Treating non-small cell lung cancer by targeting the PI3K signaling pathway

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Abstract

The phosphosphatidylinositol-3-kinase (PI3K) signaling pathway is one of the most important intracellular signal transduction pathways affecting cell functions, such as apoptosis, translation, metabolism, and angiogenesis. Lung cancer is a malignant tumor with the highest morbidity and mortality rates in the world. It can be divided into two groups, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC accounts for >85% of all lung cancers. There are currently many clinical treatment options for NSCLC; however, traditional methods such as surgery, chemotherapy, and radiotherapy have not been able to provide patients with good survival benefits. The emergence of molecular target therapy has improved the survival and prognosis of patients with NSCLC. In recent years, there have been an increasing number of studies on NSCLC and PI3K signaling pathways. Inhibitors of various parts of the PI3K pathway have appeared in various phases of clinical trials with NSCLC as an indication. This article focuses on the role of the PI3K signaling pathway in the occurrence and development of NSCLC and summarizes the current clinical research progress and possible development strategies.

Keywords: Phosphosphatidylinositol-3-kinase signaling pathway; Protein kinase B; Mammalian target of rapamycin; Non-small cell lung cancer

Introduction to Phosphatidylinositol-3-Kinase (PI3K) Pathway

Phosphatidylinositol 3-kinase (PI3K) is an intracellular lipid phosphokinase and the starting point of the PI3K–protein kinase B (AKT)–mammalian target of rapamycin (mTOR) signaling pathway. It is involved in various cellular functions, such as cell growth, proliferation, differentiation, movement, migration, invasion, intracellular transport, and angiogenesis, which are essential for tumorigenesis.[1]

PI3K can be divided into Type I, Type II, and Type III based on differing structures, functions, and substrate specificity.[2] For example, Type I and Type II are involved in cell signal transduction, while Type II and III play an important role in membrane transportation. Type I PI3K maintains the proliferation and survival of human tumor cells. It is composed of a regulatory and a catalytic subunit and can be further divided into IA and IB.[3] The catalytic subunit of class IA PI3K is one of the p110α, p110β, and p110δ encoded by the *PIK3CA*, *PIK3CB*, and *PIK3CD*, respectively. The regulatory subunit is one of the five isoforms of p85 encoded by the *PIK3R1* gene, which are p85α, p85β, p55α, p55γ, and p50α. They are regulated by the upstream growth factor receptor tyrosine kinases. Class IB PI3K is composed of the catalytic subunit p110γ encoded by PIK3CG, and one of two related regulatory subunits activated by G protein-coupled receptors, p101 or p87. p110α and p110β are expressed in different types of human cells, while the expression of p110δ and p110γ is limited to immune and hematopoietic cells.[4] After the activation of the PI3K upstream pathway ligand, it directly interacts with the p85 regulatory subunit and inhibits the binding. This leads to the inhibitory effect of p85 on the catalytic subunit p110, and to the activation of PI3K.[5] Activated PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate

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(PIP2) to phosphatidylinositol 3,4,5-triphosphate (PIP3). PIP3 can then act as a second messenger, by recruiting pyruvate dehydrogenase kinase 1 (PDK1) and AKT to the plasma membrane, and phosphorylating serine 473 through the mammalian target of rapamycin complex 2 (mTORC2), which partially activates AKT in the membrane. This will stimulate PDK1 to phosphorylate threonine 308, which will lead to the complete activation of AKT.[6]

AKT is a member of the AGC (protein kinase A [PKA]/protein kinase G [PKG]/protein kinase C [PKC]) protein kinase family, which has serine–threonine protein kinase activity.[7] It is composed of AKT1, AKT2, and AKT3. They are located on chromosomes 14q32, 19q13, and 1q44, respectively. The downstream targets of AKT can be divided into three groups: apoptotic proteins, transcription factors, and protein kinases, which play key roles in various cellular processes, including cell metabolism and apoptosis.[8] It is worth noting that AKT phosphorylates tuberous sclerosis complex 2 (TSC2), and then activates mTORC1 through phosphorylation, which further promotes tumorigenesis, cell cycle regulation, and apoptosis inhibition.[9]

mTOR is an evolutionarily conserved serine/threonine kinase that is divided into two types[10]: mTORC1, which interacts with raptor protein, and mTORC2, which interacts with rictor protein. mTOR stimulates cell growth and proliferation by promoting various anabolic processes and limiting catabolic processes. mTORC2 mainly controls the actin cytoskeleton and contributes to the complete activation of AKT.[11] mTORC1 can regulate translation. Two related downstream effectors are eukaryotic initiation factor 4E (eIF4E) binding protein 1 (4EBP1) and p70 ribosomal S6 kinase 1 (p70S6K1),[12] which can increase translation activity and participate in cell proliferation.

Tumor suppressor phosphatase and tensin homologs (PTEN) are key negative regulators of the PI3K pathway.[13] They regulate downstream signaling pathways by dephosphorylation of PIP3 to PIP2 and prevent further signal transduction by acting as the main regulator agent of the PI3K pathway. Other PI3K negative regulators also include inositol polyphosphate 4-phosphatase type II (INPP4B)[14] and protein tyrosine phosphatase non-receptor 12 (PTPN12).[15]

PI3K Pathway in NSCLC

Lung cancer is one of the most common forms of cancer. It is a solid tumor with extremely high incidence and mortality rates, with a 5-year survival rate of approximately 5%.[16] Lung cancer can be divided into two major categories, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for 75–85% of lung cancers. Currently, patients with NSCLC can be treated with surgery, radiotherapy, chemotherapy, immunotherapy, and targeted therapy; however, the prognosis and survival rate remain poor.[17] Only some patients can receive surgical resection, which carries a risk of recurrence after surgery. Radiotherapy can cause DNA double-strand break (DSB) in cancer cells to inhibit their growth, but there are still disadvantages, such as radioresistance, metastasis, and local disease progression. Platinum-based chemotherapy used to be the standard treatment for NSCLC, with a poor response rate (17–32%) and overall survival (OS) (7.4–11.3 months).[18,19] Immunotherapy prolongs OS in patients with negative driver genes, but the effect of immunotherapy in patients with positive driver genes is limited. In 2016, the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved pembrolizumab as the first-line treatment for advanced NSCLC (tumor proprotion score [TPS] ≥50%) with negative epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations.[20]

The emergence of new therapies that target specific genetic changes has altered the prospects for the treatment of NSCLC.[21] The genes in key signaling pathways change, which provides advantages for tumor cell survival and proliferation. *EGFR* is one of the most altered genes involved in NSCLC, and EGFR tyrosine kinase inhibitors (TKIs) improve response rates, postpone time to progression, and prolong OS of NSCLC patients with *EGFR* mutations.[22] These therapies have produced significant clinical effects when applied to patients with positive mutations in the target gene. Although the response rate of these drugs in mutation-positive patients has been greatly improved compared with chemotherapy, the tumor eventually progresses due to drug resistance. Recently, new oncogene changes have been discovered in NSCLC, including *HER2* exon 20 insertion mutations,[23] *RET*,[24] *ROS1* rearrangements,[25] and genetic changes in the PI3K pathway.

There are multiple mutations in the PI3K pathway in NSCLC

The PI3K pathway is involved in the regulation of various cellular functions. Dysregulation of the PI3K signaling pathway can induce various human diseases, especially cancer. Mutations in the PI3K–AKT–mTOR pathway can be observed in many different cancers, such as glioma, liver cancer, breast cancer, colon cancer, ovarian cancer, stomach cancer, and lung cancer.[26]

In NSCLC, changes in the PI3K pathway often appear in high-grade tumors and advanced diseases, which may be related to the degree of lung cancer malignancy.[27] The dysregulation of this pathway occurs through various mechanisms, including the expansion of different subtypes, changes in important targets in the pathway, loss of PTEN, and changes in cell biological behavior.

Mutations and amplifications of *PIK3CA* are often found in patients with NSCLC.[28] *PI3KCA* is located at 3q26 on chromosome 3 and encodes the catalytic subunit of PI3K (p110α). The mutations of *PIK3CA* mainly exist in exons 9 and 20. Exon 9 of *PIK3CA* encodes the helical domain of p110, and mutations of *E542K*, *E545K*, and *E545Q* in exon 9 may inhibit the inhibitory effect of the N-terminal Src homology 2 (SH2) domain of p85 on the catalytic subunits of p110, leading to excessive PI3K pathway activation.[29,30] Exon 20 encodes the kinase domain of p110, so a mutation in H1047 of exon 20 may promote constitutive activation of the PI3K signaling pathway. In addition to mutations, the more common *PI3KCA* change is amplification.[31] The *PI3KCA* gene is amplified to

varying degrees in about 35% of lung squamous cell carcinoma (LUSQ) and about 7% of lung adenocarcinoma (LUAD). As the result of a study of 86 NSCLC cell lines, and 356 resected NSCLC tumor tissues, *PIK3CA* mutation and expansion were found in 12.8% of NSCLC cell lines and 19.1% of tumor tissues.[32] The results of another study showed that *PIK3CA* mutations were found in 3.7% of tumor tissues of 1144 patients with NSCLC using next-generation sequencing.[28] Among these mutation-positive patients, *E545K* mutations of exon 9 (57.1%) were the most common. It is worth noting that the *PIK3CA* mutation in NSCLC may occur simultaneously with *EGFR*, *KRAS*, and *ALK* mutations.

Genetic changes in the AKT family have also been found in NSCLC. E17K is an activating mutation in the lipid-binding pleckstrin homology (PH) domain of AKT1.[33] It is rare and exists in 1–2% of LUSQ cases. However, studies have shown that there is an overexpression of AKT1 and AKT2 in 19% and 32% of LUSQ cases, and 16% and 12% of LUAD cases, respectively.[27] A study of 110 NSCLC tumor specimens showed that 51% of the tumor tissues had increased AKT activity.[34] It has been reported that there may be a certain correlation between PI3K–AKT dysregulation and the grade or stage of the tumor.[35]

The upregulation of the mTOR pathway has also been confirmed in a large population of patients with NSCLC,[33,36,37] and active phosphorylated mTOR (p-mTOR) is present in 90% of patients with LUAD, 60% of patients with large cell carcinoma, and 40% of patients with LUSQ. The presence of mTOR activity may also be a poor prognostic factor for early NSCLC. Several studies have shown that increased mTOR expression is associated with poor survival.[38]

PTEN is another common gene change in the PI3K pathway in NSCLC, and it is one of the key mechanisms that enhance the PI3K pathway signal to initiate and enhance cancer. The loss of PTEN function may be caused by mutations, deletions, or inhibition of transcription by promoter hypermethylation.[13] According to reports,[26,39] PTEN deletions are present in 8–59% of LUSQ cases, and 4–46% of LUAD cases, while PTEN mutations are distributed in 3–10% of LUSQ cases, and 2%–5% of LUAD cases. A series of early NSCLC specimens showed that PTEN expression was completely lost in 44% of tumors, 29% had a reduced expression level, and 27% had a normal expression level. A retrospective analysis of the Phase III FLEX study[40] of chemotherapy combined with cetuximab in patients with EGFR-expressing advanced NSCLC showed that 35% of patients had negative PTEN expression, suggesting that the presence of PTEN expression may be associated with improved survival.

Activating the PI3K pathway promotes the proliferation and metastasis of NSCLC

The PI3K–AKT–mTOR pathway is involved in various cellular processes that promote tumor growth and metastasis, such as cell survival, cell proliferation, autophagy, cell migration and movement, cell metabolism, genome stability, and angiogenesis [Figure 1].

In the PI3K pathway, PTEN is a key regulator for regulating cell cycle progression. Blocking the PI3K pathway can reduce the expression level of S-phase kinase-associated protein 2 (SKP-2) protein in lung cancer cells and block the cell cycle in the G1/S phase.[41] Constitutive activation of AKT or loss of PTEN is one of the most common causes of altered cell survival. The activation of AKT can downregulate the pro-apoptotic B-cell lymphoma 2 (BCL2) family members, BCL2-associated agonist of cell death (BAD) and BCL2-associated X protein (BAX), and promote the activation of apoptosis-related caspase hydrolases, caspase-3 and caspase-9, thereby inhibiting cell apoptosis.[7,42] AKT can also phosphorylate the proto-oncogene murine double minute 2 (MDM2), leading to downregulation of p53-mediated apoptosis.[43] In addition, activated AKT can also block the inhibition of the nuclear factor kappa-light chain enhancer of B cells (NFκB), by members of the inhibitor of nuclear factor kappa-B (IκB) family.[44] NFκB has a wide range of actions and can regulate the expression of hundreds of genes involved in cell apoptosis, cell cycle, cell adhesion, differentiation, and immune regulation.

The PI3K–mTOR pathway negatively controls autophagy through various mechanisms.[45] First, when mTORC1 is inhibited, adenosine 5-monophosphate-activated protein kinase (AMPK) phosphorylates and activates autophagy-promoting UNC-51-like kinase 1 (ULK1), which promotes autophagosome formation. mTORC1 phosphorylates ULK1 at multiple sites or phosphorylates and inhibits ULK1's positive regulators, autophagy-related (ATG) 14 and ATG13, to inhibit its interaction with AMPK, thereby preventing AMPK-dependent activation of phosphorylation and preventing autophagy. In addition, transcription factor EB (TFEB) is responsible for genes involved in lysosomal biogenesis. mTORC1 can also indirectly inhibit autophagy through phosphorylation and inhibition of nuclear translocation of TFEB.

The PI3K pathway also plays an important role in cell migration and movement. PI3K and AKT can regulate the epidermal–mesenchymal transition (EMT) of NSCLC.[46] EMT promotes tumor invasion and metastasis and increases cell motility and invasiveness. The loss of PTEN function can change the tumor microenvironment, inhibit the remodeling of the extracellular matrix, and promote tumor cell invasion and metastasis. Ras homolog (Rho) family proteins are involved in the assembly and formation of actin,[47] and are related to membrane folds, cell movement, and cell proliferation. mTORC1 can regulate the activity of Rho family GTPases, thereby changing cell migration and invasion capabilities. Additionally, mTORC1 has been shown to upregulate matrix metalloproteinase 9 (MMP-9) for the proteolytic digestion of extracellular matrix,[48] thereby regulating F-actin reorganization, focal adhesion formation, and tissue remodeling, and further regulating cell migration and invasion.

More importantly, the activation of the PI3K–AKT pathway regulates tumor angiogenesis through multiple downstream effectors, such as mTOR, forkhead box O3 (FOXO3), nitric oxide synthase (NOS), and glycogen synthesis kinase 3 (GSK3).[49,50] These effectors usually upregulate the expression of hypoxia-inducible factor 1

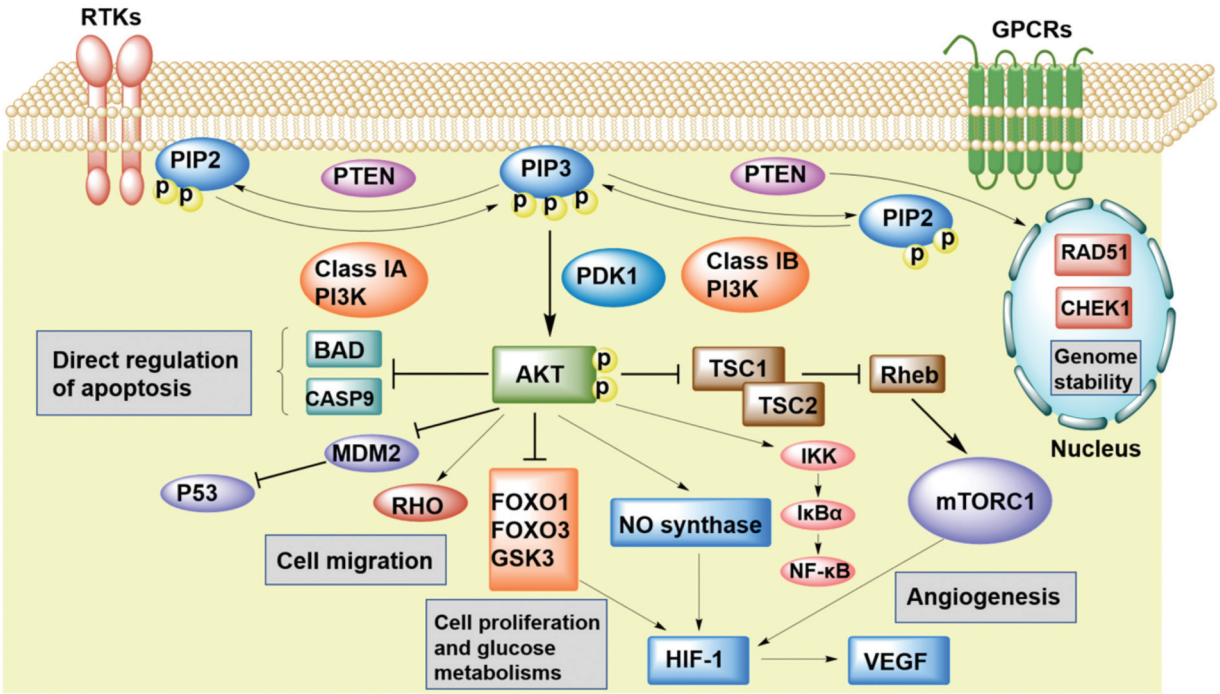

Figure 1: PI3K pathway and its role in the occurrence and development of NSCLC. AKT: Protein kinase B; BAD: Bcl-xL/Bcl-2 associated death promoter; CASP: Caspase; CHEK1: Checkpoint kinase 1; FOXO: Forkhead box O; GPCR: G protein-coupled receptor; GSK3: Glycogen synthesis kinase 3; HIF-1: Hypoxia-inducible factor 1; IκB: Inhibitor of nuclear factor kappa-B; IKK: Inhibitor of nuclear factor kappa-B kinase; MDM2: Murine double minute 2; mTORC: Mammalian target of rapamycin complex; NF-κB: Nuclear factor kappa-light chain enhancer of activated B cells; NO: Nitric oxide; NSCLC: Non-small cell lung cancer; P53: Protein 53; PDK1: Pyruvate dehydrogenase kinase 1; PI3K: Phosphoshatidylinositol-3-kinase; PIP2: Phosphatidylinositol 4,5-bisphosphate; PIP3: Phosphatidylinositol-3,4,5-triphosphate; PTEN: Phosphatase and tensin homolog; RHO: Ras homolog; RTKs: Receptor tyrosine kinases; TSC: Tuberous sclerosis complex; VEGF: Vascular endothelial growth factor.

(HIF-1), thereby stimulating transcriptional activation of vascular endothelial growth factor (VEGF), a powerful stimulator of neovascularization, and promote tumor angiogenesis. Additionally, the PI3K–AKT signaling pathway can also upregulate the expression of tumor necrosis factor (TNF),[51] promote endothelial cell migration, and regulate tumor angiogenesis.

The Warburg effect refers to the conversion of glucose into lactic acid by cancer cells through high-rate anaerobic glycolysis,[52] which produces a large amount of energy and biological macromolecules. The PI3K pathway plays an important role in this process. On one hand, inhibiting the PI3K pathway prevents the activation of Tre-2/BUB2/cdc 1 domain 4 (TBC1D4) to increase the translocation of the glucose transporter 4 (GLUT4),[53] and prevents gluconeogenesis by inhibiting FOXO1 and peroxisome proliferator activated receptor gamma coactivator-1 alpha (PPARGC1A). On the other hand, inhibiting the PI3K pathway can also inhibit cholesterol biosynthesis and GSK3, which are necessary for fatty acid uptake and biosynthesis,[54] stimulate the activation of sterol regulatory element-binding protein 1C (SREBP1C), and inhibit the synthesis of cholesterol and fatty acids. Additionally, the lack of PTEN has been shown to promote adipogenesis and β-oxidation by increasing the levels of peroxisome proliferator activated receptor gamma (PPAR-γ) and SREBP1,[55] and by accelerating the production of energy and biological macromolecules.

PTEN plays a powerful role in maintaining genome stability and DNA repair in the nucleus.[56] Checkpoint kinase 1 (CHEK1) is a protein kinase that regulates DNA damage response and cell cycle checkpoint response. Deletion of PTEN will inhibit CHEK1 and cause genome instability. In addition, nuclear PTEN upregulates RAD51 recombinase,[57] which is a component of the DNA DSB repair system. Therefore, PTEN loss can cause homologous recombination defects in human tumor cells and damage to the DNA repair system.

PI3K signaling pathway affects the sensitivity of NSCLC to chemotherapy drugs and EGFR–TKIs

The dysregulation of the PI3K signaling pathway is closely related to resistance to radiotherapy, chemotherapy, and hormone-targeted therapy. Cisplatin and its analogs are one of the standard treatment options for the initial treatment of NSCLC. However, many patients develop resistance to chemotherapy in a short period of time. Chemotherapy resistance is a multifactorial phenomenon, in which the dysregulation of the pro-apoptotic and anti-apoptotic pathways plays an important role.[58] In lung cancer, cells become resistant to cisplatin by AKT gene amplification and overexpression. Several studies have confirmed that the PI3K–AKT signaling pathway can regulate anti-apoptosis-related proteins and is closely related to NSCLC chemotherapeutic drug resistance.[59,60] In addition, studies have shown that activation of p53 reverses the resistance of NSCLC cells resistant to chemotherapy with cisplatin by downregulating the PI3K signaling pathway and promoting the production of intracellular reactive oxygen species (ROS).[61]

In addition to chemotherapy, targeted therapy is one of the most important methods for the treatment of NSCLC. There is constitutive activation of the PI3K pathway in 67% of NSCLC patients with *EGFR* mutations.[62] Clinical studies have shown that overexpression of the PI3K pathway in advanced NSCLC is a poor prognostic factor. Patients with *EGFR* mutations with PI3K pathway activation had shorter progression-free survival (PFS) and OS.[63] In patients with NSCLC treated with EGFR–TKI, mutations in the *PIK3CA* gene may be an important indicator for predicting and evaluating patient response and prognosis.[64] Various resistance mechanisms of EGFR–TKI treatment have been reported, among which PI3K pathway changes are one of the most studied.[65] In NSCLC, the absence of *PTEN* is associated with poor clinical outcomes and resistance to many anticancer drugs including gefitinib and erlotinib.[66,67] Everolimus is an mTOR inhibitor that can overcome resistance to EGFR inhibitors.[65] Part of the resistance mechanism may involve the activation of related pathways caused by negative feedback interruption of the PI3K signaling pathway. AKT can phosphorylate FOXO1, leading to drug resistance.[68] Additionally, AKT can also mediate PIKfyve phosphorylation,[69] promote EGFR transport and degradation, and subsequently reduce EGFR levels, resulting in weakened sensitivity to EGFR inhibitors. The PI3K signaling pathway may have an important regulatory role in NSCLC resistance. Therefore, overcoming PI3K pathway-related drug resistance may increase the clinical benefit of EGFR–TKIs.

PI3K signaling pathway affects NSCLC brain metastasis

The most common distant metastasis site of lung cancer is the brain, with a 20–40% incidence rate.[70,71] Without treatment, patients with brain metastases (BM) will survive for up to 1–2 months after metastasis. Although treatment for BM of NSCLC has made progress, the efficacy of all treatment methods is low. The process of NSCLC BM is very complex,[71] involving the shedding of lung tumor cells to form circulating tumor cells, which migrate through the blood circulation and pass through the blood–brain barrier (BBB) to establish and grow new tumors in the brain tissue. In recent years, some studies have identified the key molecules involved in this process and their impact on BM. A retrospective study of 61 patients who underwent surgical resection of primary NSCLC and BM showed that changes in genes encoding the PI3K signaling pathway were enriched in BM,[72] indicating that the PI3K pathway may be associated with an increased risk of metastasis. The BM-free survival of patients who have activated PI3K signals in primary NSCLC tumor tissues is significantly shorter, and their disease spreads to the brain significantly faster than patients without PI3K activation. This study highlights the significant correlation between PI3K signaling and the increased risk of metastasis in NSCLC patients.

Research of PI3K Inhibitors in NSCLC

The PI3K–AKT–mTOR signaling pathway has attracted widespread attention as a single or combined target for the treatment of cancer in the past few decades. In 2014, idelalisib (Gilead Sciences) became the first PI3K inhibitor approved for marketing, and it is mainly used for specific B-cell malignancies.[73] Subsequently, in 2017, the pan-I PI3K inhibitor copanlisib (Bayer)[74] and the dual PI3Kδ/PI3Kγ inhibitor duvelisib (Verastem)[75] were approved in 2017. PI3Kα inhibitor alpelisib (Novartis)[76] was approved for the treatment of advanced breast cancer in 2019 and umbralisib (TG Therapeutics)[77] for the treatment of chronic lymphocytic leukemia, follicular lymphoma, and marginal zone lymphoma in 2021 has also been approved for listing. In addition to these PI3K inhibitors approved by the FDA for clinical treatment, there are several new PI3K inhibitors for NSCLC in various experimental stages. Targeting the PI3K pathway has provided promising preclinical results,[78] and its efficacy for NSCLC treatment in clinical trials is currently being actively evaluated [Table 1].

Pan class I PI3K inhibitors have a certain inhibitory effect on all subtypes of PI3K, including GDC-0941, BKM120, PX-866, and XL-147. GDC-0941 mainly inhibits p110α and p110δ subtypes, and shows a synergistic effect with mitogen-activated protein kinase kinase (MEK) inhibitors in the treatment of advanced solid tumors.[79] In a phase IB dose escalation trial, patients with advanced NSCLC received GDC-0941 combined with standard first-line chemotherapy, namely carboplatin and paclitaxel, or cisplatin and pemetrexed, and optionally added bevacizumab.[80] Experimental results showed that 43.9% of patients achieved partial response (PR), and 30.9% of patients had stable disease. However, the results of the phase II study showed no significant prolongation of PFS or OS.[81] BKM120 is another oral pan class I PI3K inhibitor. Compared with wild type (WT)-PIK3CA, BKM120 showed better efficacy in the treatment of cancer patients with *PIK3CA* mutations.[82] In a phase I trial of 43 patients with relapsed and refractory solid tumors using PX-866 combined with docetaxel, one patient with NSCLC and *PIK3CA* mutation achieved PR.[83] In a phase I trial of XL-147, either as a single agent or in combination with erlotinib, PR was achieved in one patient for each type.[80,84]

In addition to pan class I PI3K inhibitors, various inhibitors targeting PI3K subtypes have also been studied to increase efficacy and reduce toxicity in the treatment of NSCLC. PI3Kα-specific inhibitors have better anticancer activity in tumors with *PIK3CA* mutations. Among them, the p110α-specific inhibitors, which are entering clinical trials, mainly include alpelisib[85] and serabelisib.[86] Aspirin has also been found to specifically inhibit p110α.[87] It is reported that PI3Kβ plays an important role in PTEN-deficient cancers.[88] Specific p110β inhibitors mainly include GSK2636771,[89] AZD818670,[90] SAR26030171,[91] and taselisib.[92]

AKT's adenosine triphosphate (ATP) competitive inhibitors include, but are not limited to, GSK-690693, perifosine, and MK2206. GSK-690693 is a new type of AKT inhibitor, which can inhibit the proliferation and induce apoptosis of H460 and A549 NSCLC cells.[93] Perifosine, an AKT inhibitor, produced a PR in a patient in a phase I trial with 15 patients with advanced NSCLC.[94] MK2206 is an allosteric small-molecule inhibitor that can

Table 1: Inhibitors of the PI3K–AKT–mTOR pathway in clinical development in NSCLC (as of November 2021).

Drug	Target	In combination with	Tumor type	Phase	State	Ref.
BKM 120	Pan Class I PI3K	Carboplatin and pemetrexed	NSCLC	Phase I	Completed	NCT01723800
		None	NSCLC	Phase II	Completed	NCT01297491
		Gefitinib	NSCLC	Phase I	Unknown	NCT01570296
		Erlotinib	NSCLC	Phase II	Completed	NCT01487265
		Gemcitabine and cisplatin	Advanced solid tumors	Phase I	Withdrawn	NCT01971489
		None	NSCLC	Phase I	Completed	NCT02128724
		MEK162	Advanced solid tumors	Phase Ib	Completed	NCT01363232
GDC-0941	Pan Class I PI3K	Either paclitaxel and carboplatin (with or without bevacizumab) or pemetrexed, cisplatin, and bevacizumab	NSCLC	Phase I	Completed	NCT00974584
		Carboplatin/paclitaxel or carboplatin/paclitaxel/ bevacizumab	NSCLC	Phase II	Completed	NCT01493843
		Erlotinib	Advanced solid tumors	Phase I	Completed	NCT00975182
Gedatolisib	PI3K/mTOR	Paclitaxel and carboplatin	NSCLC	Phase Ib–II	Terminated	NCT02920450
		Paclitaxel and carboplatin	Advanced solid tumors	Phase I	Completed	NCT02069158
Ipatasertib	AKT	None	NSCLC	Phase II	Recruiting	NCT04467801
Everolimus	mTORC1	None	NSCLC	Phase II	Completed	NCT00124280
		None	NSCLC	Phase I	Completed	NCT00401778
		Atalanib	Advanced solid tumors	Phase I	Completed	NCT00655655
Aspirin	PI3Kα	Osimertinib	NSCLC	Unknown	Not yet recruiting	NCT04184921, NCT03543683, NCT03532698
AZD8186	PI3Kβ/PI3Kδ	As monotherapy and in combination with abiraterone acetate or AZD2014	Advanced squamous NSCLC, CRPC, TNBC	Phase I	Completed	NCT01884285
XL765	PI3K/mTOR	Erlotinib	Solid tumors	Phase I	Completed	NCT00777699, NCT00692640
		MSC1936369B	Advanced solid tumors	Phase I	Completed	NCT01390818
Alpelisib	PI3Kα	None	NSCLC	Phase II	Completed	NCT02276027
XL147	Pan Class I PI3K	XL647	Solid tumors	Phase I	Withdrawn	NCT00704392
		Paclitaxel and carboplatin	Solid tumors	Phase I	Completed	NCT00756847
Idelalisib	PI3Kδ	Pembrolizumab	NSCLC	Phase Ib–II	Unknown	NCT03257722
Buparlisib	Pan Class I PI3K	Docetaxel	NSCLC	Phase I/II	Terminated	NCT01911325
PX-866	Pan Class I PI4K	Docetaxel	Solid tumors	Phase I/II	Completed	NCT01204099
MK-2206	AKT	None	NSCLC, SCLC, and thymic malignancies	Phase II	Active, not recruiting	NCT01306045
BGB-10188	PI3Kδ	Tislelizumab	Solid tumors	Phase I/II	Recruiting	NCT04282018
BEZ235	PI3K/mTOR	MEK162	Advanced solid tumors	Phase Ib	Completed	NCT01337765

Table 1 (continued).

Drug	Target	In combination with	Tumor type	Phase	State	Ref.
IPI-549	PI3Kγ	Nivolumab	Advanced solid tumors	Phase I	Active, not recruiting	NCT02637531
CC-223	mTORC1	Erlotinib or azacitidine	NSCLC	Phase I	Completed	NCT01545947
		None	Advanced solid tumors	Phase I/II	Completed	NCT01177397
Temsirolimus	mTORC1	None	NSCLC	Phase II	Completed	NCT00079235
Sirolimus	mTORC1	Auranofin	NSCLC and SCLC	Phase I/II	Recruiting	NCT01737502
		Pemetrexed	NSCLC	Phase II	Terminated	NCT00923273
		Gold sodium thiomalate	Advanced squamous NSCLC	Phase I	Withdrawn	NCT01383668
		Durvalumab	NSCLC	Phase Ib	Recruiting	NCT04348292
Panitumumab	mTOR	None	NSCLC	Phase I	Completed	NCT00352950
ABI-009	mTOR	Nivolumab	Advanced sarcoma and certain cancers	Phase I/II	Recruiting	NCT03190174
AZD2014	mTOR	None	NSCLC	Phase II	Recruiting	NCT02664935
Sorafenib	mTOR	None	NSCLC	Phase II	Completed	NCT00098254
DS-3078a	mTOR	None	Advanced solid tumors or lymphomas	Phase I	Completed	NCT01588678

AKT: Protein kinase B; CRPC: Castrate-resistant prostate cancer; mTOR: Mammalian target of rapamycin; mTORC1: Mammalian target of rapamycin complex 1; NSCLC: Non-small cell lung cancer; PI3K: Phosphosphatidylinositol-3-kinase; SCLC: Small cell lung cancer; TNBC: Triple-negative breast cancer.

inhibit all AKT subtypes. Its phase I clinical trials for NSCLC have shown promising effects in causing tumor shrinkage, and it is well-tolerated as a monotherapy in patients.[95] In addition, the combined treatment of MK2206 with paclitaxel, docetaxel, or erlotinib in patients with advanced solid tumors has also been tested in phase I clinical trials, in which one patient with NSCLC achieved PR.[96] In a phase II trial of MK2206 for NSCLC, the combination with erlotinib was evaluated in patients with NSCLC who had previously progressed on erlotinib therapy. Patients were stratified according to *EGFR* mutation status. The median PFS of patients with *EGFR* mutations was 4.4 months, and that of *EGFR* wild-type patients was 4.6 months.[97]

So far, the mTORC1 inhibitors approved by the FDA for clinical trials in patients with NSCLC mainly include temsirolimus and everolimus, both of which are derivatives of rapamycin. Rapamycin was originally isolated from the soil of Rapa Nui Island and has antifungal activity.[98] Various rapamycin analogs have been developed. Rapamycin binds to FK506 binding protein 12 (FKBP12) to destroy raptor interaction with mTOR, leading to the dissociation and inactivation of the mTORC1 complex to prevent cell proliferation. Temsirolimus, as monotherapy, has a clinical benefit rate (confirmed response and confirmed stable disease) of 35% in newly treated patients with NSCLC.[99] Everolimus can selectively inhibit mTORC1 signaling, but in the phase II trial, when combined with erlotinib, it failed to show significant efficacy in patients with advanced NSCLC.[100] In addition to rapamycin, various ATP-competitive mTOR kinase inhibitors have entered clinical trials targeting mTORC1 and mTORC2. AZD2014 has played a great role in slowing down the progression of LUSQ by inhibiting two mTOR kinases. In the dose-escalation group of the TAX-TORC study, the combination of AZD2014 and paclitaxel achieved a remission rate of 33% in previously treated LUSQ patients. AZD8055 has shown anti-tumor activity, and it has initially shown a certain therapeutic effect in the treatment of patients with advanced solid tumors.[101]

Given that mTOR and PI3K belong to the same phosphoinositide 3-kinase-related kinase (PIKK) superfamily, with similar structural compositions and activation mechanisms, small molecule inhibitors targeting both PI3K and mTOR were discovered during the development of mTOR inhibitors.[102] PI3K–mTOR inhibitors have been developed and tested in preclinical models or cancer cell lines and are expected to be used in the treatment of NSCLC. As a single drug, PKI-587 has the effect of reducing lung cancer growth in *in vitro* cell culture and mouse xenotransplantation tests.[103] XL765 has been tested in combination with erlotinib in a phase I trial in patients with NSCLC, and the combination is generally well tolerated. Gedatolisib has been evaluated in a phase I trial in combination with chemotherapy (docetaxel or cisplatin) in the treatment of patients with NSCLC or with dacomitinib in the treatment of patients with *EGFR*-mutant NSCLC, and the results showed that the toxicity profile can be controlled. There are currently ongoing phase I/II trials.[104]

Adverse Reactions of PI3K Inhibitors

Although PI3K inhibitors have good therapeutic effects and prospects, their side effects limit their clinical applications. In *in vitro* experiments and xenotransplantation studies, PI3K inhibitors mainly have anti-proliferative effects on cancer cells.[105] However, these experimental conditions do not reflect *in vivo* situations. It cannot be ruled out that PI3K inhibitors may cause anti-angiogenesis and active immune response *in vivo*, leading to the death of cancer cells and possible drug-related toxicity.

Inhibition of PI3K destroys insulin signals in muscles and liver,[106] resulting in hyperinsulinemia and hypoglycemia. Higher insulin levels may also reduce the degree of inhibition of PI3K inhibitors in cells. Additionally, PI3K inhibitors could also cause high blood pressure through insulin-induced vasoconstriction.[106]

Because the PI3K–AKT–mTOR signals in healthy cells regulate the basic cell functions, PI3K inhibitors are prone to off-target side effects,[107] which affects the treatment and patient's quality of life. Pan class I PI3K inhibitors act on all type I subtypes. Depending on the specific cancer target and its status, they lack isotype specificity and have varying degrees of toxicity. Therefore, increasing the selectivity of PI3K isomers may result in less off-target toxicity.

However, specific PI3K inhibitors will still produce different adverse reactions based on the selected targets, including diarrhea caused by PI3Kα inhibitors[108] and a series of immune-related toxicities of PI3Kδ inhibitors. For example, idelalisib, a PI3Kδ inhibitor, may induce neutropenia and cause bacterial infection.[109-111] Additionally, corresponding inflammation and autoimmunity are caused by the excessively active immune response of the tissue site exposed to the external immunogen toxicity, presenting as skin rash, colitis, liver toxicity, and pneumonia. In a report of the PI3Kδ inhibitor AMG 319,[112] it was found that AMG 319 reduced tumor-infiltrating immunosuppressive Treg cells and enhanced cytotoxic tumor-infiltrating CD8+ and CD4+ T cells. This also leads to immune-mediated adverse reactions. In addition, in the treatment with AMG 319, patients who had not received immunosuppressive chemotherapy previously had different and more severe adverse reactions than the patients with previously treated lymphoma. This indicates that immunosuppression may reduce the sensitivity of patients to PI3Kδ inhibitors.

To safely use PI3K inhibitors,[4] its clinical guidelines now include antibiotic prevention and cytomegalovirus (CMV) monitoring.[113] Additionally, it is recommended to regularly monitor neutropenia during early treatment and to use growth factors as a preventive measure. Other side effects can usually be controlled by interrupting or reducing the dose, or by discontinuing the drug.

Another reported potential side effect of PI3Kδ inhibition is to induce genomic instability in B cells by activating activation-induced cytidine deaminase (AID),[114] thereby promoting changes in DNA recombination. These observations raise concerns about the potential mutagenic risk for patients treated with long-term PI3Kδ inhibitors. However, since many patients discontinue treatment due to toxicity after short-term treatment, the clinical extent of this biological side effect is unclear.

Development Prospects

Based on the results of the current preclinical and clinical trials of PI3K pathway inhibitors, it is evident that PI3K inhibitors have great therapeutic potential in NSCLC, but their significant side effects and immunotoxicity hinder clinical progress in this field. These toxicities may be related to the nature and dosage of the drug. More effective strategies need to be adopted in the future to reduce possible toxicity problems and to improve treatment results by overcoming potential drug resistance mechanisms. The current research directions in this field are summarized below.

Patient selection

At present, most of the clinical trials of PI3K inhibitors are mainly conducted in people who have not undergone molecular selection, which may be one of the reasons for the unsatisfactory results.[115] Therefore, it is possible to use precision medicine to select effective biomarkers based on molecular biology to further stratify patients in greater detail according to their mutation spectrum, and further implement the individualized treatment with PI3K inhibitors.

Improvement of selectivity

Compared with PI3Kα, PI3Kβ, and PI3Kγ, umbralisib is far more selective for PI3Kδ than idelalisib and duvelisib. Moreover, it causes fewer adverse events, such as colitis.[116] Thus, improving the selectivity of PI3K inhibition may be one of the ways to reduce its adverse reactions.

In addition, these inhibitors can also be directly applied to tumors to reduce off-target toxicity. To overcome the limitations of current PI3K inhibitors, scientists are developing better organ targeting, and more effective drug delivery systems, such as allosteric inhibitors, nanoparticles, multivalent drug targeting, and protac.[117-119] It is thought that the toxicity related to PI3K inhibitors can be reduced through effective targeted drug delivery or local treatment.

Combination therapy

It can be seen from clinical studies that most PI3K inhibitors have been combined with other drugs to increase the therapeutic efficacy. The anti-tumor activity of single-agent PI3K inhibitor is limited, so they are combined with other treatments. These include other targeted drugs, chemotherapy, radiotherapy, and immune checkpoint blocking therapy. As it involves multiple pharmacological strategies to achieve synergistic treatment and to improve efficacy, this treatment

model is expected to become the main focus of future research.

The PI3K signaling pathway is widely interconnected with many other cancer signaling pathways, including multiple pathways in cancer development and progression, such as RAS/mitogen-activated protein kinase (MAPK), EGFR, and poly adenosine diphosphate (ADP)-ribose polymerase (PARP),[25] with multiple convergence points, crosstalk, and feedback loops. The inhibition of a pathway can affect the activation or inhibition of another pathway. Therefore, based on dose-effect and mitigating compensation, inhibiting the PI3K signaling pathway and other NSCLC-related signaling pathways may show a synergistic effect in inhibiting tumor growth. Because the role of PI3K-targeted drugs is mainly to inhibit cell growth, studies have shown that by targeting the PI3K pathway in combination therapy, it can inhibit tumor cells from developing resistance to radiotherapy, chemotherapy, or other targeted drugs. For example, to improve the efficiency of PI3K-targeted drugs, the combination of the PI3Kα inhibitor alpelisib and cetuximab or dacomitinib can reduce cell growth in previously resistant cells.[120,121]

Negative feedback pathways reactivate upstream signals, and other effects make it unlikely for single-agent inhibitors to completely block the PI3K–AKT–mTOR pathway.[122] Compared with single-agent therapy, the combination of rapamycin and chemotherapeutic drugs increased synergistic inhibition of the PI3K–AKT–mTOR pathway.[123] In addition, the combined treatment of AZD8055 and erlotinib or MEK inhibitor trametinib can further inhibit the tumor metastasis ability in mice.[124] On the basis of samotolisib, the combined use of checkpoint kinase 1 (CHK1) inhibitor and prexasertib, also produced significantly enhanced anti-tumor activity.[125] In conclusion, the combination of PI3K pathway inhibitors and other treatments has been widely evaluated in NSCLC, which is expected to improve the clinical benefit for patients and reduce the incidence of drug resistance.

Dual-target therapy

Although combination therapy can solve certain problems of individual medication, it also has problems such as asymmetric pharmacokinetics, drug–drug interactions, and compliance.[126] Based on this, scientists have developed dual-target therapy. Dual-target therapy refers to a single drug that can interact with two different proteins to produce a synergistic effect.[127] In addition to the aforementioned PI3K/mTOR drugs, PI3K dual-target drug development includes PI3K/histone deacetylases (HDACs) and PI3K/MEK.[128] HDACs are an important family of epigenetic enzymes by catalyzing the removal of acetyl groups from ε-amino lysine residues on histones and other proteins.[129] HDAC inhibitors (HDACi) are used in combination with PI3K pathway inhibitors. It has shown good anti-tumor effects in clinical studies. BEBT-908 is a dual inhibitor of PI3K/HDAC, which can target both PI3K and HDAC signaling pathways.[130] In human NSCLC H2122 cells, the anti-tumor effect of BEBT-908 was significantly higher than that of PI3K inhibitor (GDC-0941) and HDAC inhibitor (SAHA) alone or in combination. Studies have shown that BEBT-908 can effectively inhibit tumor growth by promoting ferroptosis, and can also enhance tumor cell immunogenicity and the effect of immune checkpoint inhibitors. MEK is a key amplification kinase in the Ras–Raf–MEK–extracellular signal-regulated kinase (ERK) signaling pathway, which mediates cell growth and survival signals. The new PI3K/MEK dual-target inhibitor ST-162 can block both PI3K/Akt/mTOR and Ras/MEK/ERK signaling pathways.[131] The drug inhibited tumor growth in A549 cells and A549 tumor-bearing mice in a dose-dependent manner, and its efficacy was similar to the combined administration of PI3K inhibitor ZSTK474 and MEK inhibitor PD-0325901 at equivalent concentrations.

Intermittent administration

There is evidence that intermittent administration of PI3K inhibitors can be better tolerated, and can even produce a better anti-cancer effect. For example, intermittent administration of PI3Kα/PI3Kδ dual inhibitor AZD8835 can induce an effective immune-mediated, anti-tumor response in a syngeneic solid tumor model in mice.[132] Pulsed administration of copanlisib also produced an effective anti-tumor immune response in an animal model.[133] Therefore, to determine the full potential of PI3K inhibitors, clinical pharmacological characteristics, such as dose and dosing interval, can be further studied to minimize toxicity while maintaining efficacy.

Conclusion

Each component of the PI3K–AKT–mTOR pathway may be changed in NSCLC, and its abnormal activation may be one of the mechanisms of acquired resistance to EGFR–TKIs in patients with NSCLC and *EGFR* activating mutations. At present, various PI3K pathway inhibitors are being evaluated for efficacy and safety in NSCLC treatment in preclinical and clinical studies, including pan class I PI3K inhibitors and selective PI3K inhibitors, AKT inhibitors, mTOR inhibitors, and dual PI3K–mTOR inhibitors. At present, small-molecule inhibitors targeting the PI3K signaling pathway have been clinically verified in phase I and phase II clinical trials. Although they have not produced exciting therapeutic effects, based on their important role in the development of NSCLC, PI3K inhibition drugs can still be further developed and applied through strategies such as patients selection. In view of their adverse reactions and potential drug resistance mechanisms, and the consideration of improving drug efficiency, it is necessary to further improve the regulatory mechanism of PI3K in NSCLC. The development of new biomarkers to stratify patients, the use of combination therapy with other treatments, the dual-target therapy, and the development of improved and more selective inhibitors and drug delivery systems, will provide new options for curing NSCLC in the near future.

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Conflicts of interest

None.

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