Role of *STK11* in *ALK*-positive non-small cell lung cancer (Review)

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Abstract. Anaplastic lymphoma kinase *(ALK)* inhibitors have been shown to be effective in treating patients with *ALK*-positive non-small cell lung cancer (NSCLC), and crizotinib, ceritinib and alectinib have been approved as clinical first-line therapeutic agents. The availability of these inhibitors has also largely changed the treatment strategy for advanced *ALK*-positive NSCLC. However, patients still inevitably develop resistance to *ALK* inhibitors, leading to tumor recurrence or metastasis. The most critical issues that need to be addressed in the current treatment of *ALK*-positive NSCLC include the high cost of targeted inhibitors and the potential for increased toxicity and resistance to combination therapy. Recently, it has been suggested that the serine/threonine kinase 11 (*STK11*) mutation may serve as one of the biomarkers for immunotherapy in NSCLC. Therefore, the main purpose of this review was to summarize the role of *STK11* in *ALK*-positive NSCLC. The present review also summarizes the treatment and drug resistance studies in *ALK*-positive NSCLC and the current status of *STK11* research in NSCLC.

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Abbreviations: NSCLC, non-small cell lung cancer; ALK, anaplastic lymphoma kinase; IR, insulin receptor; ALCL, anaplastic large cell lymphoma; EML4, echinoderm microtubule-associated protein like protein 4; CNS, center nervous system; FDA, food and drug administration; AMPK, amp-activated protein kinase; EGFR, epidermal growth factor receptor; MEK, MAP kinase-Erk kinase; ERK, extracellular signal-regulated kinase; NRF2, nuclear related factor 2; NADPH, nicotinamide adenine dinucleotide phosphate; PFS, progression-free survival; OS, overall survival; ORR, objective remission rate; LKB1, liver kinase B1; TMB, tumor mutation burden; ATP, adenosine triphosphate; IO, immunotherapy; *STK11*, serine/threonine kinase 11; STK11m, STK11 mutation; STK11wt, STK11 wild-type; PD-1, programmed death 1; PD-L1, programmed cell death-ligand 1

Key words: non-small cell lung cancer, anaplastic lymphoma kinase-positive, *STK11*, drug resistance, targeted therapies

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1. Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) being the most common subtype (1). The majority of patients with NSCLC are diagnosed at an advanced, inoperable stage (2) and have an overall 5-year survival rate of just 5% (3). This poor prognosis may be associated with tumor heterogeneity, acquisition and intrinsic resistance to therapeutic agents in NSCLC (4). If the most appropriate treatment is identified early and drug resistance is addressed to a satisfactory degree, patient survival can be significantly improved. Current non-surgical treatments for NSCLC in clinical practice include systemic chemotherapy, radiotherapy, targeted therapy and immunotherapy (IO). In recent years, rapid developments have been made in cellular and molecular biotechnology, and targeted gene therapy and IO are gradually gaining traction (5). Molecular testing is commonly used in NSCLC, and the detection of epidermal growth factor receptor (*EGFR*), B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) and MET proto-oncogene, receptor tyrosine kinase (*MET*) mutations, as well as anaplastic lymphoma kinase (*ALK*), ROS proto-oncogene 1, receptor tyrosine kinase (*ROS1)*, ret proto-oncogene (*RET*) and neurotrophic receptor tyrosine kinase 1 (*NTRK1*) translocations have been incorporated into the diagnostic criteria for NSCLC, and inhibitors of these kinases are now

routinely used in the clinic (6). An increasing number of signaling pathways and driver genes are being identified, and therapeutic drugs for NSCLC are emerging (7,8). Targeted drugs can bind specifically to the oncogenic site and induce cancer cell-specific death (9). Targeted drugs have a higher efficacy and fewer side effects than chemotherapy (10,11). However, each generation of targeted drugs shows different degrees of resistance; therefore, identifying new therapeutic targets following resistance is crucial. Multiple mutations are not uncommon in clinical practice in recent years, and exploring serine/threonine kinase 11 (*STK11*) co-mutations in *ALK*-positive NSCLC patients is important.

A number of recent studies have linked the presence of *STK11* mutations to the lack of response to IO in NSCLC (12-16). In addition, several clinical studies have further elucidated the biological role of *STK11* mutations leading to primary resistance to IO (17-19). The implementation of *STK11* mutations as a routine biomarker in NSCLC remains controversial and is not performed in daily practice (20).

Therefore, the aim of the present study was to investigate the role of *STK11* in *ALK*-positive NSCLC, review the treatment of patients with *ALK*-positive NSCLC, and compare the clinical efficacy, resistance mutations and appropriate resistance solutions of three generations of *ALK* inhibitors.

2. Current research advances in *ALK*-positive NSCLC

ALK and NSCLC. As a receptor tyrosine kinase of the insulin receptor (IR) subfamily, ALK has been found to play an important role in various types of cancer, particularly in anaplastic large cell lymphoma (ALCL), NSCLC and neuroblastoma (21). In 2007, the echinoderm microtubule-associated protein like protein 4 (*EML4*)-*ALK* fusion gene was identified in a group of NSCLC patients (22). This fusion is the result of an inversion of the short arm of chromosome 2, where the human *EML4* and *ALK* genes are present (23). *EML4* contains a coiled oligomeric structural domain, which mediates the dimerization and structural activation of *ALK*. Like in ALCL, many different *ALK* fusions have been identified, but *EML4-ALK* is the most common variant (24). *ALK* has been reported to regulate several different pathways involved in cell proliferation and survival, such as the phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian targets of rapamycin (mTOR), RAS/RAF/MAP kinase-extracellular signal-regulated kinase (ERK) kinase (MEK)/ERK and JAK/STAT pathways (Fig. 1), once it is dimerized and activated by autophosphorylation upon binding to its ligands, pleiotrophin and midkine (25,26). Direct evidence for the oncogenic potential of *EML4-ALK* in lung carcinogenesis has been found in mice. The transgenic overexpression of *EML4-ALK* in type II alveolar cells via the surface activated protein-c or Clara cell secretory protein promoter leads to the rapid development of tumors with features of lung adenocarcinoma (27,28). A total of 3-7% of NSCLC (mainly adenocarcinoma subtypes) cases are characterized by *ALK* rearrangements, which occur in a mutually exclusive manner with *KRAS* and *EGFR* mutations (29,30). Of note, a previous study developed *in vivo* induction models by inducing *EML4-ALK* rearrangement, which leads to lung carcinogenesis. These models have shown a sensitivity to *ALK* inhibition, thus serving as valuable tools to explore the mechanisms of *EML4-ALK*-induced lung cancer and response to *ALK*-targeted therapy (31). Of note, *ALK*-positive NSCLC patients have a healthy weight, are non-smokers or are young (32).

Current targeted therapies for patients with ALK-positive NSCLC. Prior to the discovery of the *EML4-ALK* fusion protein, chemotherapy was the first-line treatment option (33). *ALK* inhibitors have shown potent clinical activity in patients with NSCLC (34). Three generations of *ALK* inhibitors have been approved for clinical use (2). Ten years ago, the first-generation *ALK* inhibitor crizotinib was approved for clinical treatment. Table I documents clinical studies associated with ALK inhibitors (35-46). In a series of subsequent clinical trials, crizotinib demonstrated good clinical efficacy, including in 149 patients with NSCLC and *ALK* mutations (PROFILE1001), with an objective remission rate (ORR) of 60.8% and progression-free survival (PFS) of 9.7 months in 143 patients evaluated; several other phases of clinical trials also achieved useful results (35) (Table I). However, since crizotinib cannot easily cross the blood-brain barrier, it leads to brain metastases and resistance in patients (24). The rapid development of resistance during the treatment cycle is the main limiting factor associated with crizotinib (47). Since then, progeny *ALK* inhibitors have demonstrated significant efficacy and better central nervous system (CNS) activity compared with crizotinib (48-50). Among the clinical studies of second-generation *ALK* inhibitors, the ASCEND series was a series of studies evaluating the safety and efficacy of ceritinib. Based on this series, ceritinib was approved by the food and drug administration (FDA) for clinical treatment in 2014, mainly for patients who were intolerant to crizotinib or whose disease progressed after taking crizotinib in *ALK*-positive patients (33). As a result, the FDA approved brigatinib for patients who had failed prior *ALK* inhibitor therapy (33). In the J-Alex study in Japan, alectinib was compared head-to-head with crizotinib. The latest data from this trial demonstrated a PFS of 34.1 and 10.2 months in the alectinib and crizotinib groups, respectively (42). In the global ALEX study, a new record was set with a PFS of 34.8 months for first-line treatment with alectinib (Table I), which was approved for the treatment of pure *ALK*-positive patients based on the results of the randomized phase III ALEX trial. In addition, alectinib was effective in preventing the development of brain metastasis and significantly reduced the risk of CNS progression in patients by 84% (43,44). The ALTA-1L study was a study comparing the efficacy and safety of brigatinib with those of crizotinib as first-line treatment for patients with *ALK*-positive metastatic NSCLC (51). The final results showed that when multiple targeted drugs cause resistance, patients can still benefit from brigatinib. Thus, brigatinib has a unique advantage in follow-up therapy. The third-generation *ALK* inhibitor lorlatinib was found to inhibit both the *ALK* and *ROS1* pathways and overcome the multi-resistance associated with first- and second-generation *ALK* inhibitors, while also crossing the blood-brain barrier (45). Regarding IO, irrespective of the histological type, patients treated with atezolizumab showed a significantly longer overall survival than platinum-based chemotherapy in patients with NSCLC with a high programmed cell death-ligand 1 (PD-L1) expression, with a significantly superior efficacy (52).

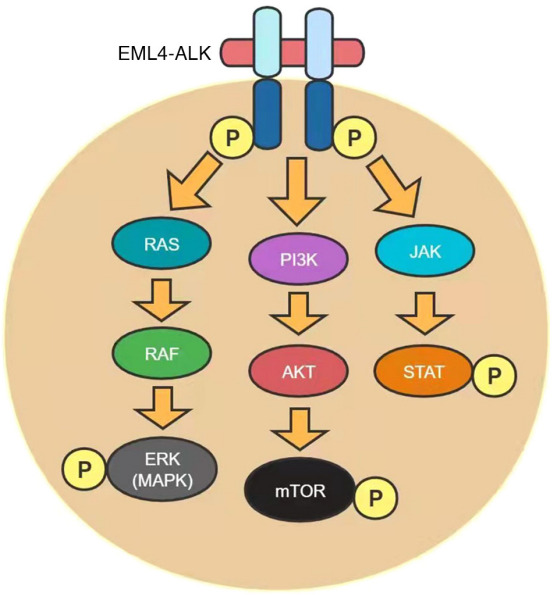

Figure 1. Signaling pathway of *EML4-ALK* activation. *EML4*, echinoderm microtubule-associated protein like protein 4; *ALK*, anaplastic lymphoma kinase; *ERK*, extracellular signal-regulated kinase; PI3K, phosphatidylinositol-3-kinase; *mTOR*, mammalian targets of rapamycin; JAK, Janus kinase; STAT, signal transducer and activator of transcription; P, phosphorylated.

Table I. Clinical studies associated with ALK inhibitors.

Clinical study	Drug	mPFS (month)	ORR (%)
PROFILE 1001 (35)	Crizotinib	9.7	60.8
PROFILE 1005 (36)	Crizotinib	8.4	54.0
PROFILE 1007 (37)	Crizotinib	7.7	65.0
PROFILE 1014 (38)	Crizotinib	10.9	74.0
ASCEND-1 (39)	Ceritinib	18.4	72.0
ASCEND-2 (40)	Ceritinib	5.7	38.6
ASCEND-4 (41)	Ceritinib	16.6	72.5
J-ALEX (42)	Alectinib	34.1	92.0
ALEX (43,44)	Alectinib	34.8	82.9
ALTA-1L (45)	Brigatinib	24.0	71.0
B7461001 (46)	Lorlatinib	9.6	46.0

ALK, anaplastic lymphoma kinase; mPFS, median progression-free survival; ORR, objective response rate.

Mechanisms of ALK inhibitor resistance. Although *ALK* inhibitors are clinically effective, patients still experience various types of drug resistance. This usually occurs in the form of *ALK* kinase structural domain mutations, *ALK* site amplification or activation of 'bypass' signaling pathways, ~1/3 of which are *ALK* kinase structural domain mutations (53). The first mutations identified were the L1196M and C1156Y (54), and L1196M is a residue known as the 'gatekeeper' that controls the entry of small-molecule *ALK* inhibitors into a hydrophobic pocket within the catalytic site and can spatially block inhibitor binding (55). Meanwhile, *L1196M* is the most common mutation in which patients develop resistance to crizotinib (47), while *C1156Y* develops resistance through other different mechanisms. Cysteine is similar to the catalytically important αC-helix within the structural domain of *ALK* tyrosine kinase, so its substitution for tyrosine is thought to prevent inhibitor binding by stabilizing the activity of *ALK* (47). Other resistant mutations that map to the same region with the same mechanism of resistance include *1151Tins*, *F1174C/L*, *L1198P*, *L1152R/P* (47,56,57) and *L1171T* (12,13,58). Acquired resistance to crizotinib usually emerges after 1 year of treatment. *ALK-E1210K* mutations have been detected in patients treated with crizotinib (14). Other secondary mutations that occur following crizotinib treatment include *L1196M*, *G1269A*, *G1202R*, *S1206Y*, *G1269A*, *L1152R*, *D1203N*, *I1171T*, *V1180L* and *C1156Y* (13,47). The second-generation *ALK* inhibitors ceritinib, alectinib and brigatinib were found to show a stronger anti-*ALK* activity compared with crizotidnib (16). In addition, they exhibited greater CNS permeability and the ability to target multiple secondary *ALK* mutations. The direct application of second-generation *ALK* tyrosine kinase inhibitors has been shown to result in better therapeutic outcomes. In addition to *ALK*, ceritinib inhibits insulin-like growth factor 1 (IGF1), *ROS1* and the IR (17,18). In addition, ceritinib inhibits multiple *ALK* mutations resistant to crizotinib, including *L1196M*, *G1269A* and *S1206Y* (47). However, *C1156Y/T, I1151Tins* and *L1152P/R* mutations have been associated with the emergence of ceritinib resistance (19). Alectinib has a better efficacy against *G1269A*, *L1196M*, *F1174L* and *C1156Y* mutations (20); however, alectinib treatment has been shown to cause the emergence of resistance mutations (*I1171T/N/S*, *V1180L* and *G1202R*) (14,58), and the activated bypass signaling pathway to be mediated by hepatocyte growth factor (HGF) and *MET* (59). Epithelial-mesenchymal transition (EMT) is a potential mechanism of alectinib resistance, characterized by the loss of E-cadherin and increased expression of waveform proteins (60). Brigatinib is a novel inhibitor of *ALK*, *ROS1* and *EGFR*. Brigatinib inhibits crizotinib-resistant mutations, including *ALK L1196M* and *EGFR T790M* (51). Lorlatinib can be used to treat all known *ALK* inhibitor-induced resistance mutations and is the treatment of choice for patients with alectinib resistance (61). The *L1198F* mutation was recently reported to exhibit resistance to lorlatinib mainly by interfering with drug binding through spatial site block. It has also been reported that *L1198F* mutation enhances the binding of crizotinib, reduces the effect of *C1156Y* and enhances susceptibility to crizotinib resistance (62). However, as for how to overcome *L1198F* mutation, the clinical efficacy and resistance mechanisms of lorlatinib need to be elucidated.

Known mechanisms of resistance include point mutations, fusion gene amplification and bypass signaling through the activation of other oncogenes (Fig. 2) (63), and AMPK, which is closely associated with *STK11* mutation and is one of the important pathways in the mechanism of *ALK* inhibitor resistance (30).

3. Current research progress on *STK11*

Function of STK11. *STK11* is considered an important tumor-suppressor gene with a wide range of metabolic functions (64). It encodes the serine/threonine kinase liver kinase B1 (*LKB1*), which activates a family of 12

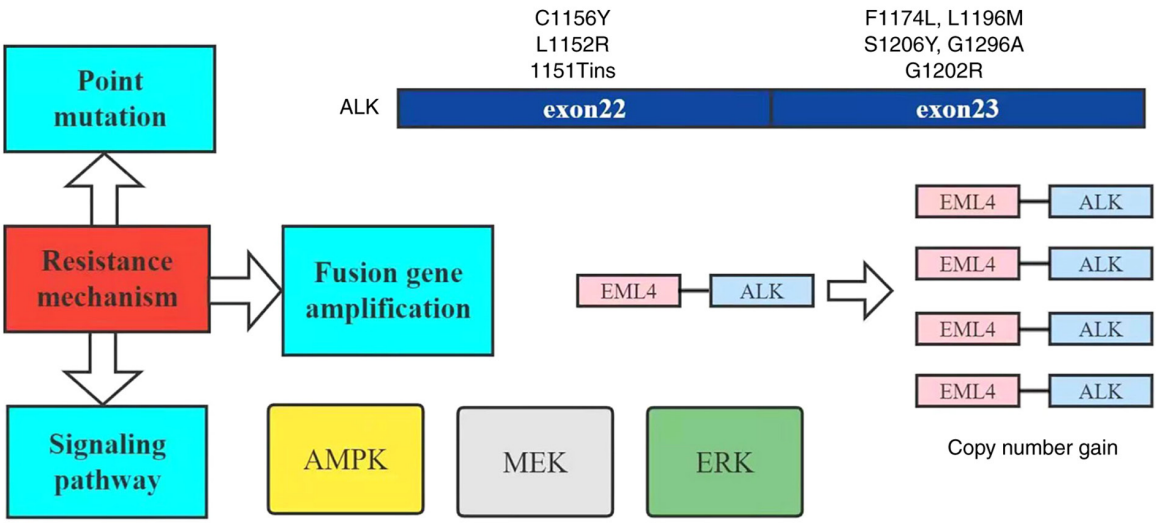

Figure 2. Mechanisms of resistance to *ALK* inhibitors. *ALK*, anaplastic lymphoma kinase; *EML4*, echinoderm microtubule-associated protein like protein 4; AMPK, AMP-activated protein kinase; MEK, MAP kinase-ERK kinase; ERK, extracellular signal-regulated kinase.

downstream kinases, including AMPK, and plays a role in essential biological functions, including cellular energy regulation (65). It is also involved in several physiological processes, including the regulation of cellular metabolism, cell polarity and DNA damage response (65,66). Tumor cells with inactivated or lost *STK11* are unable to activate adenosine monophosphate-activated protein kinases, and are therefore particularly vulnerable to energy stress states (67). *STK11* inactivation was initially identified in human tumors associated with Peutz-Jeghers genetic syndrome (68). *STK11* also negatively regulates mTOR signaling through its substrate AMPK, and *STK11* loss leads to the aberrant activation of mTOR in a variety of tissues. mTOR inhibitor everolimus has been shown to be effective (69,70). *STK11/LKB1* loss of function has been found in several cancer types, mainly through somatic alterations in the *STK11* gene, such as nonsense mutations, loss of heterozygosity, insertions, intragenic deletions or chromosomal deletions (71-79), while in Asian populations, *STK11* is mainly inactivated through focal deletions (80,81). Although *STK11* is inactivated by a large spectrum of truncating mutations and behaves like a tumor-suppressor gene in different tumor models through mTOR repression (77,82,83), recent studies have shown that *STK11* may also acquire oncogenic properties. Subsequently, somatic *STK11* mutations have been reported in other cancer types (69), including NSCLC (71,84,85). It has now been demonstrated that the loss of *LKB1* affects tumor progression through energy metabolism, cytokine inhibition, tumor immunosuppression and altered cell viability (86-90). Several types of tumors exhibit aberrant mutations in the *STK11* gene. For example, *STK11* deletion in cervical cancer and melanoma is associated with extensive and high-grade metastasis, and a heterozygous deletion of the *STK11* locus in primary breast cancer is associated with metastasis (91,92). *STK11*-mutant lung cancer constitutes a genetic subgroup of aggressive NSCLC with an *in vitro* inhibition of mitogen-activated protein kinase and mTOR signaling-increased sensitivity (93). *STK11* abnormalities have also been associated with cancer-related immune dysfunction. For example, *STK11*-mutant lung cancer suppresses immune surveillance responses (94) and *STK11* deficiency decreases PD-L1 expression (95).

STK11 and NSCLC. *STK11* is one of the most commonly mutated genes in lung adenocarcinoma, and the *LKB1* protein encoded by the *STK11* gene is the second most common tumor suppressor in NSCLC, with mutations or genomic loss occurring in 17-23% of NSCLC cases (84,96,97). In lung cancer, the short *STK11* isoform, lacking 124 N-terminal amino acids, is defined as an oncogene (98). Indeed, it has been shown that cytoplasmic *STK11* interacts with estrogen receptor (ER) α/SRC/PI3K to stimulate the AKT pathway and is associated with a shorter survival (99). These findings suggested that *STK11* may play a tumor-suppressor or oncogene function. This dual mechanism may explain the lack of a clear association between *STK11* alterations and prognosis in lung cancer (100). *In vitro* studies have shown that *STK11* inactivation increases the motility and invasiveness of lung cancer, and facilitates epithelial-to-mesenchymal transition (EMT) in lung cancer, thus enhancing metastatic potential (101,102). In addition, it was shown that *STK11/LKB1* inactivation promotes cancer cell growth and survival through the upregulation of hypoxia-inducible factor 1 (HIF-1). The inactivation of *STK11/LKB1* in lung cancer cells leads to the upregulation of mTOR signaling, providing a growth advantage associated with mitochondrial dysfunction, due to autophagic injury (103,104). The aberrant activation of the PI3K/AKT/mTOR pathway has been identified in 90% of lung adenocarcinomas and 40% of squamous cell carcinomas (105). The PI3K/AKT/mTOR signaling pathway is mainly activated by receptor tyrosine kinases [e.g. epidermal growth factor receptor (EGFR), insulin-like growth factor receptor 1 (IGFR1), vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PGFR)] and is involved in a variety of biological functions, such as proliferation, differentiation, survival, adhesion, motility, invasion and cellular metabolism (106,107). In addition to the activation of the PI3K/AKT/mTOR pathway by growth factors and insulin, different nutritional and environmental signals,

Table II. Chemotherapy and immunotherapy for STK11 mutation status in NSCL.

	OS (month)		PFS (month)	
Variable	STK11m	STK11wt	STK11m	STK11wt
Chemotherapy (130)				
First-line	11.7	18.9	4.5	6.1
Second-line	13.1	15.2	4.2	4.5
Immunotherapy (131)				
First-line	14.2	20.1	4.1	5.4
Second-line	6.6	13.6	2.2	3.1

NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; STK11, serine/threonine kinase 11; STK11m, STK11 mutation; STK11wt, STK11 wild-type.

such as high levels of adenosine triphosphate (ATP), oxygen and elevated serum amino acid levels can also increase the activity of mTOR complex 1 (mTORC1). By contrast, intracellular and environmental stress signals, such as low ATP levels, hypoxia and DNA damage, inhibit mTORC1 activity mainly through AMPK activation (106). mTOR pathway activation has been found to be associated with poor clinical outcomes, invasiveness and metastasis (108-111). It is important to highlight that *LKB1*, encoded by *STK11*, is also associated with AMPK, and that *LKB1*/AMPK may counteract oxidative stress by inhibiting the synthesis of nicotinamide adenine dinucleotide phosphate (NADPH)-consuming fatty acids and increasing the oxidation of NADPH-producing fatty acids (112). At the same time, activated AMPK phosphorylates and activates the transcription factor nuclear related factor 2 (NRF2) (113). NRF2 then activates the transcription of antioxidant genes involved in NADPH production. High NADPH levels, together with autophagy, protect *LKB1*-savvy cancers from oxidative stress and reactive oxygen species (ROS)-induced chemotherapy (cisplatin, paclitaxel and adriamycin) (114). Thus, the activation of NRF2 is associated with more aggressive lung cancers and reduced patient survival (115). Of note, the activation of the *LKB1*/autophagy pathway enables circulating tumor cells to resist loss-of-nest apoptosis (116). Thus, cells lacking *LKB1* undergo apoptosis in response to metabolic stress because they are unable to respond to energy deficiency and restore homeostasis *in vivo* (117). The regulation of *STK11* expression and its role in cancer cell proliferation remains highly complex (118). For example, recent research has shown that asparagine and aspartic acid can regulate AMPK-mediated *p53* activation by physically binding to *LKB1* and regulating *LKB1* activity. *P53* has been reported to control cell survival by generating an auto-amplifying loop through asparagine-aspartate-mediated *LKB1-AMPK* signaling to regulate asparagine metabolism (118). In lung cancer, *STK11*/*LKB1* alterations are the only marker significantly associated with PD-L1 negativity in patients with high/medium tumor mutation burden (TMB) (119). Both elevated TMB and increased PDL1 expression are associated with IO response (120,121). Kelch like ECH associated protein 1 (KEAP1) mutations or double allelic deletions are enriched in patients with *LKB1*-mutant NSCLC tumors. NRF2 is a transcriptional factor and KEAP1 is a negative regulator of NRF2 that binds to the antioxidant response element on DNA and initiates the transcription of several genes involved in the regulation of redox homeostasis and cellular detoxification (122). Clinical studies have shown that in *KRAS*-driven NSCLC, *STK11* mutations leading to loss of function are associated with resistance to anti-programmed death 1 (PD-1) monoclonal antibody therapy, but the molecular mechanisms of pathogenesis are not yet clear (123). Despite some uncertainties, *STK11* functional status is emerging as a reliable biomarker for predicting a lack of response to anti-PD-1 therapy in NSCLC patients. It has been reported in the literature that *STK11* is significantly and significantly associated with decreased survival in meningiomas (124). Although the evidence on the biological role of *STK11* is not sufficient, its prognostic significance in advanced NSCLC needs to be confirmed; clarifying the role of *STK11* will facilitate the analysis of *STK11* mutational status, which may also provide more options for targeted therapy and IO (125). The role and significance of *STK11* in NSCLC needs to be further explored.

Current STK11 mutation therapies for NSCLC. Cancer typically evades immune surveillance by aberrantly expressing immune checkpoints (e.g. PD-1) that isolate tumor cells from the host immune system. Immune blockade using monoclonal antibodies against the immune checkpoint PD-1 and its primary ligand PD-L1 can greatly improve survival in advanced NSCLC, with the greatest impact in patients with stage III and first-line stage IV lung cancer (126-128). However, in patients with other types, the response rate was just 20% (129). In a retrospective cohort study, data from the Clinico-Genomic Database were used to identify patients with metastatic NSCLC who received first-line IO (alone or in combination) or chemotherapy in routine clinical practice. The results suggested that in NSCLC, patients with *STK11* mutation *(STK11m)* exhibit poorer overall survival (OS) and PFS compared with patients with *STK11* wild-type *(STK11wt)* receiving IO or chemotherapy. Survival outcomes analyzed by treatment line and type showed that OS and PFS were worse in the IO treatment group for *STK11m* vs. *STK11wt* (Table II) (130). The results of the study were not optimistic, which further suggested that *STK11* mutations reduce the

survival rate of patients with NSCLC. Most importantly, it is unclear whether STK11 can be used as a predictive biomarker to guide treatment selection, and prospective evaluation is still lacking. Therefore, immunotherapy should not be administered to patients with *STK11*-mutated tumors at the present time (131). At the same time, it has also been reported that *LKB1* encoded by the *STK11* gene may be associated with radioresistance in patients, and several previous studies have shown the role of *LKB1* expression in regulating the response to radiotherapy, based on preclinical experiments (132-134). However, to the best of our knowledge, there are no clinical trials on *STK11* mutations, so a comprehensive evaluation of patients with *STK11* mutations in NSCLC could not be performed.

4. Conclusions and perspectives

Both *STK11* and *ALK* can regulate tumor proliferation and growth through the mTOR pathway, and *STK11* can be oncogenic in NSCLC through the AMPK pathway, which is included in the mechanism of drug resistance in patients with *ALK*-positive NSCLC. mTOR signaling is known to be a master regulator of homeostasis and to integrate various environmental signals to regulate cell growth, proliferation and metabolism. The deregulation of mTOR signaling, particularly its overactivation, is frequent in human cancer. Recent advances in molecular profiling have identified certain genes involved in encoding the mTOR pathway, including *STK11*, *PIK3CA, PTEN* and RPTOR independent companion of MTOR complex 2 (RICTOR), whose amplification or mutation induces mTOR pathway activation. AMPK is a central metabolic sensor that coordinates cell growth and energy balance. In terms of oncogenesis, *LKB1* (mentioned previously) can directly phosphorylate and activate AMPK; therefore, in cells with *LKB1* mutations, the AMPK protein is oxidized and inactivated, leading to cell death. In terms of drug resistance, if the AMPK pathway is abnormally regulated, patients with *ALK*-positive NSCLC then become resistant to the drug.

In conclusion, *STK11* plays an important role in the treatment and drug resistance of patients with *ALK*-positive NSCLC. Although there is no definitive evidence on how *STK11* affects the prognosis of *ALK*-positive patients with NSCLC, the results of this review showed that *STK11* mutations may reduce the survival of *ALK*-positive NSCLC patients.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

XCP and JC contributed to the design of this review. WZ, MW, MXM and ZQY reviewed the references. WZ, JC and XCP wrote the manuscript. WZ, LDY, YYC and NL designed and produced the tables and figures. YYC and NL revised the manuscript critically for important intellectual content. NL acquired the funding. YHY analyzed the data and designed the figures. LDY put a lot of effort into revising the manuscript and is listed as co-first author. Data authentication is not applicable. All authors read and approved the manuscript for publication.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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