortalities.[1] The therapeutic approach for this malignancy is contingent upon a myriad of variables, encompassing the patient's histopathologic classification, tumor gradation, molecular hallmarks, and a holistic evaluation of the patient's overall well-being.[2] Among the delineated lung cancer subtypes, non-small cell lung cancer (NSCLC) is preeminent, constituting ~85% of cases.[3] Owing to its aggressive phenotype, NSCLC exacts a profound impact on patients, their familial networks, and the broader societal milieu.

Pertaining to the pathogenesis of NSCLC, its exact etiology continues to elicit scholarly discourse. Nonetheless, a wealth of evidence accentuates the cardinal influence of multigenic anomalies and the sophisticated dynamics within signaling cascades.[4–6] Remarkably, ~60% of patients with lung adenocarcinoma possess identifiable driver gene aberrations, inclusive of EGFR, ALK, and ROS1.[7] Such mutations instigate modulations in receptors and protein kinases, potentially precipitating disruptions in interconnected signaling pathways, leading inexorably to rampant tumor cell growth, infiltration, and persistence.[8] Moreover, this malignant expansion undermines the balance of angiogenesis, compelling neoplastic cells to orchestrate novel vascular networks, thereby facilitating their accelerated expansion.[9]

For decades, surgical modalities, radiotherapy, and chemotherapy have been the mainstay defenses against NSCLC.[10] However, their therapeutic efficacy is often limited, especially in cases presenting advanced disease stages.[11] A notable proportion of patients experience recurrence or metastatic spread subsequent to their initial therapeutic course. Furthermore, traditional modalities are often accompanied by a spectrum of deleterious side effects. In spite of a sobering 5-year survival rate for NSCLC hovering around 15%,[12] the advent of chemotherapy and precision-targeted therapies has heralded significant enhancements in patient outcomes. In addressing advanced NSCLC, the contemporary medical consensus advocates for individualized treatment strategies based on specific patient biomarkers, thereby accentuating the growing significance of molecular genetic assays and PD-L1 protein expression profiling for NSCLC cases.[13,14] As our understanding of the genetic intricacies of NSCLC deepens, an array of innovative targeted therapeutic approaches has surfaced. This review explores these avant-garde modalities in advanced NSCLC, endeavoring to provide cogent, evidence-informed therapeutic guidelines for those patients with NSCLC presenting with distinct pathogenic genetic alterations.

PATHOGENESIS OF NSCLC

Driver Gene Mutation

With rapid advancements in genome sequencing technology, our understanding of tumors, particularly NSCLC, has experienced a profound transformation. Driver genes, essential to cellular carcinogenesis, can instigate tumor initiation, progression, and metastasis due to mutations or aberrant expressions. In NSCLC, a myriad of driver gene mutations have been identified, each carrying significant clinical implications.[15]

EGFR

EGFR, a member of the HER family, is expressed on the surfaces of various mammalian cells, including epithelial cells and fibroblasts.[16] Its signaling is pivotal for cellular processes, such as growth and differentiation. EGFR mutations, predominantly localized to exons 18-21 of the tyrosine kinase, are prevalent in around 20% of NSCLC cases.[17] The high expression of EGFR in tumors may also be attributed to its reduced degradation after activation.[18] Some studies indicate that c-Src can upregulate EGFR levels by inhibiting receptor ubiquitylation and endocytosis.[19] EGFR ligands promote cell

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proliferation by activating EGFR, and their coexpression often predicts a poor prognosis for tumors. For instance, in studies of invasive ductal carcinoma of the breast, TGFα was found coexpressed with EGFR, and this coexpression significantly correlated with patient survival rates.[20] A study by Pabla et al on colorectal cancer revealed that the tumor's autocrine growth arises from the combined overexpression of EGFR and its ligand.[21] We can liken EGFR to a beacon that signals cell proliferation. When it receives a signal, it conveys this instruction to the cell via messengers to promote growth. If there is a malfunction in this beacon (such as a persistent activation due to an EGFR gene mutation), it continuously sends out messengers to stimulate cell proliferation, which is one of the reasons tumors develop.

ALK

ALK is an abbreviation derived from its discovery in the subtype of anaplastic large-cell lymphoma and typically plays a critical role in embryonic development under physiological conditions.[22] ALK signaling in cancer cells is mainly activated through 3 mechanisms: gene fusion, gene amplification, and activating point mutations.[23] In 2007, Professor Manabu Soda of Japan and colleagues first identified the fusion of ALK with EML4 in non-small cell lung cancer specimens.[24] EML4 can promote the activation of the ALK kinase domain, thereby promoting cell proliferation, ultimately leading to tumor initiation and progression. In in vitro experiments, EML4-ALK promoted the proliferation of BAF3 lung cancer cells independently of IL-3.[25,26] To further explore the mechanism by which EML4-ALK induces NSCLC, researchers have experimentally confirmed that EML4-ALK exerts its oncogenic role through the JAK-STAT6 signaling pathway. Besides the JAK-STAT6 pathway, ALK activation can also promote cell proliferation and inhibit apoptosis via the MAPK, PI3K/mTOR, and SHH pathways. The activation mechanism of ALK is not yet fully elucidated, and the role of ALK rearrangement in NSCLC remains to be further studied. The proportion of ALK fusion gene mutations in non-small cell lung adenocarcinoma in China is 3% to 7%.[27] However, the survival rate after targeted treatment is better than that of patients with lung cancer with other gene mutations, and there are more drug options available; hence, it is also referred to as the "diamond mutation."

KRAS

KRAS, an integral member of the RAS family, is located on chromosome 12 and encodes for the KRas protein—a GTPase responsible for the conversion of GTP to GDP.[28] In a physiological context, the activation of the EGFR signaling pathway briefly engages KRAS, subsequently transmitting signals to downstream effector proteins. Following this ephemeral activation, KRAS promptly reverts to its dormant state.[29,30] In contrast, under pathologic conditions, an imbalance in KRAS can perpetuate its activation within the EGFR signaling cascade, fostering unrestrained cellular growth and potentially culminating in tumorigenesis.[31] Research indicates that KRAS modulates a variety of cellular activities by engaging several effector proteins. Hsu et al[32] elucidated that KRAS has the capacity to activate TFCP2, thereby promoting angiogenesis and advancing CRC progression. In addition, oncogenic KRAS mutations robustly induce a range of chemokines, cytokines, and growth factors, such as IL-6, IL-8, CCL9, and IL-23, which serve as principal cues for matrix reprogramming. Notably, KRAS perpetuates an interstitial inflammatory phenotype by producing IL-6 and IL-8 in pancreatic and lung cancers.[33] Among patients with NSCLC in China, KRAS mutations rank second in prevalence after EGFR mutations, with 6.7% of patients exhibiting KRAS mutations.[34] Yet, due to the absence of pharmacological pockets in certain mutation subtypes, KRAS has historically been labeled as "undruggable." However, recent strides in research targeting KRAS directly have yielded promising advancements.

ROS1

ROS1, situated on chromosome 6, is responsible for encoding the receptor for insulin. Vulnerable to chromosomal rearrangements,[35] the ROS1 gene frequently undergoes fusion with other genes in NSCLC cases. Such fusions produce oncogenic drivers that incessantly activate the ROS1 kinase and subsequent downstream signaling pathways, thereby promoting cell growth, proliferation, and migration. Although ROS1 gene fusions play a pivotal role in NSCLC, their occurrence is relatively rare, with a positivity rate of 2.59% among Chinese patients with NSCLC.[36,37] Numerous studies have attested to the oncogenic potential of ROS1 fusions. The expression of ROS1 fusions induces transformation in in vitro NIH3T3 and Ba/F3 cells, as well as tumorigenicity in vivo.[38] Yet, the precise mechanism of ROS1 kinase activation within the fusion proteins remains to be determined. Intriguingly, the localization of ROS1 fusion proteins varies, and upon activation, ROS1 signals through the MAPK/ERK, PI3K/AKT, JAK/STAT3, and SHP1/2 pathways to bolster cell growth and survival.[39] Whether different ROS1 fusions bestow varying expression levels, kinase activations, and oncogenicities is still an open question.

BRAF

BRAF, located on chromosome 7, encodes a serine/threonine protein kinase.[40] In the context of NSCLC, BRAF mutations occur in ~1.5% to 3.5% of cases.[41] Based on signaling mechanisms and kinase activity, BRAF mutations can be classified into 3 categories: class I, which includes V600 mutations, specifically BRAF V600D/E/K/R, are kinase-activated monomers that significantly enhance BRAF kinase activity. Class II consists of kinase-activated dimers, such as BRAF K601, L597, G464, and G469 mutations. Class III contains kinase-inactivated heterodimers, such as BRAF G466, N581, D594, and D596 mutations.[42] The most prevalent type of BRAF mutation is V600E, which markedly amplifies the kinase activity of BRAF. Previous research has demonstrated that BRAF conventionally regulates tumor invasion and metastasis by activating the MAPK signaling pathway.[43] However, a recent study by Pan et al[44] unveiled that oncogenic BRAF can promote tumor metastasis by directly modulating the phosphorylation of the cytoskeleton-associated protein VASP. This revelation offers novel insights for the future development of drugs targeting BRAF-mutated tumors.

MET

MET, situated on the long arm of chromosome 7, is primarily encoded by exon 14 and functions as the tyrosine kinase receptor for hepatocyte growth factor (HGF).[45] Under pathologic conditions, mutations in the MET gene can cause aberrant activation of exon 14.[46] Such sustained tyrosine kinase activity fosters tumor cell migration, proliferation, and infiltration.[47] Studies suggest that MET mutations are found in 3% to 5% of patients with NSCLC, with MET amplification observed in 1% to 5%.[48] Within NSCLC, aberrant MET gene activation chiefly appears in 4 variations: MET gene amplification, protein overexpression, and MET Δex14.[49] HGF triggers various downstream signaling pathways, including PI3K/AKT, RAS/ERK/

MAPK, Wnt/β-catenin, SRC, and STAT320-2950.[50] This cascade of events can result in uncontrolled cell growth, potentially precipitating tumor initiation, invasion, and dissemination.

RET

Situated within the 11q22.2 locus of chromosome 10, RET codes for a transmembrane tyrosine protein kinase receptor.[51] Perturbations in RET's structural and functional integrity are implicated in tumorigenesis, with gene mutations emerging as the predominant oncogenic variant. Among such mutations, RET M918T reigns supreme, though other mutations like A883F44 and E768D have been documented. In addition, gene fusions such as KIF5B-RET present another oncogenic dimension of RET, holding a significant prevalence in NSCLC,[52,53] and contributing to 60% to 70% of such fusions[54]—notably, the K15:R12 variant. Intriguingly, while KIF5B-RET or RET is absent in normal lung tissues, its expression is markedly upregulated in lung adenocarcinoma specimens. Despite their relative rarity, RET gene fusions still constitute about 1% to 2% of NSCLC cases.

Owing to the central role of driver gene mutations in NSCLC pathogenesis, scientific endeavors have increasingly concentrated on this realm, culminating in the design of a suite of drugs tailored to target these aberrations. Presently, a multitude of clinical trials are in progress, evaluating prospective gene targets.

Angiogenesis

Tumor growth is inherently tethered to its vascular support. As such, angiogenesis furnishes the essential microenvironment for tumor inception and progression, accompanying its evolution at every juncture. In the context of NSCLC, neovascularization is particularly pivotal. These emergent vessels serve not only the oxygenation and nutrient demands of the tumor microenvironment but also potentiate its metastatic capacity.[55] Moreover, angiogenesis is recognized as a canonical feature of malignancy, wielding a decisive influence over tumor growth, presentation, and its interaction with normal physiological processes.

Under physiological conditions, angiogenesis originates from extant vasculature, a process meticulously modulated by a plethora of proangiogenic and antiangiogenic factors. Yet, malignant entities, like proliferative tumors, unsettle this balance, culminating in exacerbated vascular proliferation.[56] Inadequate vascular supply within the tumor matrix can precipitate hypoxic conditions and an acidic environment. This not only catalyzes enhanced angiogenic activity but also bolsters resistance to radiotherapy, chemotherapy, and immunotherapy.

Key orchestrators of angiogenesis include VEGF, FGF, and PDGF, with the VEGF family holding primacy. VEGF, a cohort of secretory glycoproteins, predominantly modulates endothelial activities through the interaction of VEGF-A and its cognate receptor, VEGFR-2.[57] VEGF is instrumental in tumor vascularization, influencing tumor initiation, growth, and metastatic potential directly. Indeed, as early as 1971, Professor Judah Folkman[58] pioneered the concept of angiogenesis inhibition as a potential therapeutic strategy against tumors. Modern therapeutic interventions largely focus on the aforementioned signaling cascades, with particular emphasis on the VEGFR pathway.

Aberrations in the Cell Cycle and Signaling Pathways

Within both benign and malignant cells, Cyclin-dependent kinases (CDKs) act as critical regulators. These kinases, working synergistically with cell cycle proteins known as Cyclins, oversee the cellular proliferation process. Stringent regulation of the cell cycle is crucial for accurate DNA replication and cellular division. However, conditions such as NSCLC can perturb this delicately balanced mechanism.

In NSCLC, cell cycle pathway dysregulation is common. Approximately 22% to 25% of patients exhibit cyclin D1-3 and CDK4/6 amplifications or point mutations, causing excessive cellular proliferation.[59] Many external signals govern the cell cycle via CDK4/6. In healthy cells, growth-promoting signals like RAS, RAF, Jun, PI3K, AKT, and β-Catenin activate Cyclin D. Cyclin D then partners with CDK4/6, leading to Retinoblastoma protein (Rb) phosphorylation. This, in turn, activates Cyclin E-CDK 2, further phosphorylating Rb.[60] Consequently, Rb dissociates from E2F, allowing the cell to progress beyond the restriction point into the proliferative phase.[61] In NSCLC, altered Rb expression, CDK4 (INK4) protein mutations, and KRas mutations disrupt the cell cycle, promoting unchecked proliferation and the typical malignant growth seen in NSCLC.

PI3K acts as a precursor activator for CDK4/6, via Cyclin D stimulation. The PI3K/AKT/mTOR pathway controls cell survival, proliferation, and angiogenesis.[62] An imbalance in this pathway accelerates tumor initiation and progression. Mutations in EGFR, PTEN alterations, and PI3K mutations/amplifications activate it. PTEN dephosphorylates PIP3, inhibiting PI3K/Akt/mTOR activation. PTEN deficiency or mutations lead to PIP3 buildup, sustaining Akt and the pathway.[63] About 90% of NSCLC cell lines show PI3K/AKT/mTOR activation.[64] Targeted drugs counter these anomalies, proving effective in clinical trials and treatments.

Molecularly Targeted Drugs for NSCLC

As the intricacies of NSCLC pathogenesis become clearer, a burgeoning interest in molecular targeted therapies has emerged. In the ensuing section, we will delineate the principal targeted therapeutics employed for NSCLC management, especially spotlighting those that have made their mark in clinical trials with disseminated results. Furthermore, we will succinctly expound upon the operative mechanisms of these pharmaceutical agents (as shown in Fig. 1).

Major Target Sites and Drugs for NSCLC

EGFR-TKIs

EGFR-TKIs have prominently emerged as key contenders in the NSCLC therapeutic landscape,[65] second only to platinum-based compounds (as detailed in Table 1). Presently, 3 generations of EGFR-TKIs have been launched in the market. First-generation agents have a limited therapeutic scope, targeting solely the EGFR receptor. Conversely, the second-generation drugs extend their inhibition to both EGFR and HER-2 receptors. Although these agents markedly increase the median overall survival (mOS) for patients, their amplified toxicity necessitates ongoing refinements to enhance their safety profile. The third generation establishes an irreversible bond with receptors such as EGFR, L858R, T790M, and Exon 19 deletion mutants. This makes it especially potent for metastatic patients with NSCLC who exhibit resistance to their predecessors.

The landmark IPASS trial[66] was the inaugural large-scale study to establish that EGFR-TKI offers a survival benefit to patients with advanced NSCLC harboring EGFR mutations. It highlighted a superior median progression-free survival (mPFS) for the gefitinib cohort (10.9 mo) compared to the chemotherapy group (7.4 mo); however, the OS rates were comparable between the two. Subsequent phase III randomized trials have corroborated these findings, endorsing gefitinib as a

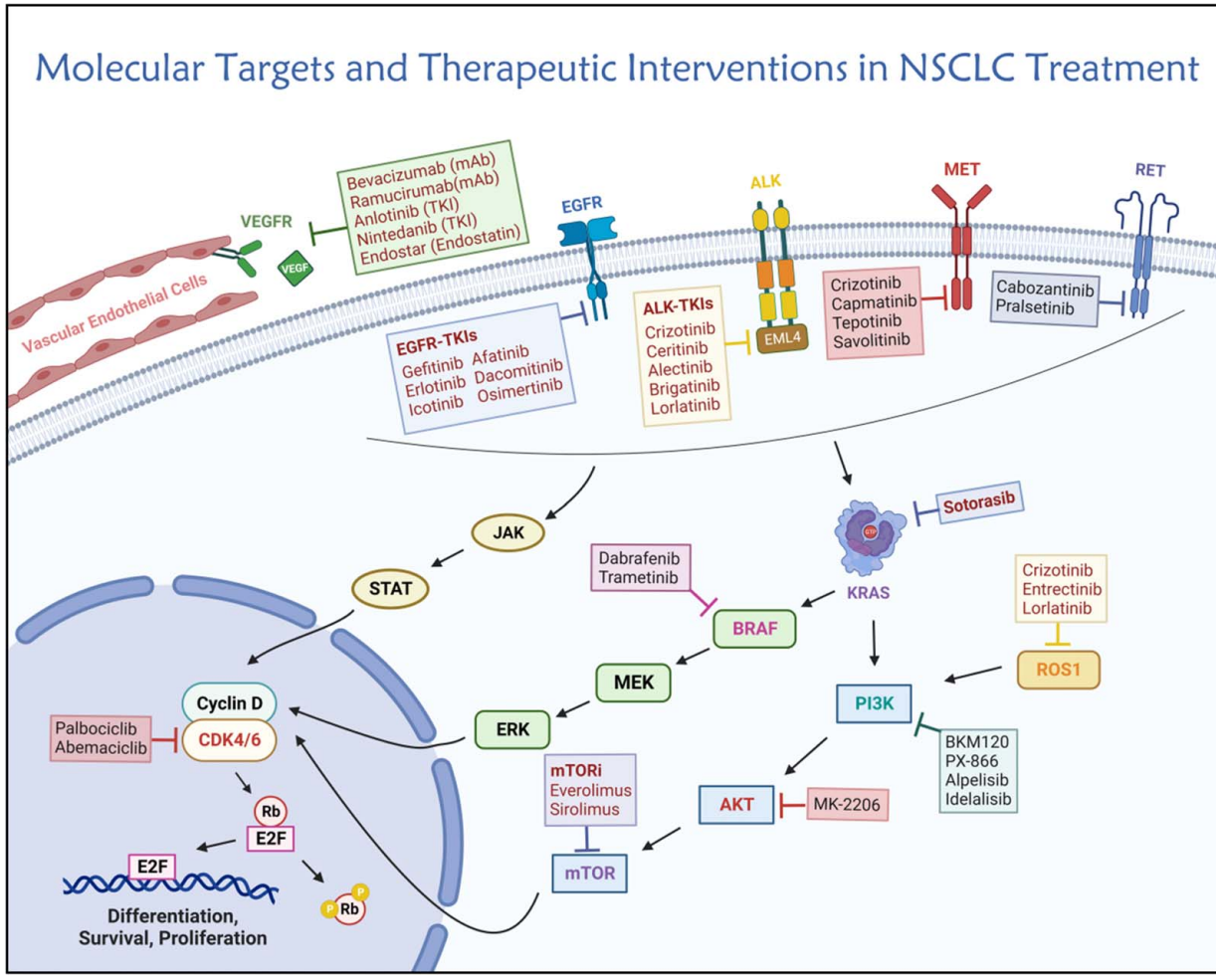

FIGURE 1. Molecular targets and therapeutic interventions in non-small cell lung cancer treatment. The depicted schematic provides a concise overview of the key molecular targets in NSCLC and the suite of targeted therapies designed to intervene. It encompasses a spectrum of inhibitors for pathways such as EGFR, ALK, VEGFR, MET, and RET, as well as agents that modulate the KRAS, BRAF, MEK, and the PI3K/AKT/mTOR cascades. Featured as well are the CDK4/6 inhibitors, a novel class of drugs that govern cell cycle progression. Each therapeutic agent is specified by its target, underscoring the targeted approach integral to contemporary NSCLC treatment paradigms. full color online

preferred first-line treatment for this patient subset.[67] The ENSURE study[68] demonstrated that the mPFS for erlotinib was 11.0 months, almost double that of the cisplatin/gemcitabine group (5.5 mo), yet their mOS remained statistically analogous. Erlotinib has since been sanctioned for first-line administration in EGFR mutation–positive patients with NSCLC. Icotinib, an innovative oral EGFR-TKI, yielded an mPFS of 11.2 months, overshadowing the 7.9 months recorded for the cisplatin/pemetrexed combination.[69] Moreover, icotinib exhibited a reduced incidence of drug-induced adverse effects, notably diarrhea. While next-generation drugs are perceived to possess a modest adverse effect profile, the spectrum of TRAE could influence therapeutic decisions in routine clinical settings.

The efficacy of first-generation EGFR-TKIs in treating NSCLC was inevitably marred by resistance, with the T790M mutation accounting for 50% to 60% of these cases. This led to the development of second-generation EGFR-TKIs, designed for irreversible binding, aiming to circumvent resistance.[70] Afatinib, emblematic of this generation, showed inhibitory potential against the T790M mutation in vitro. However, its widespread clinical application was curtailed by notable dermal and gastrointestinal side effects. Its selective nature allowed for reduced dosages, mitigating adverse reactions, and positioning it as a frontline treatment for EGFR mutation–positive patients with NSCLC. Yet, in the LUX-Lung7 trial,[71] afatinib's results were less than stellar, particularly in terms of mOS. While it slightly outperformed gefitinib in efficacy, a heightened side effect profile, especially severe diarrhea and rashes, led to a higher discontinuation rate. In contrast, dacomitinib, another second-generation EGFR-TKI, showcased superior outcomes in the ARCHER1050 study.[72] With an mPFS of 14.7 months and an mOS of 34.1 months, it significantly eclipsed gefitinib's results, underlining dacomitinib's enhanced capability in managing disease progression and improving survival in patients with NSCLC.

The third-generation EGFR-TKIs, exemplified by osimertinib, were developed to overcome resistance issues associated with earlier TKI generations. Specifically designed to target the T790M mutation—a major resistance factor—osimertinib's approval by both the EMA and the FDA stands

TABLE 1. Major Target Sites and Drugs for NSCLC

Gene	Generation	Drug name	Clinical trial	Median OS (mo)	Median PFS (mo)	Side effects
EGFR	1st	Gefitinib	IPASS	21.6	9.5	Skin rash/acne,abnormal LFT, anorexia
	1st	Erlotinib	ENSURE	26.3	11.0	Skin rash, abnormal LFT, diarrhea
	1st	Icotinib	CONVINCE	30.5	11.2	Skin rash, cough, diarrhea, abnormal LFT
	2nd	Afatinib	LUX-LUNG7	27.9	11.0	Diarrhea, paronychia, skin rash
	2nd	Dacomitinib	ARCHER1050	34.1	16.0	Diarrhea, skin rash/acne, paronychia
	3rd	Osimertinib	FLAURA	38.6	18.9	Diarrhea, skin rash, dry skin, paronychia
ALK	1st	Crizotinib	Profile1014	59.8	10.4	Vision disorder/ nausea/diarrhea
	2nd	Ceritinib	ASCEND-4	—	16.6	Diarrhea/nausea vomiting
	2nd	Alectinib	J-ALEX	—	—	AST elevation/CK elevation/fatigue
	2nd	Brigatinib	ALTA-1L	40.6	24.0	Nausea/diarrhea/cough
	3rd	Lorlatinib	CROWN	—	—	Hypercholesterolemia/edema/peripheral neuropathy
KRAS	—	Sotorasib	CodeBreak 200	12.5	6.8	Diarrhea/nausea/elevated LFT/fatigue

Gene	Drug name	Clinical trial	Median OS (mo)	Median PFS (mo)	Side effects
ROS1	Crizotinib	Profile1001	51.4	19.3	Visual impairment/nausea/edema/diarrhea/nausea/anorexia/ dyslipidemia
	Entrectinib	STARTRK-2	24	15.7	
	Lorlatinib	NCT01970865	—	—	
BRAF	Dabrafenib and trametinib	NCT01336634	—	10.9	Fatigue/pyrexia/nausea
MET	Crizotinib	Profile1001	10.1	4	Peripheral edema/amylase increased/nausea
	Capmatinib	NCT01014936		5.4	
	Tepotinib	NCT02864992	—	8.5	
	Savolitinib	NCT02897479	—	6.8	
RET	Cabozantinib	NCT01639508	9.9	5.5	Dry mouth/diarrhea/hypertension anemia/hypertension/neutropenia
	Pralsetinib	ARROW	—	—	

Carbo indicates carboplatin; Cis, cisplatin; EP, etoposide and cisplatin; Gem, gemcitabine; GI, gastrointestinal; LFT, liver function test; OS, overall survival; PFS, progression-free survival; Taxol, paclitaxel.

as a testament to its enhanced efficacy and safety. The landmark FLAURA study[73] further underscored osimertinib's superiority. It clearly outperformed gefitinib and erlotinib, showcasing improved mPFS and response duration, all while exhibiting fewer adverse events, underscoring its preferable safety profile. Among its defining features is osimertinib's ability to penetrate the blood-brain barrier—a crucial attribute considering the propensity of lung cancers to metastasize to the central nervous system. While previous EGFR-TKIs struggled with cerebral metastases due to limited permeability, osimertinib offers a potent remedy for patients previously without effective treatments for brain metastases. Bolstered by strong clinical data and a unique pharmacological footprint, osimertinib undeniably occupies a leading position in treating EGFR-mutated NSCLC, particularly in cases with T790M-driven resistance. However, an intriguing question arises from the FLAURA study: If the third generation surpasses the combined efficacy of the first and third generations, does it relegate the first generation to obsolescence as a primary treatment? While tempting to think so, it is likely not the reality. For newly diagnosed patients bearing lower tumor burdens, the first-generation agents remain a pertinent choice.

ALK-TKIs

In NSCLC, around 5% of patients exhibit an ALK gene rearrangement, with the EML4-ALK fusion gene being the most common.[74] Notably, tumors harboring the EML4-ALK fusion manifest heightened sensitivity to ALK-targeted inhibitors, highlighting the imperative of screening for this specific gene fusion in NSCLC cases. The FDA has sanctioned several therapeutic agents for advanced NSCLC cases presenting with ALK fusion.

Crizotinib emerged as the pioneering therapeutic for ALK-positive cases, distinguished by its small molecular stature and multitarget capabilities, efficaciously targeting both ALK and ROS1 fusion genes in a dose-responsive fashion. The landmark PROFILE1014 study[75] highlighted crizotinib's advantage over the conventional first-line pairing of pemetrexed and platinum for late-stage ALK-positive NSCLC cases, with a notable improvement in both mOS and mPFS. As such, crizotinib's effectiveness transcends standard chemotherapy, marking it as the preferred therapeutic avenue for ALK-positive NSCLC.

While crizotinib stands as a cornerstone for ALK-positive cases, resistance or intolerance occasionally emerges. As a response, second-generation ALK-TKIs came into the limelight, with half of crizotinib-refractory patients showing receptiveness. The ASCEND-4 trial[76] posited that patients with untreated late-stage ALK-positive NSCLC on ceritinib achieved a considerably longer mPFS than those on standard chemotherapy (either pemetrexed-platinum or carboplatin). However, its pronounced side effects constrained its primary therapeutic deployment. The J-ALEX research[77] found that after an approximate 18-month surveillance, alectinib's mPFS remained elusive compared to crizotinib's 11.1 months. Alectinib's superior safety trajectory thus marked it as the frontrunner for ALK-rearranged NSCLC therapy. The ALTA-1L trial[78] heralded brigatinib's post-crizotinib mPFS at 24 months in ALK-positive NSCLC, with notable intracranial relief and a protracted mPFS, accentuating its continuous advantage over crizotinib as a first-line option in advanced ALK-positive NSCLC.

Considering structural disparities and consequent resistance mutations seen with second-generation ALK-TKIs, lorlatinib, a potent brain-permeable ALK/ROS1 inhibitor, emerged as a third-generation alternative. The CROWN trial,[79] enrolling patients with stage IIIB/IV ALK-positive NSCLC, pitted lorlatinib against crizotinib. Preliminary data suggest that the lorlatinib arm's BICR-evaluated mPFS remained undefined, contrasting with 9.3 months in the crizotinib cohort. This marks a substantial 73% decline in the risk of disease advancement or mortality when treated with lorlatinib versus crizotinib.

The NCCN guidelines predominantly recommend alectinib, brigatinib, and lorlatinib for ALK-positive patients, demoting crizotinib to a secondary option. Nevertheless, retrospective analysis posits an mOS of 86 months for ALK-positive NSCLC cases, hinting at a diminished emphasis on long-term mOS. Consequently, the pronounced mPFS superiority of alectinib over crizotinib emerges as a decisive factor for selection. Economically speaking, crizotinib remains a feasible option for individuals bearing minimal tumor burdens. However, recognizing the elevated prevalence of brain metastases among ALK fusion patients, the consistent efficacy of both second-generation and third-generation ALK inhibitors is evident. Therefore, for patients presenting with brain metastases at diagnosis, crizotinib is not a judicious selection.

KRAS G12C Inhibitor

Sotorasib stands as the inaugural global inhibitor tailored for KRAS mutations. It irreversibly binds to the distinctive cysteine of KRAS G12C, supplanting glycine and thereby locking the protein in its dormant GDP-bound form, mitigating downstream signaling without perturbing wild-type KRAS. The FDA endorsed Sotorasib as the primary targeted therapy for KRAS G12C mutated advanced NSCLC, drawing insights from the CodeBreak 200 trial.[80] This phase 3, randomized, open-label trial illuminated sotorasib's potency in monotherapy for patients with advanced NSCLC harboring the KRAS G12C mutation. Demonstrated results encompassed a 37.1% overall response rate (ORR), a 6.8-month mPFS, and a 12.5-month mOS. The adverse events linked to the treatment were largely mild and controllable, fostering either neutral or enhanced patient prognosis.

Frankly, I harbor significant enthusiasm for the potential synergy of sotorasib and immunotherapy. Data stratification from various trials and consolidated insights from numerous meta-analyses position the KRAS mutation, notably the KRAS G12C variant, as a favorable harbinger for immunotherapeutic response. The CodeBreaK 100/101[81] trial illuminated that amalgamating sotorasib with either pembrolizumab or atezolizumab culminated in a confirmed response for 17 patients over a median scrutiny of 12.8 months, an ORR standing at 29%, and an mOS extending to 15.7 months when deploying combination therapy. While efficacy metrics are encouraging, it is paramount to also scrutinize TRAEs. Hepatic complications stemming from this therapeutic pairing were notably accentuated, and the therapeutic gains did not eclipse these adverse manifestations to render them negligible.

The eagerly anticipated debut of the KRAS therapeutic has taken center stage. After a prolonged dormancy, KRAS G12C inhibitors have recently emerged as front-runners, reflecting the unwavering dedication of foundational researchers and clinical experts. Yet, mirroring the trend observed with EGFR-TKIs, I argue that there is an overemphasis on drugs singularly targeting the KRAS G12C mutation. The scientific community holds high hopes for the advent of treatments tailored to other KRAS mutations.

ROS1-TKI

Owing to the marked homology between ROS1 and ALK, crizotinib has elicited notable therapeutic outcomes in patients

with NSCLC harboring ROS1 translocations. The Profile1001 trial[82] illuminated crizotinib's substantial antitumoral potency in individuals clinically identified with advanced ROS1-rearranged NSCLC. The agent mustered an impressive response rate of 72%, with a complete response observed in 6% of participants. An mPFS of 19.3 months was reported, with minimal adverse events. All ROS1 fusion variants manifested therapeutic advantages. Entrectinib, a potent multikinase inhibitor, targets ROS1, ALK, and TRK. Its capacity to traverse the blood-brain barrier renders it adept at countering brain metastases. In vitro analyses indicate that its anti-ROS1 efficacy supersedes crizotinib's by a factor of 40. Data from the phase II STARTRK-2 basket trial[83] upheld entrectinib's efficacy in a cohort of 161 patients with ROS1-positive NSCLC previously untreated, where 34.8% bore brain metastases at baseline. The latest scrutiny unveiled an ORR of 67.1% with an mPFS extending to 15.7 months. Lorlatinib is a potent TKI targeting both ALK and ROS1, with pronounced CNS penetration, showing potential benefits for patients with brain metastases. Presently, lorlatinib's efficacy against ROS1-positive NSCLC is under phase I evaluation.[84] In addition, studies on drugs like brigatinib, cabozantinib, ceritinib, repotrectinib, and taletrectinib have demonstrated their activity against ROS1.

As ROS1 inhibitors continue to evolve, determining treatment strategies for ROS1-translocated NSCLC becomes more intricate. Selecting the right treatment now requires careful consideration of CNS activity, resistance patterns, and patient tolerability. Although the medical community still grapples with choices for first-line therapies, advances in molecular biology and genomics promise to further refine and expand the range of targeted therapies for ROS1 rearrangements.

BRAF-TKI

The BRAF V600E mutation is not exclusive to NSCLC. Interestingly, this genetic anomaly is also implicated as a factor for resistance to EGFR-TKI in NSCLCs, and its occurrence is far from infrequent. The intricacies of the BRAF gene are intriguing. Across diverse cancer types, while the V600E mutation stands out with therapeutic significance, other mutations in the BRAF gene often have limited clinical implications. Specifically in lung cancer, it is the V600E mutation that holds paramount therapeutic relevance.

In a phase II clinical trial assessing the combination of dabrafenib and trametinib for treatment,[85] 36 patients with previously untreated BRAF V600E mutation–positive advanced NSCLC were included. The study found a radiographic ORR of 64%, which encompassed 2 complete responses and 21 partial responses. Researchers determined the mPFS to be 10.9 months. Adverse events were ubiquitous; every participant experienced at least one, ranging in severity. Notably, 25 patients (69%) encountered grade 3 or more severe adverse events.

The FDA has granted approval to both dabrafenib and trametinib for the treatment of patients harboring BRAF V600E mutation–positive conditions that have advanced post chemotherapy. Drawing from the outcomes of the combined therapy trials, experts posit that the synergistic approach may proffer superior therapeutic advantages compared to single-agent treatment.

MET Inhibitor

Studies have shown that crizotinib exerts strong antitumor effects in patients with NSCLC with MET amplifications and exon 14 skipping mutations. Yet, for those who do not respond to crizotinib, capmatinib, an MET inhibitor, presents as a potent therapeutic alternative. Demonstrating pronounced selectivity and responsiveness, capmatinib markedly improves survival outcomes, particularly in patients with NSCLC with MET exon 14 skipping mutations. Subsequently, the FDA has accorded accelerated approval to capmatinib for the treatment of patients with advanced NSCLC with these specific mutations,[86] establishing it as the inaugural FDA-sanctioned targeted therapy for this subset of patients.

Furthermore, the FDA has sanctioned the use of another MET inhibitor, tepotinib, for patients with MET-positive advanced NSCLC. A phase II trial[87] encompassing 152 patients with NSCLC with MET exon 14 skipping mutations evaluated the efficacy of tepotinib. Within this cohort, the objective response rate was 46%. Tepotinib not only exhibits pronounced selectivity but also demonstrates significant central nervous system penetration. Notably, peripheral edema emerged as the predominant adverse event in patients experiencing grade 3 or higher toxicities. Concurrently, emerging MET-targeted inhibitors like savolitinib and cabozantinib are advancing through clinical trials,[88–90] with their therapeutic potential yet to be ascertained.

RET Inhibitor

In recent years, the advent of highly selective RET inhibitors has revolutionized the treatment approach for patients with NSCLC with RET gene fusions. The results of the ARROW study[91] underscore this advancement: pralsetinib exhibited an ORR of 62% and an mPFS of 16.5 months in patients previously treated with platinum. In contrast, for those untreated with platinum, the ORR rose to 73% with an mPFS of 12.8 months. Notably, a substantial portion of patients with RET fusion-positive NSCLC presented with brain metastases. In the ARROW study, ~38% of participants had brain metastases, and remarkably, 3 achieved complete remission. In terms of safety, pralsetinib demonstrated good tolerability, with the majority of adverse events being of grades 1-2. Common treatment-related side effects included neutropenia, anemia, and hypertension. Based on these findings, the FDA approved pralsetinib for adult patients with metastatic RET fusion-positive NSCLC.

Immune checkpoint inhibitors have heralded a new era in treating metastatic NSCLC without driver mutations. Yet, their therapeutic efficacy in patients with NSCLC harboring driver mutations like EGFR and ALK remains underwhelming. Notably, most RET-positive NSCLC cases exhibit diminished PD-L1 expression coupled with a low tumor mutation burden. Despite the groundbreaking advances ICIs offer in lung cancer therapy, their efficacy in RET-positive NSCLC appears suboptimal, with anticipated benefits remaining elusive. As per NCCN guidelines, in advanced or metastatic NSCLC, if markers like RET positivity are identified, the administration of PD-1/PD-L1 inhibitors is advised against.[92] Neither monotherapy with ICIs nor a combined regimen of ICIs and chemotherapy is advocated as the primary systemic treatment. Future studies should delve deeper into the resistance patterns of advanced RET fusion-positive NSCLC to RET inhibitors. Emphasis should be on pioneering treatment modalities that concurrently inhibit RET and related resistance pathways. Moreover, the ongoing assessment of emerging selective RET-TKIs will be crucial, aiming to broaden the therapeutic horizons for patients with RET fusion-positive NSCLC.

Angiogenesis Inhibitors

Targeting the VEGF-VEGFR interaction with monoclonal antibodies or downstream signaling inhibitors curtails tumor angiogenesis, facilitating antitumor outcomes. Presently, 3 antiangiogenic agents—bevacizumab (a VEGF inhibitor), anlotinib (a TKI), and endostar (a recombinant human endostatin)—are approved for advanced NSCLC treatment (as detailed in Table 2). Yet, only a subset of patients gain from isolated antiangiogenic therapy. Hence, the synergy of antiangiogenic agents with chemotherapy, EGFR-TKIs, and immune checkpoint inhibitors has become a pivotal research avenue.

Monoclonal Antibody to VEGF/VEGFR

Bevacizumab was pioneered as the first angiogenesis inhibitor sanctioned for the primary treatment of advanced NSCLC. It is a humanized monoclonal antibody designed to bind VEGF-A, thwarting its interaction with VEGFR and consequently neutralizing the VEGF signaling pathway. This process not only regularizes malformed blood vessels but also augments the potency of other antitumor agents. The ECOG 5499 trial,[58] which integrated bevacizumab into the first-line regimen for advanced NSCLC, evidenced that pairing it with paclitaxel/carboplatin amplifies patient OS, mPFS, and ORR, solidifying its cornerstone status in advanced NSCLC chemotherapy. The phase II JO25567 trial[93] from Japan evaluated the pairing of erlotinib with bevacizumab against erlotinib monotherapy for treating EGFR mutation–positive advanced NSCLC. Remarkably, the combination registered an mPFS of 16.0 months, overshadowing erlotinib's 9.7 months, slashing disease progression risk by 46%. Adverse reaction severity remained consistent between groups, with no marked disparities in ORR and mOS, advocating its frontline status for advanced cases. There is a pronounced synergy between immunotherapy and antiangiogenic treatments. Angiogenesis modulators predominantly dictate immune responses, curtailing T-cell tumor infiltration and modulating immune cell function. Atezolizumab,[94] when combined with bevacizumab/chemotherapeutic agents, emerges as a prime contender for treating metastatic NSCLC. Irrespective of PD-L1 expression or EGFR/ALK gene fluctuations, atezolizumab considerably augments OS and PFS. Consequently, the fusion of bevacizumab with immunotherapy reveals a tantalizing therapeutic prospect, supported by numerous ongoing randomized trials with prolonged monitoring.

Ramucirumab is a human IgG1 monoclonal antibody targeting the extracellular domain of VEGFR-2. By binding to VEGFR-2, it disrupts its interaction with VEGF ligands, subsequently halting the associated signaling pathway and the spread and migration of endothelial cells. Both the FDA and EMA have endorsed the efficacy of combining ramucirumab with docetaxel for treating advanced NSCLC as a second-line therapy. Clinical data[95] have advocated for concurrent blockade of EGFR and VEGF pathways in EGFR mutant NSCLC. The RELAY trial,[96] which assessed 449 patients, revealed that while the combination of ramucirumab and erlotinib had a higher incidence of primarily grade 1-2 side effects (notably hypertension, proteinuria, and bleeding) compared to a placebo and erlotinib, it demonstrated superior PFS for initial treatment of metastatic patients. This approach is recommended for patients with NSCLC with EGFR mutations, excluding those with central brain metastases. The Lung-MAP substudy S1800A[97] examined the pairing of ramucirumab with pembrolizumab against standard-of-care (SOC) in patients with advanced NSCLC previously treated with immunotherapy. The findings displayed an mOS of 14.5 months for the combined treatment versus 11.6 months for the SOC. However, both PFS and ORR were analogous between the groups. While the significant extension in OS is evident, the PFS and ORR similarities are somewhat perplexing. Nevertheless, under certain conditions, this regimen could be a viable therapeutic alternative.

TKI

Anlotinib is a contemporary multitarget TKI developed to counteract tumor angiogenesis and growth signals. It chiefly acts on receptors such as tyrosine kinase, VEGFR(1-3), EGFR, FGFR(1-4), PDGFR(α/β), and stem cell factor receptors. The ALTER-L004 phase II trial,[98] which encompassed multiple centers, evaluated the combined effects of anlotinib and icotinib on 60 patients with NSCLC with EGFR-sensitive mutations. The combined treatment resulted in an mPFS of 15.1 months and an mOS of 30.0 months. Notably, the side effects, including hypertension and elevated thyroid-stimulating hormone levels, were manageable. Given these promising results,

TABLE 2. Antiangiogenics in NSCLC

Drug name	Clinical trial	Combined agent	Median OS (mo)	Median PFS (mo)	Side effects
Monoclonal antibody to VEGF/VEGFR					
Bevacizumab	ECOG 5499	Carbo/Taxo	12.3	6.2	Hypertension/fatigue/ diarrhea/abdominal pain
	JO25567	Erlotinib	24.0	16.0	
	NCT02366143	Atezolizumab	19.2	8.3	
Ramucirumab	REVEL	Docetaxel	10.5	4.5	Skin rash/hypertension/ diarrhea/anorexia, oral mucositis/abnormal LEF proteinuria/ hyperlipemia/fatigue
	RELAY	Erlotinib	—	19.4	
	Lung-MAP-S1800A	Pembrolizumab/SOC	14.5	4.5	
TKI					
Anlotinib	ALTER-L004	Icotinib	30.0	15.1	Hypertension/proteinuria/fatigue/abnormal LEF/abnormal thyroid function
Nintedanib	LUME-Lung 1	Docetaxel	12.6	12.6	
Vascular endostatin					
Endostar	HELPER	EP synchronous chemotherapy	34.7	13.3	Leukopenia and oesophagitis

SOC indicates standard of care (docetaxel/ramucirumab, docetaxel, gemcitabine, and pemetrexed).

the combination of anlotinib and icotinib stands as an effective and tolerable first-line therapeutic option for patients with EGFR mutation–positive advanced NSCLC, regardless of the presence of other concurrent mutations. Subsequently, anlotinib has received approval from China's National Medical Products Administration for treating patients with advanced NSCLC. Nintedanib is a small molecule TKI that predominantly targets VEGFR, PDGFR, and FGFR, inhibiting their pathway activations. The LUME-Lung 1 trial[99] assessed the efficacy and safety of combining docetaxel with either nintedanib or a placebo for patients with NSCLC as a second-line treatment. The nintedanib group exhibited notably extended PFS compared to the placebo group, though OS differences were marginal. Intriguingly, patients with adenocarcinoma witnessed a marked extension in OS when treated with nintedanib. Thus, the combination of nintedanib and docetaxel emerges as a potent second-line therapeutic strategy for advanced NSCLC, particularly benefiting patients with adenocarcinoma. Given that most small molecule TKIs possess broad-spectrum targets and often lack selectivity, their discernible side effects, and suboptimal therapeutic impacts warrant further investigations into optimal combination regimens and potential biomarker correlations.

Vascular Endostatin

Endu stands out as a potent antiangiogenic agent, targeting the migration of endothelial cells pivotal for blood vessel development. Its precision in obstructing tumor angiogenesis deprives tumor cells of essential nutrients, curbing their growth or metastasis, thereby enhancing patient survival. The HELPER study[100] highlighted that Endu, when used in tandem with the EP regimen and concurrent radiotherapy for inoperable stage III NSCLC, exhibited superior survival advantages, with side effects deemed manageable. These findings hint at a transformative approach in tumor radiotherapy, with concurrent chemoradiotherapy paired with antitumor angiogenesis targeted treatments. This might redefine therapeutic approaches for advanced NSCLC. While Endu's side effects predominantly concern the cardiovascular system, they are generally mild and reversible.

Antiangiogenic drugs, while groundbreaking in cancer therapy, present a nuanced position in treatment paradigms. Rather than label them strictly as targeted therapy, I would deem them "pan-targeted therapy." They operate beyond the realm of specific gene mutations, focusing instead on thwarting angiogenesis, setting them apart from chemotherapy. While their anticancer mechanisms and clinical efficacy spotlight them in certain cancers like HCC, RCC, and GIST, in NSCLC, their role is more supportive than central. Tumor treatment remains intricate and multifaceted. Simply inhibiting a major signaling pathway often foreshadows impending resistance. Yet, there is optimism: the ideal counterpart for antiangiogenic drugs might still be unveiled, potentially revolutionizing future treatment strategies.

Cell Cycle and Signaling Pathway Inhibitors

CDK4/6 Inhibitors

CDK4/6 inhibitors, like palbociclib, initiate tumor cell G1 phase arrest by targeting pivotal nodes in the ER pathway, leading to enhanced antitumor responses (as detailed in Table 3). Palbociclib, the pioneering CDK4/6 inhibitor, selectively blocks CDK4/6, reinstating cell cycle oversight and curbing tumor cell growth.[101] While most palbociclib NSCLC studies are early-stage, 1 phase II trial[102] encompassing patients with p16 loss and first-line treatment failure saw a 50.0% disease control rate, with an mPFS of 3.2 months and an mOS of 7.7 months. Impressively, stable disease patients exhibited an mPFS of 6.1 months and an mOS of 16.5 months, outperforming patients with progressing disease. This underscores PFS and OS as superior clinical endpoints for CDK4/6 inhibitors compared to ORR. Another drug, abemaciclib, studied in advanced NSCLC, did not surpass docetaxel's efficacy in second-line treatment for advanced squamous lung cancer when used as monotherapy.[103]

In conclusion, while CDK4/6 inhibitors show some promise in advanced NSCLC, their standalone efficacy remains limited, prompting a search for improved therapeutic approaches. The synergistic potential exists when combining CDK4/6 inhibitors with other drugs, though much of this evidence is preclinical and awaits clinical validation. A phase II trial[104] assessed the combination of abemaciclib with gemcitabine, docetaxel, and pemetrexed in metastatic NSCLC, underscoring the regimen's safety and tolerability for patients with untreated advanced/metastatic NSCLC. Another ongoing phase I/II trial[105] pairs inimetinib with palbociclib for advanced NSCLC. Despite CDK4/6 inhibitors' suboptimal monotherapeutic outcomes in NSCLC, coadministration with other drugs often yields improved results. Identifying molecular-level patient subsets with enhanced response rates remains a research priority.

TABLE 3. Cell Cycle and Signaling Pathway Inhibitors in NSCLC

Drug name	Combined agent	Clinical trial	Phase	State
CDK 4/6 inhibitors				
Palbociclib	—	NCT01291017	II	Completed
	Inimetinib	NCT03170206	I/II	Active, not recruiting
Abemaciclib	—	NCT02152631	III	Active, not recruiting
	Gemcitabine/docetaxel/pemetrexed	NCT02450539	II	Completed
Pan-PI3K inhibitors				
BKM120	—	NCT01297491	II	Completed
	Carbo and pemetrexed	NCT01723800	I	Completed
PX-866	Docetaxel	NCT01204099	I/II	Completed
Selective PI3K inhibitors				
Alpelisib	—	NCT02276027	II	Completed
Idelalisib	Pembrrolizumab	NCT03257722	Ib-II	Recruiting
AKT inhibitors				
MK-2206	—	NCT01306045	II	Active, not recruiting
mTOR inhibitors				
Everolimus	—	NCT00124280	II	Completed
Sirolimus	Pemetrexed	NCT00923273	II	Terminated

PI3K/AKT/mTOR Pathway Inhibitors

In the evolving landscape of NSCLC treatment, inhibitors targeting the PI3K, AKT, and mTOR pathways are gaining attention (as detailed in Table 3). BKM120, an oral PI3K inhibitor, showcased modest antitumor effects as a standalone therapy in a phase II trial,[106] indicating potential advantages when paired with other agents. PX-866, another PI3K inhibitor, exhibited encouraging outcomes when combined with chemotherapy in initial studies.[107] Alpelisib, a specific PI3K inhibitor, was particularly effective against tumors with PIK3CA mutations or amplifications.[108] Nonetheless, due to the integral role of PI3K signaling in regular cellular processes, PI3K inhibitors can lead to notable side effects, such as insulin resistance. MK-2206, a targeted AKT inhibitor, is currently in phase II trials[109] for advanced NSCLC. On the other hand, mTOR inhibitors, like everolimus and sirolimus, have a broader spectrum of use and are being assessed in combination therapies for NSCLC.[110,111] The PI3K/AKT/mTOR pathway has captivated researchers for years. Despite the enthusiasm surrounding inhibitors targeting this pathway, their potential toxicities present substantial clinical hurdles. Looking ahead, there is optimism for emerging PI3K inhibitors that combine potent anticancer effects with minimized side effects. In summary, preliminary data from CDK4/6 inhibitors and agents targeting the PI3K/Akt/mTOR pathway in NSCLC have fallen short of expectations in terms of overall efficacy. For more promising outcomes, future research should focus on tailored patient selection through precise biomarker-driven strategies and consider combination therapies to optimize therapeutic responses in NSCLC.

DISCUSSION

In our detailed review, we explore the nuanced realm of targeted therapies in NSCLC, discussing molecular targets with proven therapeutic benefits. Despite the wide array of 53 NSCLC treatments, many patients still find effective pharmacological interventions elusive. The current trend in NSCLC and solid tumor treatment heavily favors immunotherapy, with promising prospects in CAR-T/NK cell therapies and tumor vaccines. However, the tempered growth of PD-1/PD-L1 medications signals a transformative trend in the medical landscape: drugs showing limited efficacy in clinical trials are progressively being sidelined. This evolution mirrors an adaptive and discerning approach to cancer treatment, where the focus is pivoting toward therapies demonstrating more substantial clinical benefits. The predominance of PD-1/PD-L1 immunotherapy is being challenged by the necessity for combination therapy, bringing traditional chemotherapy and targeted drugs back into the spotlight.

As research delves deeper each year, molecular biotechnology ushers in a new era of precision therapy for NSCLC. Targeted drugs, noted for their high efficacy, safety, and convenience, are providing better choices for patients. With the discovery of more signaling pathways and driving factors, drugs are becoming increasingly diverse. Each generation of medication brings unique characteristics, presenting a challenge in choosing the most suitable targeted drug for each patient, a key focus for future research.

Current treatments for EGFR mutations include 2 main approaches: using osimertinib post resistance to first-generation or second-generation drugs, or as a first-line treatment. The preference between these strategies, influenced by PFS outcomes, is an area for ongoing exploration. The "diamond mutation," ALK, with its lower mutation rate and effective treatments like alectinib, also presents resistance challenges, with newer generation inhibitors being developed. For BRAF mutations, treatments like dabrafenib combined with trametinib are used, but resistance remains a challenge, calling for more research into combination therapies. When targeted therapies face resistance, the choice of subsequent treatment becomes crucial. Clinically, re-biopsy and further genetic testing are preferred to determine the mutation status. If re-biopsy is not feasible, ctDNA analysis can guide treatment. If no significant mutations are detected, chemotherapy, immunotherapy, or combined treatments become viable options.

In our forward-looking research agenda, we have pinpointed pivotal areas: (1) addressing ongoing challenges in drug resistance, particularly focusing on developing advanced EGFR-TKIs and investigating the potential of antibody-drug conjugates like DS-8201; (2) exploring the promise of bispecific antibodies, with a spotlight on amivantamab; (3) highlighting the need for integrative treatment strategies, moving beyond the constraints of single-agent therapies; and (4) harnessing the power of big data and artificial intelligence to unveil novel drug targets. These directions resonate with the deepening understanding of lung cancer's molecular intricacies and the enthusiastic drive to uncover new treatment avenues and drugs to improve patient outcomes.

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