Role of signaling pathways in lung cancer development and advances in targeted therapies (Review)

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Abstract. Lung cancer is one of the most prevalent and lethal cancers worldwide, markedly contributing to cancer-related morbidity and mortality. The development and progression of lung cancer involve intricate signaling pathways that regulate essential cellular processes such as proliferation, survival, metastasis and resistance to therapy. These pathways can be disrupted by genetic mutations, epigenetic alterations or environmental factors including tobacco smoke and air pollution. In the past decade, considerable advancements have been made in elucidating the molecular mechanisms underlying lung cancer pathogenesis. This progress has facilitated the identification of key oncogenic drivers and the development of targeted therapies that have revolutionized treatment options. The present review provides an overview of critical signaling pathways implicated in lung cancer pathogenesis, including EGFR, anaplastic lymphoma kinase, KRAS, PI3K/AKT/mTOR and immune checkpoints. It also examines recent developments in targeted therapies such as next-generation tyrosine kinase inhibitors, monoclonal antibodies and combination strategies along with their clinical implications. By highlighting the molecular complexities associated with lung cancer and emerging therapeutic innovations, the present review highlights the significance of precision medicine in improving patient outcomes and shaping future treatments for lung cancer.

Contents

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1. Introduction

Lung cancer remains one of the most common and lethal cancers worldwide, markedly contributing to cancer-related illness and death (1,2). It is the leading cause of cancer mortality, with >2 million new cases diagnosed each year and a persistently low 5-year survival rate, especially in advanced stages (3-5). The disease is mainly divided into two subtypes based on histological and molecular features: Non-small cell lung cancer (NSCLC), which accounts for ~85% of cases, and small cell lung cancer (SCLC), representing the remaining ~15% and known for its rapid growth and early spread (6). NSCLC includes adenocarcinoma, squamous cell carcinoma and large cell carcinoma, each with unique molecular profiles and clinical behaviors (7).

Lung cancer development and progression are driven by complex signaling pathways that regulate fundamental cellular

processes such as proliferation, survival, metastasis and resistance to therapy (8-10). Dysregulation of these pathways often results from genetic mutations, epigenetic alterations or environmental exposures, including tobacco smoke, air pollution and carcinogens such as asbestos and radon (11-14). Over the past decade, notable progress has been made in elucidating the molecular mechanisms underlying lung cancer pathogenesis (15,16). Advances in genomic sequencing have enabled the identification of key oncogenic drivers, including mutations in EGFR, rearrangements in anaplastic lymphoma kinase (ALK), and mutations in KRAS (17-20). These discoveries have led to the development of targeted therapies that have fundamentally transformed the clinical management of lung cancer (21). For example, EGFR-tyrosine kinase inhibitors (TKIs), such as gefitinib, erlotinib and osimertinib, have demonstrated robust efficacy in patients with EGFR-mutant NSCLC, markedly improving both progression-free survival (PFS) and overall survival (OS) compared with conventional chemotherapy (22-25). Similarly, ALK inhibitors, including crizotinib, alectinib and lorlatinib, have markedly improved outcomes for patients with ALK-rearranged NSCLC, offering durable responses and enhanced quality of life (26-28). KRAS mutations are present in 25-30% of lung adenocarcinomas and have historically been considered untreatable with drugs due to the lack of suitable binding pockets for therapeutic intervention (29,30). However, recent breakthroughs, particularly the development of KRAS G12C inhibitors such as sotorasib and adagrasib, have yielded promising clinical results, opening new therapeutic avenues for this patient population (30-32).

In addition to well-characterized signaling pathways, the PI3K/AKT/mTOR axis serves a central role in tumor growth and survival in lung cancer (33). Activation of this pathway is frequently driven by mutations or amplifications in upstream regulators such as EGFR, KRAS and PI3K itself (34). Dysregulation of the PI3K/AKT/mTOR pathway contributes to resistance against both chemotherapy and targeted therapies, thereby positioning it as a key focus of ongoing research (35). Current preclinical and clinical investigations are assessing inhibitors targeting components of this pathway, including PI3K, AKT and mTOR, both as monotherapies and in combination regimens, with the aim of overcoming therapeutic resistance and improving patient outcomes (36-38). The involvement of immune checkpoint pathways, such as programmed cell death protein 1 (PD-1)/programmed death receptor ligand-1 (PD-L1) and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), in tumor immune evasion has been established (39,40). These insights have facilitated the development of immune checkpoint inhibitors (ICIs), which have markedly reshaped treatment paradigms for both NSCLC and SCLC (41). Therapeutic agents such as pembrolizumab, nivolumab and atezolizumab have demonstrated clinically meaningful improvements in survival, particularly among patients with high PD-L1 expression or elevated tumor mutational burden (42-44). Beyond enhancing clinical outcomes, these agents have also redefined standard treatment practices, with the combination of immunotherapy with chemotherapy now widely adopted as a first-line therapy (45).

The present review provides an overview of key signaling pathways involved in lung cancer pathogenesis, including EGFR, ALK, KRAS, PI3K/AKT/mTOR and immune checkpoint pathways. It also highlights recent advances in targeted therapies, such as next-generation TKIs, monoclonal antibodies and combination strategies, and their clinical implications.

2. Key signaling pathways in lung cancer

EGFR pathway. The EGFR pathway represents one of the most extensively studied and clinically significant signaling cascades in NSCLC (46). This pathway is crucial for regulating essential cellular processes, including proliferation, survival, differentiation and migration (47,48). In NSCLC, specific genetic alterations in the EGFR gene, most notably exon 19 deletions and the L858R point mutation in exon 21, lead to constitutive activation of the receptor tyrosine kinase (RTK) (49,50) (Fig. 1). Such activation results in ligand-independent dimerization and subsequent autophosphorylation (48-50). These oncogenic changes initiate downstream signal transduction through key pathways including the PI3K/AKT/mTOR and RAS/RAF/MEK/ERK cascades, ultimately driving uncontrolled cell proliferation, suppression of apoptosis and enhanced tumor viability (51,52). The recognition of EGFR mutations as driver oncogenes in NSCLC has fundamentally reshaped the therapeutic approach to lung cancer (49). First-generation EGFR-TKIs, including gefitinib and erlotinib, have demonstrated notable efficacy in patients harboring these mutations, leading to a substantial improvement in PFS compared with conventional chemotherapy (53). These small-molecule inhibitors competitively bind to the ATP-binding site of the EGFR tyrosine kinase domain (TKD), effectively obstructing downstream signaling (54). The subsequent development of second-generation TKIs (such as afatinib and dacomitinib) alongside third-generation inhibitors (such as osimertinib) has further enhanced clinical outcomes by addressing resistance mechanisms whilst increasing target specificity (55-57).

Despite these advancements, the development of acquired resistance to EGFR-TKIs remains a major clinical challenge. The most common mechanism of resistance is the T790M gatekeeper mutation in exon 20, which increases the affinity of the receptor for ATP and physically impedes TKI binding (58). Other mechanisms contributing to resistance include MET amplification, human epidermal growth factor receptor (HER)2 amplification, histologic transformation into SCLC, and activation of alternative signaling pathways (59-64). To overcome these challenges, ongoing research is focused on the development of fourth-generation EGFR inhibitors, combination therapies targeting parallel signaling pathways and novel therapeutic approaches such as antibody-drug conjugates and bispecific antibodies directed against EGFR (65,66).

The evolution of EGFR-targeted therapies in NSCLC exemplifies a paradigm for precision medicine in oncology, wherein tumor molecular profiling directly informs clinical decision-making. Current clinical guidelines emphasize the importance of comprehensive molecular testing at both initial diagnosis and during disease progression to identify actionable genetic alterations and mechanisms of therapeutic resistance (66). Furthermore, the integration of liquid biopsy methodologies for ctDNA analysis has facilitated dynamic monitoring of EGFR mutation status and the detection of emerging resistance mutations, thereby enabling more

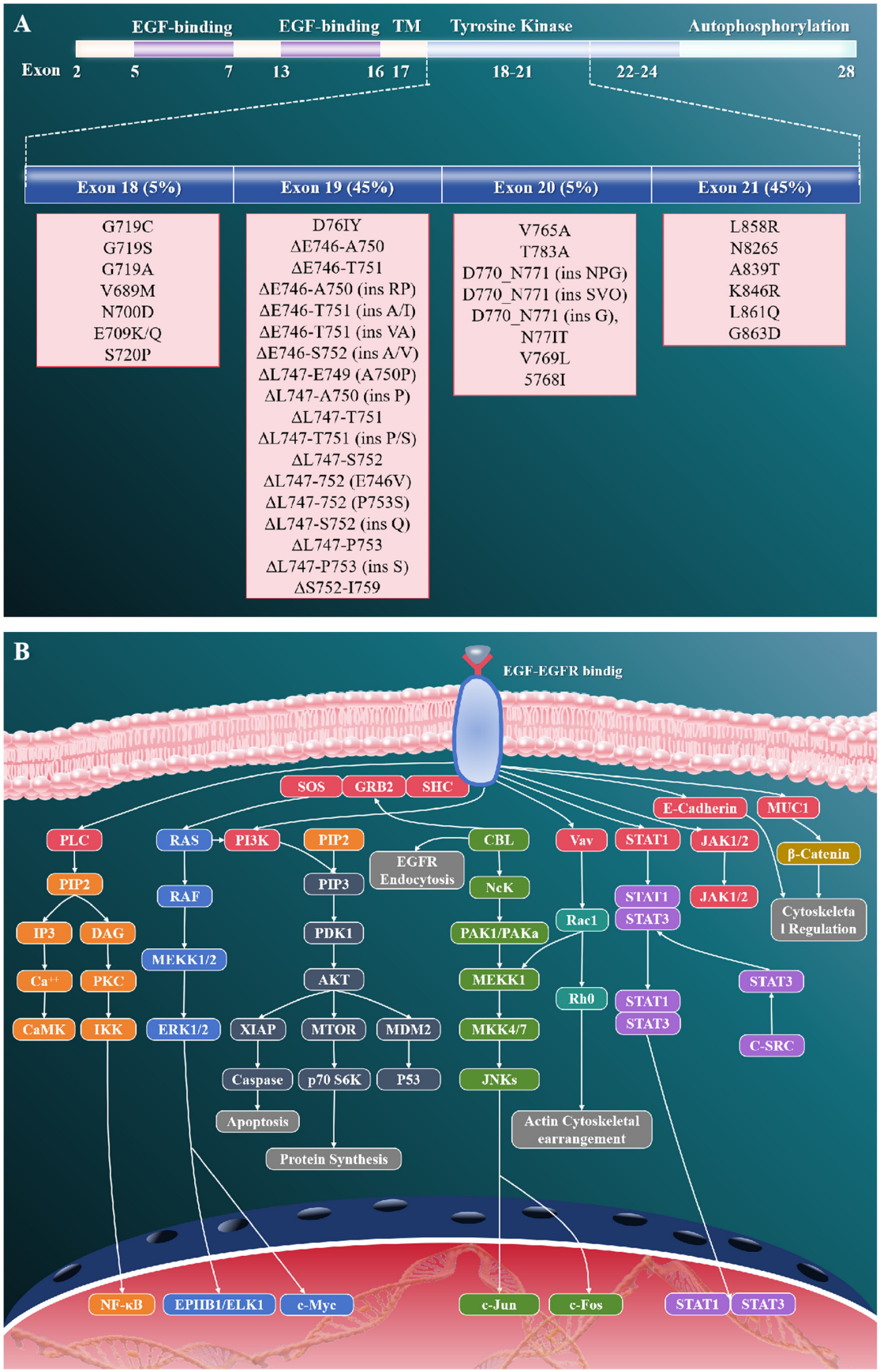

Figure 1. Role of EGFR signaling in the development of lung cancer. (A) The EGFR pathway serves a central role in the pathogenesis of NSCLC. Mutations within the EGFR kinase domain, such as exon 19 deletions, L858R and T790M, markedly increase EGFR kinase activity. (B) This hyperactivation subsequently initiates a cascade of downstream signaling pathways, including MAPK, PI3K/Akt/mTOR and IL-6/JAK/STAT3, all of which contribute to tumorigenesis in NSCLC cells. EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; MAPK, mitogen-activated protein kinases; PI3K, phosphoinositide 3-kinase, Akt, protein kinase B; mTOR, mammalian target of rapamycin; IL-6, interleukin-6; JAK, janus kinase; STAT3, signal transducer and activator of transcription 3.

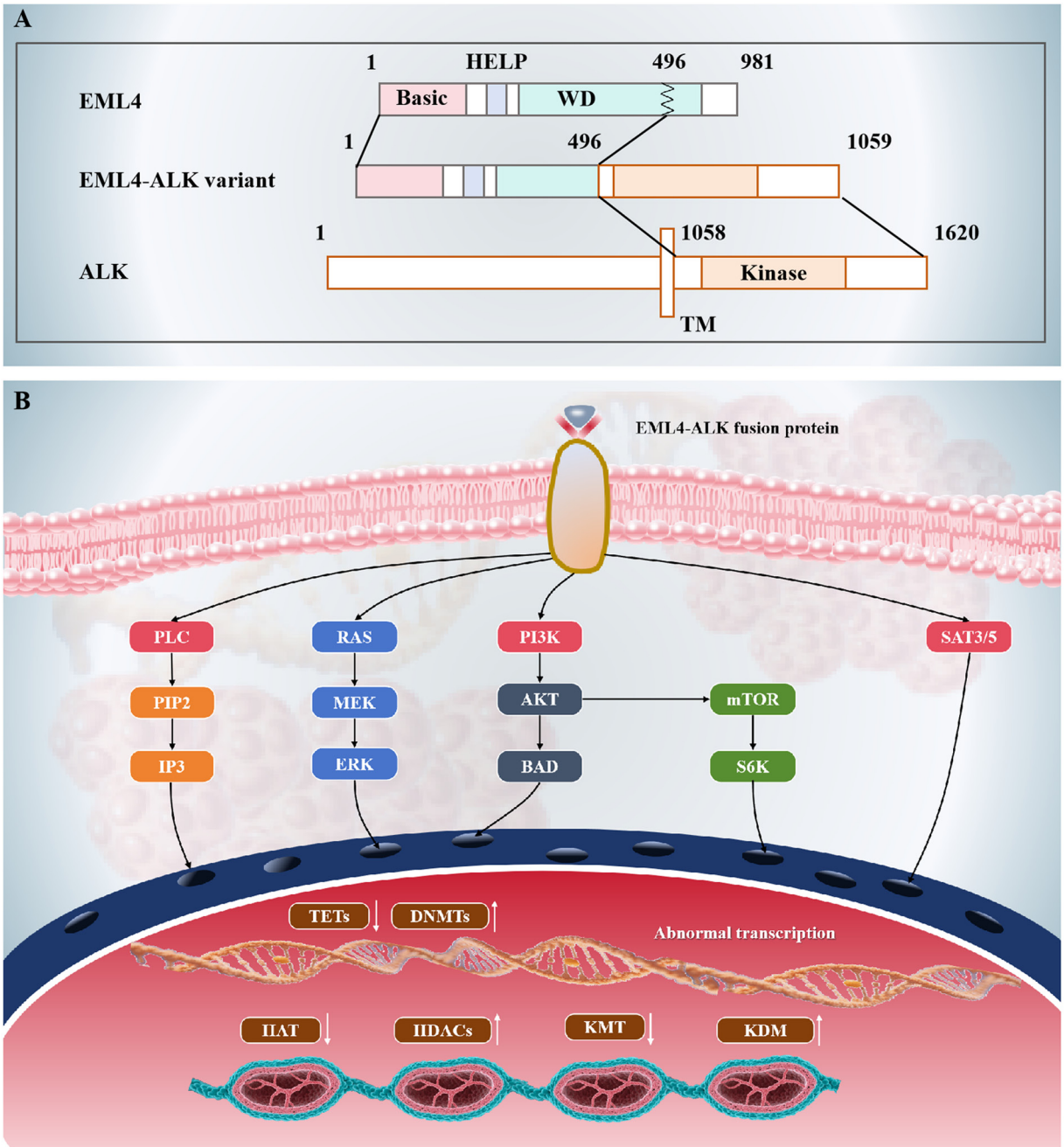

Figure 2. EML4-ALK fusion and its signaling network. (A) Schematic diagram illustrating the fusion between the N-terminal portion of EML4, which includes its basic region, the HELP domain, part of the WD-repeat region and the intracellular domain of ALK containing the tyrosine kinase domain. Notable, the TM domain is missing in the final fusion protein. (B) As a constitutively active tyrosine kinase, the EML4-ALK fusion protein activates multiple key signaling pathways involved in promoting cell proliferation, survival and metastasis. EML4, echinoderm microtubule-associated protein-like 4; ALK, anaplastic lymphoma kinase; TM, transmembrane.

timely and evidence-based treatment adjustments (67,68). As the understanding of EGFR signaling biology continues to advance, it is anticipated that novel therapeutic strategies will further improve clinical outcomes for patients with EGFR-mutated NSCLC.

ALK pathway. ALK rearrangements, particularly the echinoderm microtubule-associated protein-like 4 (EML4)-ALK fusion, constitute a clinically distinct molecular subgroup in NSCLC, occurring in 3-7% of cases (69,70). This genetic aberration originates from a chromosomal inversion on chromosome 2p, leading to the fusion of the EML4 gene with the ALK gene (71). The resulting EML4-ALK fusion protein acts as a constitutively active tyrosine kinase that drives oncogenic signaling primarily through the MAPK/ERK and PI3K/AKT pathways, which are key regulators of cell proliferation, survival and metastasis (72-74) (Fig. 2). The identification of ALK rearrangements has fundamentally reshaped the therapeutic landscape for patients with ALK-positive NSCLC (75). Targeted ALK inhibitors, such as crizotinib, alectinib and lorlatinib, have demonstrated substantial clinical benefits (76-78). Crizotinib, as the first-generation

ALK inhibitor, was the first to show marked improvements in PFS and overall response rates compared with conventional chemotherapy (76). However, despite its initial efficacy, resistance to crizotinib commonly develops (typically within 1 year of treatment initiation) due to secondary mutations within the ALK kinase domain or activation of alternative signaling pathways (79).

To overcome resistance mechanisms associated with ALK inhibition, next-generation agents, such as alectinib and lorlatinib, have been developed. Alectinib, classified as a second-generation ALK inhibitor, has demonstrated superior clinical efficacy in both treatment-naïve patients and those who have developed resistance to crizotinib (77). Its enhanced central nervous system (CNS) penetration markedly improves therapeutic effectiveness against brain metastases (77). Lorlatinib, a third-generation ALK inhibitor, is specifically designed to target a broad spectrum of ALK resistance mutations and has shown potent activity in patients who have progressed after prior ALK inhibitor therapy (78).

Despite these advancements, resistance to ALK inhibitors remains a notable clinical challenge. Resistance mechanisms include on-target mutations within the ALK gene, activation of alternative signaling pathways (referred to as off-target resistance) and histological transformation (69,80,81). Current research efforts are directed toward further characterizing these resistance mechanisms and developing innovative therapeutic strategies, including combination therapies and fourth-generation ALK inhibitors-to enhance clinical outcomes for patients with ALK-positive NSCLC (82-84). The ongoing advancement of ALK-targeted therapies underscores the essential role of precision medicine in the effective management of NSCLC.

KRAS pathway. KRAS mutations represent one of the most prevalent and clinically notable genetic alterations in NSCLC, occurring in 25-30% of cases, particularly among adenocarcinoma subtypes (85). These mutations are predominantly located at codon 12 (such as G12C, G12V and G12D), with lower frequencies observed at codons 13 and 61 (86). They result in constitutive activation of the KRAS protein, thereby promoting uncontrolled cellular proliferation and survival (87). The oncogenic activity of mutant KRAS is primarily mediated through sustained activation of downstream signaling pathways, most notably the MAPK/ERK and PI3K/AKT cascades (88). These pathways regulate essential cellular functions such as cell cycle progression, metabolic regulation and evasion of apoptosis, ultimately contributing to tumor growth, metastasis and therapeutic resistance (89,90) (Fig. 3).

For decades, KRAS was considered 'undruggable' due to its lack of conventional binding pockets and its high affinity for GTP/GDP, which posed substantial challenges in the development of small-molecule inhibitors (91). However, advances in structural biology and drug discovery have fundamentally transformed the therapeutic landscape for KRAS-mutant NSCLC (92). The identification of a unique, druggable pocket adjacent to the G12C mutation site has enabled the development of covalent inhibitors that selectively target the mutant cysteine residue (93). Among these agents, sotorasib (AMG 510) and adagrasib (MRTX849) have emerged as promising therapeutic options, demonstrating notable clinical efficacy in patients with KRAS G12C-mutant NSCLC (85,94). Sotorasib, recognized as the first US Food and Drug Administration-approved KRAS G12C inhibitor, has demonstrated an objective response rate of ~37% in pretreated patients (95). By contrast, adagrasib has shown both systemic and intracranial antitumor activity, achieving a response rate of ~43% in the KRYSTAL-1 trial (96).

These groundbreaking developments have not only introduced novel therapeutic opportunities for patients with KRAS-mutant NSCLC but have also spurred extensive research into combination strategies and next-generation KRAS inhibitors. Current clinical trials are actively evaluating the potential of combining KRAS G12C inhibitors with ICIs, Src homology 2 domain-containing protein tyrosine phosphatase 2 inhibitors or other targeted agents to overcome resistance mechanisms and improve long-term clinical outcomes (97-99). Additionally, ongoing efforts are focused on developing inhibitors specifically targeting alternative KRAS mutations (such as G12D and G12V), as well as pan-KRAS inhibitors designed to benefit a broader patient population (100). Despite these encouraging advances, several challenges remain, most notably the emergence of acquired resistance and the need for more effective therapeutic approaches targeting non-G12C KRAS mutations, which highlights the critical importance of continued research in this rapidly evolving field (101,102).

PI3K/AKT/mTOR pathway. The PI3K/AKT/mTOR pathway is a highly conserved and tightly regulated signaling cascade that governs essential cellular functions such as growth, proliferation, metabolism and survival (103-105). It integrates signals from diverse extracellular stimuli, including growth factors, hormones and nutrients, to coordinate critical cellular responses necessary for maintaining homeostasis (106-108). Dysregulation of this pathway is frequently observed in multiple malignancies, particularly lung cancer, and is often driven by genetic alterations that result in constitutive activation (109). Among the most common are activating mutations in PI3K catalytic subunit α, which encodes the catalytic subunit of PI3K and leads to elevated PIP3 levels and enhanced signaling output (110). Concurrently, loss-of-function mutations or deletions in the tumor suppressor gene PTEN, a negative regulator of the pathway, further contribute to sustained pathway activation (74). Additionally, amplification or overexpression of AKT reinforces oncogenic signaling, promoting aberrant cell survival and proliferation (111). In lung cancer, these molecular alterations are associated with aggressive tumor phenotypes characterized by resistance to apoptosis, increased angiogenesis and metabolic reprogramming-all of which facilitate tumor progression and metastasis (112) (Fig. 4).

Despite compelling biological evidence supporting the therapeutic targeting of the PI3K/AKT/mTOR pathway in lung cancer, clinical development of inhibitors has encountered notable obstacles. Although preclinical studies demonstrate that PI3K, AKT and mTOR inhibitors can effectively suppress tumor growth and induce apoptosis (73,113), their clinical utility has been hampered by dose-limiting toxicities and the emergence of resistance mechanisms (73,113). Common adverse effects, such as hyperglycemia, rash, diarrhea and

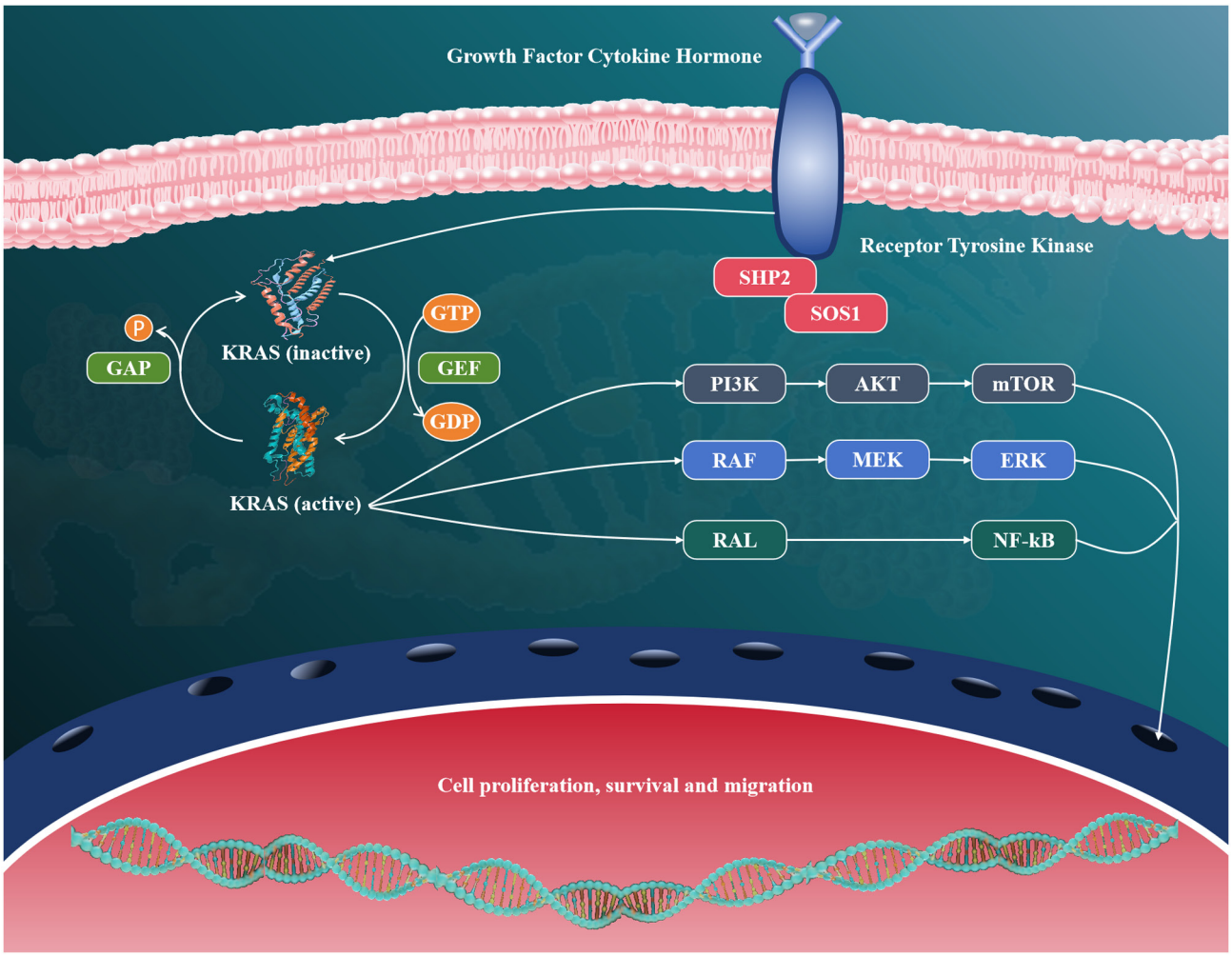

Figure 3. The KRAS protein is a critical GTPase that regulates cell proliferation, survival and differentiation through multiple signaling pathways, including the MAPK/ERK and PI3K/AKT cascades. KRAS, kirsten rat sarcoma; GTPase, guanosine triphosphatases; MAPK, mitogen-activated protein kinases; ERK, extracellular regulated protein kinases; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B.

hepatotoxicity, frequently necessitate dose reductions or treatment discontinuation, thereby compromising therapeutic efficacy (51). Resistance typically develops through compensatory activation of alternative pathways (such as MAPK/ERK), feedback loops involving RTKs or mutations in downstream effectors (114-116). These findings underscore the complexity of pathway inhibition and highlight the urgent need for innovative therapeutic strategies.

To overcome these limitations, combination therapies targeting the PI3K/AKT/mTOR pathway are under intensive investigation (117). One promising strategy involves combining pathway inhibitors with other targeted agents, such as EGFR or MEK inhibitors, to simultaneously block multiple signaling nodes and prevent adaptive resistance (118-120). For instance, dual inhibition of EGFR and PI3K/AKT/mTOR has demonstrated robust synergistic effects in preclinical models of lung cancer harboring both EGFR mutations and pathway alterations (118). Another emerging approach combines PI3K/AKT/mTOR inhibitors with ICIs, such as anti-PD-1 or anti-PD-L1 antibodies, to enhance antitumor immune responses (121,122). Preclinical evidence indicates that pathway inhibition can modulate the tumor microenvironment by reducing immunosuppressive signals and promoting T-cell infiltration, thereby augmenting the efficacy of immunotherapy (33,123). Ongoing clinical trials are evaluating these combinatorial approaches with the goal of improving clinical outcomes and overcoming resistance in patients with lung cancer.

Immune checkpoint pathways. Immune checkpoint pathways, particularly the PD-1/PD-L1 axis and CTLA-4, serve as critical mechanisms by which tumors evade immune surveillance (124). Under normal physiological conditions, these pathways regulate T-cell activation and maintain immune self-tolerance (125). However, cancer cells exploit these regulatory mechanisms to suppress antitumor immune responses, thereby facilitating tumor growth and metastasis (126). The PD-1/PD-L1 interaction serves a central role in this immune evasion process (127). PD-1 is expressed on activated T cells and binds to PD-L1, which is frequently overexpressed on tumor cells and within the tumor microenvironment (124). This interaction inhibits T-cell proliferation and effector functions, ultimately leading to T-cell exhaustion and immune tolerance (128). Similarly, CTLA-4, expressed on both regulatory T cells and activated effector T cells, competes with CD28 for binding to

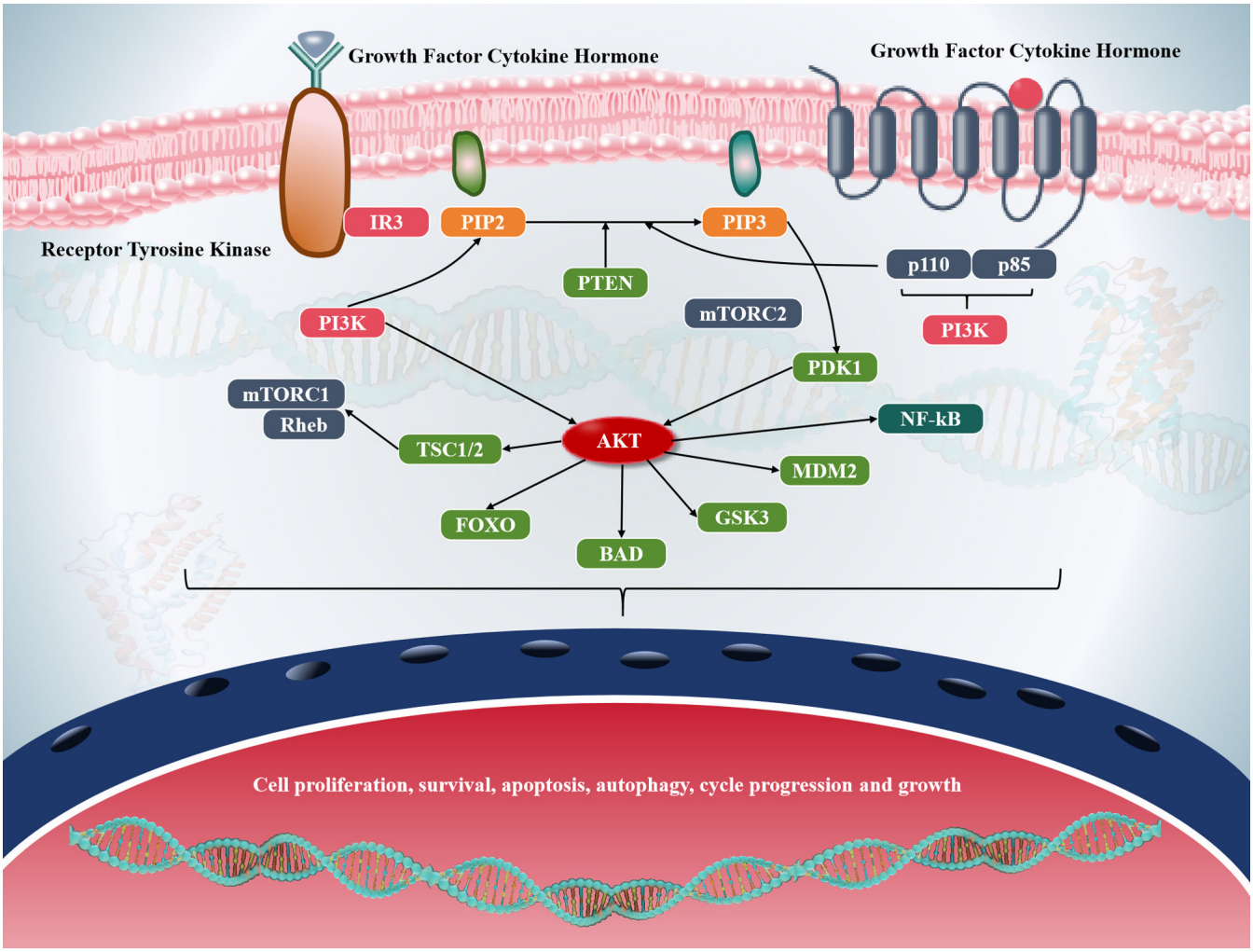

Figure 4. Schematic illustration of the PI3K/Akt/mTOR signaling pathway. The activation of the PI3K pathway is initiated by the binding of a ligand to a receptor tyrosine kinase, which results in the release of p110α (the catalytic subunit) from p85 (the regulatory subunit). Alternatively, this pathway can also be activated through GPCR signaling. Once activated, p110α catalyzes the conversion of PIP2 into PIP3. Following PIP3 production, this lipid second messenger can either directly activate Akt or assist in the recruitment of PDK1. Thereafter, both PDK1 and mTORC1 contribute to phosphorylate and activate Akt. Upon activation, Akt stimulates cell growth by modulating the mTOR complex and its downstream effector S6K. Moreover, Akt inhibits FOXO1 and activates NF-κB, thereby suppressing apoptosis. Additionally, Akt promotes MDM2 activity, which subsequently suppresses p53 function. By contrast, PTEN antagonizes PIP3-mediated signaling, thus restraining processes such as cell survival, growth and proliferation. PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; mTOR, mammalian target of rapamycin; GPCR, G protein-coupled receptors; PIP, phosphatidylinositol(4,5)bisphosphate; PDK1, 3-phosphoinositide dependent protein kinase-1; mTORC1, mechanistic target of rapamycin complex 1; FOXO1, forkhead box other 1; NF-κB, nuclear factor κB; MDM2, mouse double minute 2; PTEN, phosphatase and tensin homolog.

B7 ligands on antigen-presenting cells, thereby dampening early T-cell activation and promoting an immunosuppressive environment (73,129) (Fig. 5).

The advent of ICIs has markedly transformed the treatment landscape for advanced NSCLC (130). Monoclonal antibodies targeting PD-1 (such as pembrolizumab and nivolumab), PD-L1 (such as atezolizumab) and CTLA-4 (such as ipilimumab) have demonstrated robust clinical activity by reinvigorating antitumor immunity. Pembrolizumab was the first ICI approved as a first-line therapy for patients with NSCLC and high PD-L1 expression (≥50%), based on the KEYNOTE-024 trial (131). It notably improved PFS and OS compared with platinum-based chemotherapy. Nivolumab and atezolizumab have also shown durable clinical benefit, particularly in patients with high PD-L1 expression or elevated tumor mutational burden (TMB) (132,133). These therapies offer a favorable toxicity profile relative to conventional chemotherapy, contributing to improved patient quality of life (132).

Despite these therapeutic advances, both primary and acquired resistance to ICIs remain notable clinical barriers (134). Primary resistance refers to the absence of an initial response, whereas acquired resistance develops following an initial positive response (135). Resistance mechanisms can be broadly categorized into tumor-intrinsic and tumor-extrinsic factors. Tumor-intrinsic mechanisms include loss of antigen presentation (such as mutations in human leukocyte antigen or β2-microglobulin), activation of alternative immune checkpoints (such as T-Cell immunoglobulin and mucin domain 3 or lymphocyte activating 3) and upregulation of immunosuppressive signaling pathways (such as TGF-β or indoleamine 2,3-dioxygenase) (136-138). Tumor-extrinsic mechanisms involve an immunosuppressive tumor microenvironment enriched with regulatory T cells, myeloid-derived

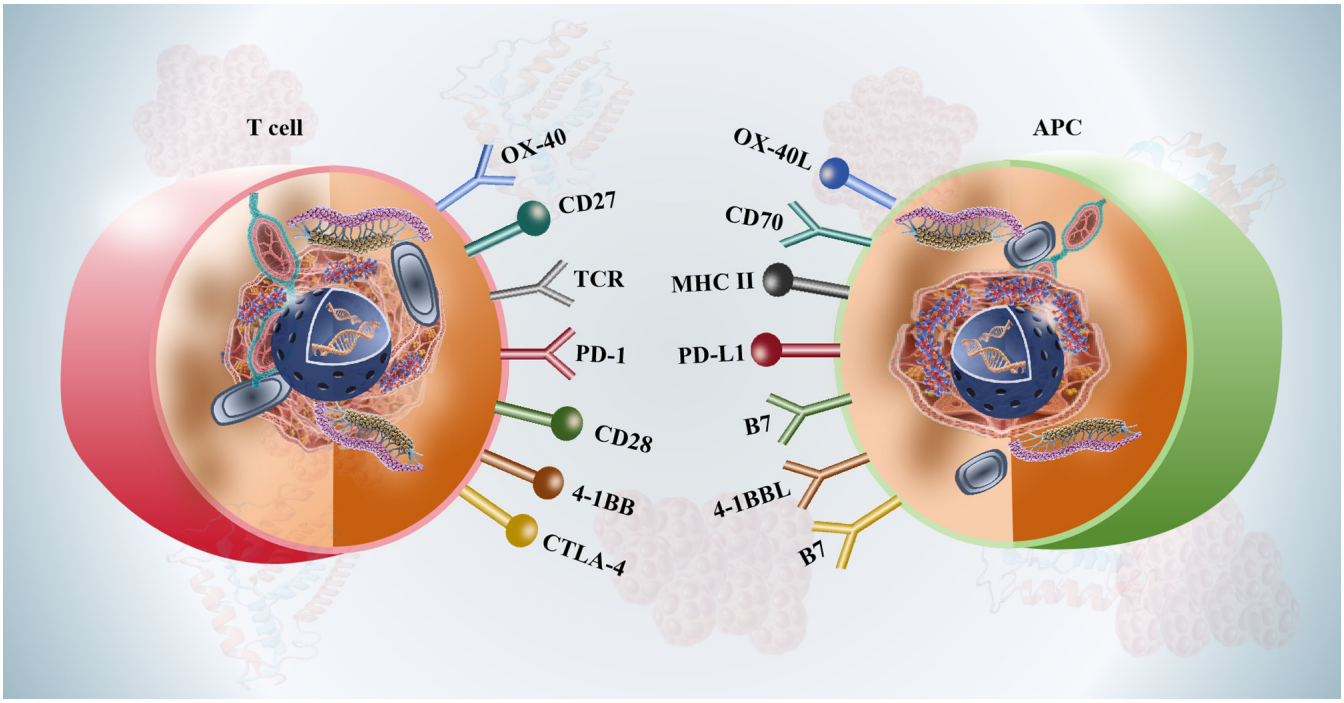

Figure 5. Costimulatory pathways in T cell activation. The activation of T cells is tightly regulated through the interactions of multiple costimulatory molecules. Stimulatory signals are provided by the binding of CD27 to CD70, OX40 to OX40L, 4-1BB to 4-1BBL, and CD28 to B7 ligands, whilst inhibitory signals are mediated by the PD-1/PD-L1 and CTLA-4/B7 interactions. OX40L, OX40 ligand; 4-1BBL, 4-1BB ligand; PD-1, programmed death-1; PD-L1, programmed death-1 ligand.

suppressor cells and M2-polarized macrophages (139). Additionally, genomic alterations, such as mutations in serine/threonine kinase 11 or kelch-like ECH associated protein 1, have been associated with reduced responsiveness to ICIs in NSCLC (140).

To enhance patient selection and optimize treatment outcomes, there is a need for reliable predictive biomarkers. Currently, PD-L1 expression assessed using immunohistochemistry is the most widely used biomarker; however, its predictive value is limited. Certain patients with low PD-L1 expression demonstrate durable responses, whilst others with high expression fail to respond. TMB, which reflects the total number of somatic mutations per megabase of genome sequenced, has emerged as a complementary biomarker (141). Higher TMB levels are associated with increased neoantigen production and enhanced immune recognition. Nevertheless, standardization of TMB assessment remains a challenge. Other emerging biomarkers under investigation include gene expression signatures, spatial patterns of immune infiltration and ctDNA analysis (142).

To overcome resistance and improve ICI efficacy, several combination strategies are being evaluated in clinical trials. Dual checkpoint inhibition, such as combined PD-1 and CTLA-4 blockade, has demonstrated synergistic effects in NSCLC (143). Combinations of ICIs with targeted therapies (such as EGFR or ALK inhibitors) are also being explored in molecularly-defined NSCLC subpopulations (144). Another promising approach involves combining ICIs with agents that modulate the tumor microenvironment, including angiogenesis inhibitors (such as bevacizumab) and drugs targeting immunosuppressive myeloid cells [such as colony-stimulating factor 1 receptor inhibitors (CSF1R)] (145). Furthermore, integrating ICIs with conventional modalities such as chemotherapy or radiotherapy has shown potential to enhance antitumor immunity through mechanisms such as immunogenic cell death and increased antigen release (146-148).

Other signaling pathways. Lung cancer is a heterogeneous disease that arises from complex interactions among multiple signaling pathways. Although targeted therapies have markedly transformed the treatment landscape for certain patient populations, the development of resistance mechanisms and pathway redundancies continue to pose substantial challenges. In addition to the well-established oncogenic drivers such as EGFR, ALK and KRAS, a multitude of other signaling pathways contribute to lung cancer pathogenesis, disease progression and therapeutic resistance. These pathways frequently interact with known oncogenic drivers, thereby modulating tumor proliferation, survival, metastasis and immune evasion. The following section provides an overview of several key signaling pathways implicated in lung cancer (Table I).

HER2 pathway. HER2, also known as ErbB2, is a transmembrane glycoprotein with intrinsic tyrosine kinase activity (149). It is encoded by the HER2/neu proto-oncogene located on chromosome 17q21 (149). As a core member of the EGFR/ErbB family, HER2 serves a pivotal role in regulating fundamental cellular processes such as proliferation, differentiation and survival (150). These functions underscore its significance in normal embryonic development as well as in the pathogenesis of several malignancies, particularly NSCLC (149,150). In lung tumorigenesis, HER2 alterations,

Table I. Characteristics of other signaling pathways in lung cancer.

Pathway	Crosstalk signaling	Pathological mechanism	Therapeutic targeting strategy	(Refs.)
HER2	PI3K/AKT/mTOR, MAPK and JAK/STAT	Promoting tumor cell survival; apoptosis resistance; and enhancing proliferation and metastatic potential	mAbs: Trastuzumab, pertuzumab, combination with trastuzumab and chemotherapy and trastuzumab deruxtecan; TKIs: Lapatinib, afatinib, neratinib, poziotinib and mobocertinib; and novel agents and emerging strategies: Bispecific antibodies, CAR-T cell therapy and combination with immunotherapy	(149-152)
FLT3	MAPK, PI3K/AKT/mTOR and STAT5	Promoting tumor cell proliferation; supporting apoptosis resistance; inducing tumor cell migration and invasion; and supporting neovascularization	Small-molecule FLT3 inhibitors: e.g., midostaurin and quizartinib; combination therapies: With MEK or PI3K/AKT inhibitors; and immunotherapeutic approaches	(153-156)
PDGFR	MAPK, PI3K/AKT/mTOR, JAK/STAT, PLCγ and Src	Promoting tumor cell proliferation; enhancing invasive potential; supporting neovascularization; and modulating tumor microenvironment	TKIs: Multi-targeted TKIs (such as imatinib, sunitinib and sorafenib) and PDGFR-selective inhibitors (such as crenolanib and olaratumab); and combination therapies: With chemotherapy, anti-angiogenics and immunotherapy	(157-160)
KIT	MAPK, PI3K/AKT/mTOR, JAK/STAT, PLCγ and Src/FAK	Enhancing tumor cell proliferation; supporting apoptosis resistance; promoting angiogenesis; and enhancing metastatic potential	TKIs: Imatinib, sunitinib, dasatinib and midostaurin; and combination strategies: With chemotherapy (such as etoposide/cisplatin), immunotherapy (such as PD-1 inhibitors) and angiogenesis inhibitors	(161-163)
FGFR	MAPK, PI3K/AKT/mTOR, PLCγ and JAK/STAT	Promoting tumor cell proliferation; reprogramming metabolic; modulating tumor microenvironment; and enhancing therapeutic resistance	Small molecule inhibitors: Pan-FGFR inhibitors (such as erdafitinib, infigratinib and pemigatinib) and selective inhibitors (such as AZD4547 and Debio1347); biological agents: FGF ligand traps (such as FP-1039), monoclonal antibodies (such as MFGR1877S) and antibody-drug conjugates (such as LY3076226); and combination strategies: With immune checkpoint inhibitors, chemotherapy (platinum-based regimens) and other targeted agents(EGFR or MEK inhibitors)	(164-168)
HGF/MET	PI3K/AKT/mTOR, MAPK, STAT3 and FAK/SRC	Promoting tumor cell proliferation; enhancing tumor cell survival; inducing tumor cell migration and invasion; promoting tumor angiogenesis; and mediating tumor cell drug resistance	TKIs: Non-selective MET inhibitors (such as crizotinib and cabozantinib), selective MET inhibitors: Capmatinib, tepotinib and savolitinib; monoclonal antibodies: Anti-MET (such as emibetuzumab), anti-HGF (such as rilotumumab) and HGF neutralizers; ADCs: e.g., telisotuzumab vedotin; and combination strategies: MET inhibitors + EGFR TKIs (such as capmatinib + gefitinib), and MET inhibitors + immunotherapy	(169-172)

Table I. Continued.

Pathway	Crosstalk signaling	Pathological mechanism	Therapeutic targeting strategy	(Refs.)
p53	Bax-Bcl-2, , p21-CDK-Cyclin GADD45 and Sestrin	Enhancing metastatic potential; mediating tumor cell drug resistance; and inducing genomic instability	Reactivation of Mutant p53: For example, PRIMA-1Met; MDM2/MDM4 inhibitors: Nutlins (such as idasanutlin) and MI-773; synthetic lethality approaches: ATR/CHK1 inhibitors and ARP inhibitors; p53-based immunotherapy: p53 vaccines and adoptive T-cell therapy; and combination strategies: p53 activators + DNA damaging agents, MDM2 inhibitors + kinase inhibitors and p53-targeted therapy + immunotherapy	(173-179)
Wnt	ERK/JNK/p38, PI3K/AKT/mTOR, Rho GTPase, NF-κB and JAK/STAT	Maintaining cancer stem cell; driving epithelial-mesenchymal transition (EMT); and remodeling tumor microenvironment	Porcupine inhibitors: e.g., LGK974 and RXC004; tankyraseinhibitors: e.g., XAV939 and G007-LK; β-catenin disruptors: e.g., PRI-724 and CWP232291; antibody-based approaches: OMP-54F28 (such as Fzd8-Fc decoy receptor) and vantictumab (such as anti-Fzd antibody); and combination therapies: With immune checkpoint inhibitors, EGFR/ALK targeted therapies and chemotherapy	(180-187)
JAK-STAT	PI3K/AKT/mTOR, MAPK and NF-κB	Promoting cell cycle progression; supporting apoptosis resistance; reprogramming metabolic; remodeling microenvironment; and enhancing therapy resistance	JAK inhibitors: Ruxolitinib fedratinib and tofacitinib; STAT inhibitors: Napabucasin, OPB-51602 and decoy oligonucleotides; and combination approaches: With EGFR/ALK TKIs, PD-1 inhibitors and chemotherapy	(192-198)
TGFβ	PI3K/AKT, MAPK and Rho-GTPase	Driving EMT; enhancing immune escape; promoting angiogenesis; and maintaining cancer stem cell	TGFβ-neutralizing antibodies: For example, fresolimumab; TβRI kinase inhibitors: For example, galunisertib; and combination therapies: With checkpoint inhibitors (such as anti-PD-1)	(199-207)
NF-κB	PI3K/AKT, MAPK and JNK	Promoting anti-apoptosis and proliferation; reprogramming tumor microenvironment; and enhancing invasion and metastasis	Direct inhibitors: Proteasome inhibitors (such as bortezomib), IκB degradation blockers and IKK inhibitors (such as bay 11-7082); Indirect approaches: Anti-inflammatory agents (such as aspirin and curcumin); and combination therapies: EGFR/NF-κB dual inhibition and immunotherapy (anti-PD-1) + NF-κB blockade	(208-218)
Insulin/IGF	PI3K/AKT/mTOR and MAPK	Promoting tumor cell proliferation; supporting anti-apoptotic survival; and enhancing metastasis and angiogenesis	Monoclonal antibodies: For example, figitumumab and xentuzumab; small-molecule TKIs: For example, linsitinib; and combination therapies: IGF1R inhibitors + EGFR TKIs (such as Erlotinib) and PI3K/mTOR inhibitors (such as everolimus) + IGF1R blockade	(219-226)

HER2, human epidermal growth factor receptor 2; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; mTOR, mammalian target of rapamycin; MAPK, mitogen-activated protein kinases; JAK, janus kinase; STAT, signal transducer and activator of transcription; mAbs, monoclonal antibodies; TKIs, tyrosine kinase inhibitors; CAR-T, chimeric antigen receptor T-cell; FLT3, fms-like tyrosine kinase 3; MEK, mitogen-activated protein kinase; PDGFR, platelet-derived growth factor receptors; PLCγ, phospholipase C-γ2; FAK, focal adhesion kinase; PD-1, programmed death-1; FGFR, fibroblast growth factor receptor; HGF, hepatocyte growth factor; MET, mesenchymal-epithelial transition; Bax, BCL-2 associated X; Bcl-2, B-cell lymphoma 2; CDK, cyclin-dependent kinases; GADD45, growth arrest and DNA damage-inducible 45; PRIMA-1, p53-reactivation and induction of massive apoptosis-1; MDM, mouse double minute; ATR, ataxia-telangiectasia-mutated-and-Rad3-related kinase; CHK1, checkpoint kinase 1; ARP, alveolar ridge preservation; Wnt, wingless-integrated; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal protein kinase; GTPase, guanosine triphosphatases; NF-κB, nuclear factor κB; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; TGFβ, transforming growth factor-β; EMT, epithelial-mesenchymal transition; TβRI, TGF-β type I receptor; IκB, inhibitor of NF-κB; IGF, insulin-like growth factor.

including point mutations, gene amplifications and protein overexpression, drive uncontrolled tumor cell proliferation, enhance metastatic potential and contribute to resistance to conventional therapeutic strategies (151). Consequently, HER2 has emerged as a key therapeutic target in oncology, leading to the development of targeted agents such as monoclonal antibodies (such as trastuzumab) and TKIs (such as lapatinib), which are specifically designed to inhibit its oncogenic signaling (152).

Fms-like tyrosine kinase-3 (FLT3) pathway. FLT3, also known as CD135 or Flk-2, is a member of the RTK III family, which includes KIT proto-oncogene, receptor tyrosine kinase (KIT), platelet-derived growth factor receptor (PDGFR) and CSF1R (153). The receptor comprises an extracellular ligand-binding domain, a transmembrane region and an intracellular TKD (153). FLT3 is predominantly expressed in hematopoietic stem and progenitor cells within the bone marrow, thymus and lymph nodes, where it regulates myeloid and lymphoid cell proliferation, survival and differentiation (152,153). Although primarily associated with hematologic malignancies such as acute myeloid leukemia (AML), FLT3 dysregulation has also been implicated in solid tumors, including NSCLC (154,155). FLT3 aberrations in lung cancer occur through three major mechanisms: i) Overexpression associated with aggressive disease and poor clinical prognosis (155); ii) rare internal tandem duplication and TKD mutations that may drive tumor progression (155); and iii) crosstalk with EGFR, MET or ALK signaling pathways, contributing to drug resistance in lung adenocarcinoma (155). Given its oncogenic potential, FLT3 is currently under investigation as a therapeutic target in lung cancer. Small-molecule inhibitors such as midostaurin and quizartinib, originally developed for AML, are now being evaluated in clinical trials involving FLT3-altered NSCLC (156). To overcome resistance, combination therapies incorporating MEK or PI3K/AKT inhibitors are actively being explored (156).

PDGFR pathway. The PDGFR is a single-chain transmembrane glycoprotein belonging to the Type III RTK family (157). It is widely expressed in several cell types, including smooth muscle cells, fibroblasts, endothelial cells, glial cells and chondrocytes (158). PDGFRα, one of its major isoforms, promotes tumor cell proliferation, invasion and neovascularization (159). Activation of the PDGFR signaling cascade engages key downstream effectors such as the RAS-MAPK and PI3K pathways (160). PDGFRα contributes to lung cancer progression through four well-defined mechanisms (159): i) Enhancing cyclin D1 expression and accelerating the G1/S phase transition; ii) increasing MMP-2 and MMP-9 levels to promote tumor invasion; iii) inducing VEGF secretion and recruiting tumor-associated fibroblasts to support angiogenesis; and iv) activating cancer-associated fibroblasts that release pro-tumorigenic cytokines. Dysregulation of PDGFR in lung cancer arises from multiple molecular alterations, including gene amplification, activating mutations, chromosomal rearrangements, and autocrine or paracrine activation loops (157-159). Therapeutic strategies targeting PDGFR include multitargeted TKIs (such as imatinib, sunitinib and sorafenib), selective inhibitors (such as crenolanib and olaratumab) and combination regimens with chemotherapy, anti-angiogenic agents or immunotherapy (159,160). Despite promising preclinical and clinical evidence, the development of drug resistance and challenges in patient stratification remain notable barriers (160). Further understanding of PDGFR biology may enable the design of more effective therapeutic strategies for PDGFR-driven lung cancers.

KIT pathway. The KIT receptor (CD117) serves a notable role in lung cancer, particularly in neuroendocrine subtypes such as SCLC and large cell neuroendocrine carcinoma (161). As a type III RTK, KIT has a unique structural organization: Its extracellular domain binds stem cell factor (SCF) through five immunoglobulin-like loops, whilst the intracellular region contains a split TKD responsible for downstream signal transduction (161). This architecture enables KIT to regulate essential cellular functions, including proliferation, survival, differentiation and migration (162). A total of 15-20% of SCLC cases exhibit KIT overexpression coupled with autocrine SCF production, establishing a self-sustaining growth loop (162). Although TKIs, such as imatinib, demonstrate robust efficacy in other KIT-driven malignancies, most notably gastrointestinal stromal tumors, their clinical benefit in lung cancer is restricted to patients harboring specific activating mutations or gene amplifications (163). Therefore, comprehensive molecular profiling is crucial for identifying patients who may derive therapeutic benefit. Research efforts have been directed toward developing next-generation KIT inhibitors with enhanced CNS penetration, such as avapritinib, as well as exploring combination strategies involving ICIs or epigenetic modulators (162,163).

Fibroblast growth factor receptor (FGFR) pathway. FGFR, a member of the RTK family, comprises four principal isoforms: FGFR1, FGFR2, FGFR3 and FGFR4 (164). Upon binding to its ligand, fibroblast growth factor, FGFR undergoes dimerization and autophosphorylation, leading to the activation of multiple downstream signaling pathways, including JAK/STAT, phospholipase Cγ, PI3K and MAPK (165). These signaling cascades regulate fundamental cellular processes such as chemotaxis, differentiation and proliferation, and also serve roles in the development of nerve cells and fibroblasts (166). Notably, the FGFR pathway functions as a key oncogenic driver in a subset of lung cancers, particularly squamous cell carcinomas (167). Although FGFR-targeted therapies show preclinical efficacy, their clinical translation requires more precise patient stratification and strategies to overcome resistance mechanisms (168). Further investigation into FGFR biology may facilitate the development of novel, molecularly tailored therapeutic approaches for distinct subtypes of lung cancer.

Hepatocyte growth factor (HGF)/MET pathway. MET is a RTK encoded by the proto-oncogene MET that binds HGF (169). It is predominantly expressed on the cell membranes of epithelial and endothelial cells (170). The MET signaling pathway regulates critical cellular functions, including cell migration, apoptosis, proliferation and differentiation (170). Dysregulated MET activation contributes to aggressive tumor phenotypes, such as immune evasion, enhanced cell survival, infiltration and invasiveness (171). Key downstream signaling pathways include Ras/Raf/MEK/ERK/MAPK, PI3K/PDK1/Akt, PLC-γ and JAK/STAT (169-171). The HGF/MET axis serves as a major oncogenic driver in lung adenocarcinoma, particularly

in tumors harboring MET exon 14 skipping mutations or other alterations (172). However, notable challenges persist in patient selection, resistance management and the optimization of therapeutic strategies (172). Future research should focus on elucidating context-specific MET signaling mechanisms, identifying robust predictive biomarkers and developing novel therapeutic agents to improve clinical outcomes. Combining molecular profiling with targeted treatments will be essential for advancing precision medicine in MET-dysregulated lung cancers.

p53 pathway. The p53 signaling pathway interacts with multiple intracellular networks and is central to maintaining cellular homeostasis and normal physiological functions (173). It activates in response to DNA damage or abnormal proliferation, causing cell cycle arrest and DNA repair (174). If damage cannot be repaired, p53 induces apoptosis by activating pro-apoptotic genes (173). Normally, p53 mRNA levels are high, but protein levels stay low due to rapid mouse double minute 2 (MDM2)-mediated ubiquitination and degradation (173-175). MDM2 binds to p53 and promotes its breakdown, forming a key negative feedback loop (176). Due to its tumor-suppressive function, p53 pathway dysregulation serves a major role in lung cancer development (177). Targeting this pathway may offer potential for personalized treatment, though challenges remain due to mutations and complex regulation (178). Advances in targeted therapy have created new opportunities for leveraging p53 in precision oncology (179). Integrating comprehensive molecular profiling with the development of novel agents and rational combination strategies will be critical to unlocking the therapeutic potential of p53.

Wnt pathway. Abnormal activation of the Wnt signaling pathway is strongly associated with lung cancer development (180). Upon binding of Wnt ligands to the Frizzled-LDL receptor related protein receptor complex on the cell membrane, Axin translocation is initiated, allowing β-catenin to accumulate in the nucleus (181). There, β-catenin interacts with Tcf/Lef transcription factors and recruits co-activators to drive the expression of Wnt target genes (182). In the absence of Wnt signals, β-catenin is phosphorylated and subsequently degraded by a destruction complex composed of adenomatous polyposis coli protein, GSK3β and casein kinase 1 α1, thereby maintaining low intracellular levels of β-catenin (183-185). Under these conditions, Tcf/Lef functions as a transcriptional repressor, inhibiting gene expression (186). Mutations in β-catenin that disrupt the regulation of Wnt signaling have been identified in several malignancies, including lung, liver, ovarian, skin, prostate cancer and melanoma (187-191). The Wnt/β-catenin pathway serves a pivotal role in lung cancer pathogenesis, particularly in tumor initiation and the maintenance of cancer stem cell properties (184). Although therapeutic targeting of this pathway remains challenging due to its pleiotropic functions and intricate regulatory mechanisms, advances in molecular profiling and targeted therapies offer promising avenues for intervention (186,187). Future progress will depend on integrating molecular stratification with novel agents and rational combination strategies to fully exploit the therapeutic potential of the Wnt/β-catenin pathway in lung cancer treatment (187-191).

JAK-STAT pathway. JAK is a non-RTK family composed of four members: JAK1, JAK2, JAK3 and TYK2 (192). STATs, which include STAT1-6, serve as direct substrates for JAKs and mediate signal transduction to the nucleus to regulate gene expression (193). The JAK-STAT pathway governs essential cellular functions such as growth, proliferation, differentiation and immune signaling (194,195). Activated JAK subsequently phosphorylates specific tyrosine residues on the receptor, generating docking sites for STAT proteins (193,195). Once phosphorylated, STATs form homo- or heterodimers and translocate into the nucleus, where they modulate gene transcription by binding to specific promoter regions (194). The JAK-STAT pathway functions as a central signaling axis in lung cancer, linking extracellular signals with nuclear gene regulation (196). Despite its structural simplicity and rapid signal transmission kinetics, therapeutic targeting of this pathway remains challenging. Ongoing research continues to elucidate the regulatory mechanisms of JAK-STAT signaling in lung cancer, offering novel opportunities for targeted intervention (197). Future advancements will hinge on the development of selective inhibitors, the characterization of context-dependent interactions, and the identification of predictive biomarkers to guide precision oncology strategies (198).

Transforming growth factor-β (TGFβ) pathway. The TGFβ family includes cytokines that inhibit the growth of normal epithelial cells (199). It consists of TGFβ isoforms, Activins, Inhibins, Nodal, bone morphogenetic proteins, anti-Müllerian hormone, and growth and differentiation factors (200-202). This pathway regulates key cellular processes such as proliferation, apoptosis, invasion, metastasis, extracellular matrix remodeling, differentiation and immune responses (203). Dysregulated TGFβ signaling disrupts cellular homeostasis and is associated with tumor initiation, progression and immune evasion (203). TGFβ initiates signaling by binding to two transmembrane receptors, TβRI and TβRII, that activate a downstream signaling cascade (199,203). Upon binding to TβRII, TGFβ recruits and phosphorylates TβRI (203). Activated TβRI subsequently phosphorylates SMAD2 and SMAD3, which associate with SMAD4 to form a transcriptional complex that translocates into the nucleus to regulate gene expression (204). As a central regulator of lung cancer progression, aberrant TGFβ signaling serves a critical role in promoting metastasis and suppressing antitumor immunity (205). Although targeting this pathway holds therapeutic promise, further research is needed to clarify its context-dependent functions and optimize combination therapies (206). A deeper understanding of how TGFβ interacts with other oncogenic pathways-such as EGFR and KRAS-is essential for developing effective precision treatments in lung cancer (207).

NF-κB pathway. The NF-κB family consists of transcription factors that regulate essential biological processes such as immunity, inflammation, cell survival, growth and differentiation (208-210). The mammalian NF-κB family consists of five members: NF-κB1 (p50), NF-κB2 (p65), RelA (p65), RelB and c-Rel (211). These proteins form homodimers or heterodimers, translocate into the nucleus, bind to κB sites in target genes and control their expression (212). Under normal conditions, NF-κB is sequestered in the cytoplasm by the inhibitory protein IκB, remaining in an inactive state (213). Aberrant

NF-κB activation, driven by overexpression or mutations in pathway components, is strongly associated with lung cancer initiation and progression (214,215). As a central regulator of inflammation and oncogenesis, NF-κB promotes tumor survival, immune evasion and metastasis (216). Although therapeutic targeting is complicated by its essential physiological roles, precision strategies, such as selective inhibition and combination therapies, offer potential for improving lung cancer treatment (217). Further research on biomarker-guided modulation of NF-κB signaling is crucial for advancing clinical applications (218).

Insulin and insulin-like growth factor (IGF) pathway. Insulin and IGF signaling pathways are central regulators of metabolic processes (219). Previous research demonstrated that these pathways contribute to tumor initiation and progression, positioning them as key therapeutic targets (220). The human insulin receptor and IGF1 receptor both have tetrameric structures with intrinsic tyrosine kinase activity (221). Upon ligand binding, they phosphorylate insulin receptor substrate proteins, which activate downstream pathways such as PI3K/AKT and MAPK, thereby promoting oncogenic processes (220,221). Studies have reported that insulin and IGF1 stimulate tumor cell proliferation, whereas inhibition of either pathway suppresses tumor growth (222). The insulin/IGF axis serves as a critical driver of lung cancer metabolism and progression, integrating metabolic dysregulation with oncogenic signaling (223,224). Although the clinical application of IGF-targeted therapies has encountered challenges, combination approaches and precision metabolic interventions offer promising avenues (225). Future research should focus on overcoming resistance mechanisms and targeting metabolic vulnerabilities in lung cancer (226).

3. Advances in targeted therapies

Next-generation TKIs. The development of next-generation TKIs marks a notable advancement in the treatment of oncogene-driven NSCLC, particularly for patients exhibiting resistance to earlier-generation inhibitors (227). These next-generation TKIs, including osimertinib for EGFR-mutant NSCLC and lorlatinib for ALK-positive NSCLC, have been specifically designed to overcome the limitations associated with their predecessors (18,228). They offer enhanced efficacy, broader activity against resistance mutations and improved penetration into the CNS (229,230). Such advancements have transformed the therapeutic landscape, providing renewed hope for patients who develop resistance to initial therapies.

Osimertinib, a third-generation EGFR-TKI, has emerged as a cornerstone in the treatment of NSCLC with EGFR mutations (228). First- and second-generation EGFR TKIs, including erlotinib, gefitinib and afatinib, have demonstrated marked clinical benefits for patients harboring activating EGFR mutations such as exon 19 deletions and L858R mutations (53-57). However, resistance to these agents inevitably develops, often due to the acquisition of the EGFR T790M mutation, which diminishes the binding affinity of earlier-generation TKIs (228). Osimertinib was specifically designed to target both activating EGFR mutations and the T790M resistance mutation, rendering it an effective option for overcoming this resistance (231). Clinical trials, including the AURA series and the FLAURA study, have reported that osimertinib offers superior PFS and OS compared with earlier-generation TKIs, even in first-line settings (232-234). Furthermore, osimertinib demonstrates enhanced CNS penetration, making it particularly effective against brain metastases, a common and challenging complication associated with EGFR-mutant NSCLC (229). This CNS activity is especially critical given that 25-40% of patients with EGFR-mutant NSCLC develop brain metastases during their disease course (235).

Similarly, lorlatinib, a third-generation ALK-TKI, has emerged as a groundbreaking therapy for ALK-positive NSCLC (18). Earlier-generation ALK inhibitors, including crizotinib, ceritinib and alectinib, have demonstrated notable efficacy in treating ALK-rearranged NSCLC (78). However, resistance frequently develops due to secondary mutations in the ALK gene or activation of bypass signaling pathways (69). Lorlatinib was specifically designed to address these resistance mechanisms and exhibits potent activity against a broad spectrum of ALK resistance mutations, notably the highly resistant G1202R mutation (236). The CROWN trial provided compelling evidence of the superior efficacy of lorlatinib compared with crizotinib in the first-line treatment setting, showing notably prolonged PFS and higher intracranial response rates (237). Similar to osimertinib, lorlatinib also demonstrates marked CNS penetration, rendering it particularly effective in managing brain metastases, a complication that affects ≤60% of patients with ALK-positive NSCLC throughout their disease trajectory (230,238).

The enhanced CNS activity of next-generation TKIs represents a critical feature, particularly given that the brain is a common site for metastasis in oncogene-driven NSCLC (239). Traditional chemotherapy and earlier-generation TKIs frequently fail to achieve sufficient drug concentrations within the CNS due to the presence of the blood-brain barrier, resulting in inadequate control over brain metastases (240). By contrast, next-generation TKIs such as osimertinib and lorlatinib are specifically designed to penetrate the blood-brain barrier more effectively, thereby facilitating robust intracranial responses and delaying the progression of CNS disease (229,230). This capability not only enhances survival rates but also preserves neurological function and improves quality of life for patients.

Despite these advancements, resistance to next-generation TKIs continues to pose a significant challenge. In the case of osimertinib, resistance mechanisms include the emergence of EGFR C797S mutations, MET amplification and histological transformation to SCLC (57). For lorlatinib, resistance may arise through compound ALK mutations or activation of alternative signaling pathways (241). To address these challenges, ongoing research is focused on developing fourth-generation TKIs, exploring combination therapies, and investigating novel strategies, such as antibody-drug conjugates and immunotherapy in oncogene-driven NSCLC (242-244).

ADCs. An ADC represents a sophisticated and innovative class of therapeutic agents that integrates the precision of monoclonal antibodies with the potent cytotoxic effects characteristic of chemotherapy (245). Structurally, an ADC consists of three core components: i) A monoclonal antibody engineered to selectively recognize and bind to a specific

antigen expressed on the surface of tumor cells; ii) a cytotoxic agent, commonly referred to as the payload, which induces cell death in targeted cancer cells; and iii) a chemical linker that stably connects the antibody to the payload (245). The monoclonal antibody functions as a 'guided missile', selectively delivering the cytotoxic payload directly to tumor cells whilst minimizing damage to healthy tissues, thereby reducing off-target toxicity (246). This targeted delivery mechanism represents one of the key advantages of ADCs, enabling the use of highly potent cytotoxic agents that would be too toxic for systemic administration (246).

ADCs are increasingly being adopted in oncology, particularly in the treatment of lung cancer, where early clinical trials have shown encouraging results (247-249). In both NSCLC and SCLC, ADCs have demonstrated notable response rates and improved survival outcomes, especially among patients who have limited remaining treatment options (250,251). For example, ADCs targeting proteins such as HER2, HER3, trophoblast cell-surface antigen 2 (TROP2), carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) and MET in NSCLC, and delta-like ligand 3 (DLL3) in SCLC, have attracted considerable attention due to their ability to produce durable responses in heavily pretreated populations (251-254). These findings highlight the potential of ADCs to address notable unmet needs in lung cancer therapy, particularly for patients with limited therapeutic alternatives.

In NSCLC, several ADCs are currently under investigation, each targeting distinct tumor-associated antigens. HER2-targeted ADCs, such as trastuzumab deruxtecan, have demonstrated notable efficacy in NSCLC characterized by HER2 mutations or overexpression (255). Although HER2 mutations are rare in NSCLC, they are associated with aggressive disease and poor prognosis; therefore, HER2-targeted ADCs represent a promising therapeutic strategy for this specific patient population (256). Similarly, HER3-targeted ADCs, including patritumab deruxtecan, are being evaluated in EGFR-mutant NSCLC, particularly in patients who have developed resistance to EGFR-TKIs (257). HER3 is frequently overexpressed in EGFR-mutant NSCLC and serves a key role in mediating resistance to targeted therapies, making it an attractive target for ADC development (258).

TROP2 is another promising target in NSCLC, as it is overexpressed in a substantial proportion of lung adenocarcinomas and is associated with poor prognosis (259). Sacituzumab govitecan, a TROP2-targeted ADC, has demonstrated encouraging activity in NSCLC, with durable responses observed in patients with advanced disease (260). In addition, CEACAM5 and MET are actively being investigated as ADC targets in NSCLC (246). CEACAM5 is overexpressed in a subset of lung adenocarcinomas, whilst MET amplification or overexpression is a well-established driver of tumor growth and therapeutic resistance in NSCLC (246,261). ADCs directed against these proteins aim to deliver potent cytotoxic payloads specifically to tumor cells, thereby overcoming resistance mechanisms and improving clinical outcomes (262). In SCLC, DLL3 has emerged as a compelling target for ADC development (263). DLL3 is highly expressed on the surface of SCLC cells but is scarcely present in normal tissues, making it an ideal candidate for targeted therapy (263). Rovalpituzumab tesirine, a DLL3-targeted ADC, has shown promising activity in SCLC, particularly among patients with high DLL3 expression (264). Although early clinical trials encountered certain challenges, ongoing research is focused on optimizing the use of DLL3-targeted ADCs and identifying biomarkers that can predict treatment response (265-267).

However, the development of ADCs for lung cancer presents multiple challenges. Key considerations include the optimization of target selection, improvement of linker stability to prevent premature release of the cytotoxic payload, and effective management of toxicities such as interstitial lung disease, which has been reported with certain ADCs (268-270). Moreover, the identification of predictive biomarkers is crucial for selecting patients most likely to benefit from ADC therapy, thereby enhancing therapeutic efficacy (253).

Combination therapies. Combination strategies, such as dual inhibition of EGFR and MET or concurrent targeting of the PI3K/AKT/mTOR pathway along with immune checkpoints, are currently under active investigation to overcome resistance and improve therapeutic outcomes (147,271,272). These approaches aim to address the complex and heterogeneous nature of cancer biology, where single-agent therapies often fail due to the development of resistance mechanisms and tumor heterogeneity (273).

For example, dual inhibition of EGFR and MET represents a promising therapeutic approach in cancers characterized by co-activation of these pathways or in cases where resistance to EGFR inhibitors arises from MET amplification or signaling activation (274). EGFR is a well-characterized oncogenic driver involved in tumor proliferation across multiple malignancies, including NSCLC (46). However, resistance to EGFR-TKIs frequently emerges through mechanisms such as activation of the MET pathway (275). By simultaneously targeting both EGFR and MET, researchers seek to block compensatory signaling pathways that tumors utilize to evade therapeutic pressure, thereby prolonging the duration of treatment response (276).

Similarly, the co-targeting of the PI3K/AKT/mTOR pathway and immune checkpoints represents a synergistic strategy in cancer therapy (277). The PI3K/AKT/mTOR pathway functions as a central regulator of cell growth, survival and metabolic processes, with its dysregulation commonly observed across multiple tumor types (120). However, inhibitors targeting this pathway frequently trigger feedback activation of compensatory signaling mechanisms, which can compromise their therapeutic effectiveness (122). Combining PI3K/AKT/mTOR inhibitors with ICIs, such as anti-PD-1 or anti-CTLA-4 antibodies, aims not only to suppress tumor proliferation directly but also to enhance the ability of the immune system to recognize and eradicate malignant cells (278). This combinatorial strategy leverages the potential of immunotherapy to counteract the immunosuppressive tumor microenvironment often reinforced by aberrant PI3K/AKT/mTOR signaling (279).

These combination strategies are supported by preclinical evidence and early-phase clinical trials, which have

shown encouraging results in terms of tumor regression and prolonged PFS (280-282). Nonetheless, several challenges remain, including the optimization of dosing regimens, mitigation of overlapping toxicities and the identification of predictive biomarkers to guide patient selection for those most likely to derive clinical benefit (283). As research progresses, these combination therapies hold promise to transform the treatment paradigm for cancers that currently present major therapeutic challenges when managed with monotherapies.

Liquid biopsies and biomarkers. Liquid biopsies, which analyze ctDNA, have emerged as a transformative, non-invasive tool for detecting targetable mutations and monitoring treatment responses in patients with cancer (284). By contrast to traditional tissue biopsies, often requiring invasive procedures and potentially failing to capture the full genetic heterogeneity of tumors, liquid biopsies offer a minimally invasive alternative that can be serially performed over time (285). This approach involves isolating ctDNA, which consists of DNA fragments shed by tumor cells into the bloodstream, and analyzing them for clinically relevant genetic alterations such as mutations, amplifications or gene fusions that drive tumorigenesis (286). By providing a real-time molecular profile of the tumor, liquid biopsies enable clinicians to identify actionable mutations, including EGFR, ALK or BRAF variants, and guide personalized therapeutic strategies accordingly (287).

One of the most notable advantages of liquid biopsies is their ability to monitor treatment response and detect emerging resistance mechanisms (288). For example, in patients receiving targeted therapies such as EGFR inhibitors, resistance mutations, such as T790M in NSCLC, can be detected early through ctDNA analysis (289). Such early identification allows for timely adjustments to treatment regimens. Moreover, liquid biopsies can assess tumor burden and minimal residual disease following surgical resection or systemic therapy, thereby offering valuable prognostic insights that support clinical decision-making regarding adjuvant or maintenance treatments (290).

Biomarker-driven approaches, which rely on the identification of specific molecular alterations, serve a fundamental role in personalizing cancer therapy and improving patient outcomes (291). By integrating liquid biopsy data with clinical and pathological information, clinicians can stratify patients into distinct molecular subgroups and select therapies most likely to achieve favorable outcomes (292,293). For instance, patients with HER2-positive breast cancer or KRAS-mutated colorectal cancer can be matched to targeted therapies or clinical trials evaluating novel agents specifically designed to target their unique genetic profiles (294,295). This precision medicine strategy not only enhances therapeutic efficacy but also minimizes unnecessary exposure to ineffective treatments and their associated adverse effects (296).

Furthermore, liquid biopsies serve an increasingly central role in clinical trials by facilitating patient selection, monitoring pharmacodynamic responses and evaluating the impact of investigational therapies on tumor genetics (297). As technological advancements, marked by improvements in sensitivity, specificity and the ability to detect low-frequency mutations, continue to evolve, liquid biopsies are poised to become a cornerstone of modern oncology care (298). These innovations hold the potential to transform how cancer is diagnosed, treated and monitored, ultimately advancing the development of more personalized, effective and patient-centered therapeutic strategies (298,299).

4. Challenges and future directions

Despite marked advancements in targeted therapy for lung cancer, several critical challenges persist that require focused attention and innovative strategies. One of the most pressing concerns is the inevitable emergence of resistance to targeted therapies, which can occur through both on-target and off-target mechanisms (300). Primary resistance affects 20-30% of patients, whilst acquired resistance typically develops within 9-14 months after treatment initiation, substantially limiting the duration of clinical benefit (301). The underlying mechanisms of resistance are complex and heterogeneous, encompassing secondary mutations in the target gene (such as EGFR T790M and C797S), activation of bypass signaling pathways (such as MET amplification and HER2 activation) and histological transformations (such as conversion to SCLC) (302-304).

The identification and validation of predictive biomarkers remain a major challenge in optimizing targeted therapeutic strategies (305). Although considerable progress has been achieved in detecting common driver mutations (such as EGFR, ALK and ROS1), there is an urgent need for more sensitive and comprehensive biomarker platforms capable of detecting rare mutations, gene fusions and intricate molecular profiles (306-308). Liquid biopsy technologies, particularly ctDNA analysis, have shown promise in this regard; however, their application remains limited by issues of sensitivity and specificity, particularly in the context of early-stage disease and minimal residual disease monitoring (309).

Moreover, the development of effective therapies for rare molecular subtypes, collectively representing 10-15% of NSCLC cases, remains a notable unmet clinical need (227). These subtypes encompass rare genetic alterations such as EGFR exon 20 insertions, HER2 mutations, RET fusions, NTRK fusions and MET exon 14 skipping mutations (64-67). Although targeted therapies have been developed for several alterations, certain patients still lack effective treatment options (71). Furthermore, the limited size of patient populations associated with these rare subtypes poses substantial challenges for clinical trial enrollment and pharmaceutical development.

Future research should focus on several key areas to effectively address the aforementioned challenges: i) Elucidating the molecular mechanisms of resistance through comprehensive genomic profiling and functional investigations; ii) developing novel therapeutic agents, including fourth-generation EGFR inhibitors, covalent KRAS inhibitors and selective RET inhibitors; iii) optimizing combination strategies that target multiple pathways concurrently whilst maintaining acceptable toxicity profiles; iv) advancing biomarker discovery through multi-omics approaches and artificial intelligence-assisted data analysis; and v) innovating clinical trial designs, such as basket trials and platform trials, to accelerate drug development for rare molecular subtypes.

Additionally, there is an increasing necessity to integrate targeted therapies with other treatment modalities, such as immunotherapy and radiotherapy, to develop more comprehensive treatment strategies. The investigation of novel drug delivery systems, including antibody-drug conjugates and nanoparticle-based therapies, may also present new opportunities to enhance therapeutic efficacy whilst minimizing systemic toxicity.

5. Conclusion

Signaling pathways serve a crucial role in the pathogenesis of lung cancer, driving essential processes such as cell proliferation, survival, invasion and metastasis. The dysregulation of these pathways, often resulting from genetic mutations or amplifications, serves as a hallmark of lung cancer and contributes to its aggressive behavior and resistance to conventional therapies. Targeted therapies that specifically inhibit these aberrant signaling pathways have transformed the treatment landscape for lung cancer, particularly in NSCLC, which constitutes the majority of cases. Advancements in understanding of these signaling pathways have also facilitated the development of innovative therapeutic strategies, including combination therapies and next-generation inhibitors aimed at overcoming resistance mechanisms. Ongoing research and clinical trials are imperative to address existing challenges and further propel advancements in the field of precision oncology.

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Competing interests

The authors declare that they have no competing interests.

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