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REVIEW

Mechanisms of Resistance to ALK Inhibitors and Corresponding Treatment Strategies in Lung Cancer

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Abstract: Lung cancer continues to be a leading cause of cancer-related mortality and morbidity worldwide. The echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) fusion gene accounts for approximately 3%-5% of gene mutation types. Targeted therapies for ALK mutations have made significant advancements in recent decades, enabling a considerable number of patients to achieve the goal of five-year survival benefits. However, overcoming the drug resistance that arises with current ALK tyrosine kinase inhibitors (TKIs) remain a major challenge in ALK-targeted therapies. In this review, we briefly discuss the primary and secondary mechanisms of resistance to ALK-TKIs, and explore treatment strategies based on progressive resistance models. Meanwhile, novel drugs and combination therapies are being actively researched and developed to address these challenges. The aim is to offer new insights into the mechanisms of resistance and the corresponding treatment strategies to ALK inhibitors.

Keywords: EML4-ALK, ALK-TKIs, resistance mechanism, treatment strategies, lung cancer

Introduction

Lung cancer is highly malignant[1] and poses a significant threat to human health and life.[2] Non-small cell lung cancer (NSCLC), one of the most prevalent types, is characterized by high invasiveness, propensity for metastasis, poor prognosis, and high mortality rate.[3] In recent years, advancements in genotyping, translational research and drug development have ushered lung cancer treatment into the era of the molecular stratification.[4] Genetic targets for NSCLC are constantly being identified, matched targeted therapies in development. Among these, epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) are the most commonly driver genes, with the ALK fusion gene present in approximately 5% of NSCLC cases, making it the second most frequent after EGFR mutations.[1] For ALK-positive NSCLC patients, the efficacy of chemotherapy is notably limited.[5] These patients are also at high risk for intracranial metastasis and are often affected by significant drug-related side effects, such as myelosuppression and gastrointestinal reactions.[6,7]

The advent of targeted drugs marks the beginning of precision medicine era in the lung cancer treatment. The application of ALK-tyrosine kinase inhibitors (ALK-TKIs) has significantly improved OS and progression-free survival (PFS) in patients with ALK mutations.[6] Additionally, ALK-TKIs offer patients a better quality of life by minimizing adverse reactions and providing convenient administration options. At present, the first-line ALK-TKIs available for clinicians to choose include crizotinib, ceritinib, alectinib, brigatinib and lorlatinib. This article focuses on ALK fusion

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genes, the indications and clinical research data of currently approved ALK inhibitors, mechanisms of drug resistance, and treatment strategies following the development of resistance.

ALK Fusion Gene

ALK was first reported as a component of a subtype of anaplastic large cell lymphoma (ALCL).[8] Abnormal activation of ALK, due to point mutation or staining of ALK, triggers downstream signals that can drive tumorigenesis.[9] ALK chromosomal rearrangement is a carcinogenic driving factor of NSCLC, typically resulting from the fusion of the 3'-terminal ALK kinase domain with the 5'-terminal gene partner. To date, more than 90 distinct fusion gene partners have been identified in NSCLC,[10] with the echinoderm microtubule associated protein like 4- anaplastic lymphoma kinase (EML4-ALK) fusion accounting for approximately 85% of cases.[11] ALK fusion, mediated by various fusion partners, can form dimers without relying on their ligands, thereby activating the protein kinase domains and triggering multiple downstream signaling pathways that contribute to tumorigenesis (Figure 1).[12] Although ALK fusion partners can influence the intrinsic characteristics of the fusion proteins by altering their stability and kinase activity,[13] ALK-TKIs are currently not selected according to the fusion type.

The EML4-ALK fusion gene results from a small inversion on the short arm of chromosome 2, where EML4 is fused with the ALK sequence fragment separated by 12 bases.[11] (Figure 2) EML4-ALK is more prevalent in young patients, nonsmokers or light smokers, Caucasian adenocarcinoma patients with a high proportion of signet ring cells, and Asian adenocarcinoma patients with a predominance of solid components.[14,15] ALK mutations are mutually exclusive with other genetic changes, so EFGR and Kirsten rats arcomaviral oncogene homolog (KRAS) mutations are rare in ALK-positive patients.[16] Due to multiple splicing sites at the 5' end of the EML4 gene, at least 17 variant subtypes of EML4-ALK have been identified, including V1, V2, V3a/b, V5a/b, V5', V7 and non-EML4-ALK. Among these, the V1 (E13; A20) and V3 variants (E6; A20) are the most common.[17] These variant subtypes have been linked to differences in drug sensitivity,[18] protein stability,[19] and the emergence of drug resistance mutations.[20] Specifically, patients with V1 and V2 variants exhibit significantly higher sensitivity to ALK-TKIs than those with V3 variants, and patients with V5a variants have significantly shorter PFS during ALK-TKIs treatment compare to those with V1 and V2 variants.[18]

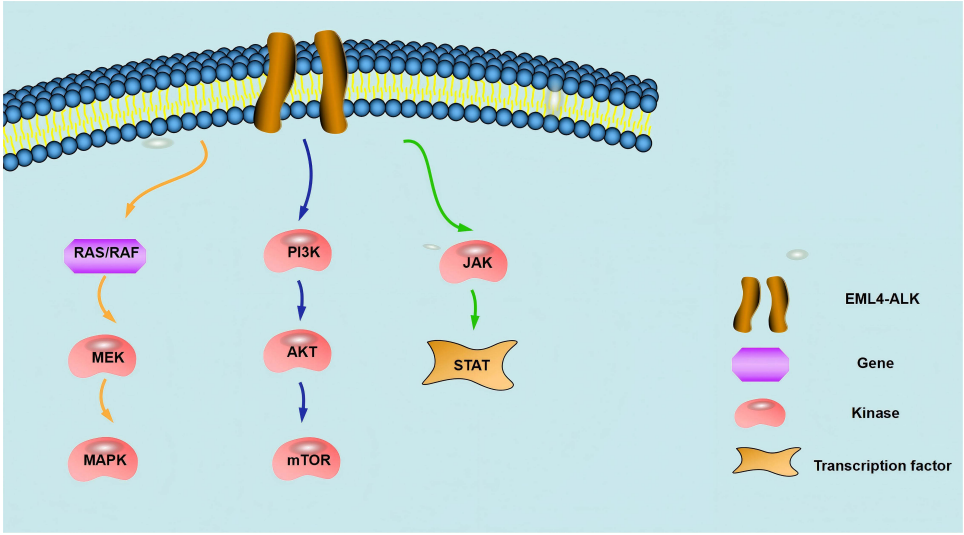

Figure 1 EML4-ALK signaling pathway.
Note: EML4-ALK is localized in the cytoplasm and primarily promotes cell proliferation, invasion, metastasis, and inhibits apoptosis through three signaling pathways: the MAPK/MEK/ERK, PI3K/AKT, and JAK/STAT3 pathways. In the figure, purple represents genes, pink denotes kinases, and light yellow indicates transcription factors.
Abbreviations: EML4-ALK, Echinoderm microtubule associated protein like 4- anaplastic lymphoma kinase; RAS/ RAF, rat sarcom/Rapidly Accelerated Fibrosarcoma; MEK, mitogen-activated extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; PI3K, Phosphatidylinositol-3-kinase; JAK, just another kinase; STAT, Signal Transducer and Activator of Transcription; mTOR, Mammalian target of rapamycin.

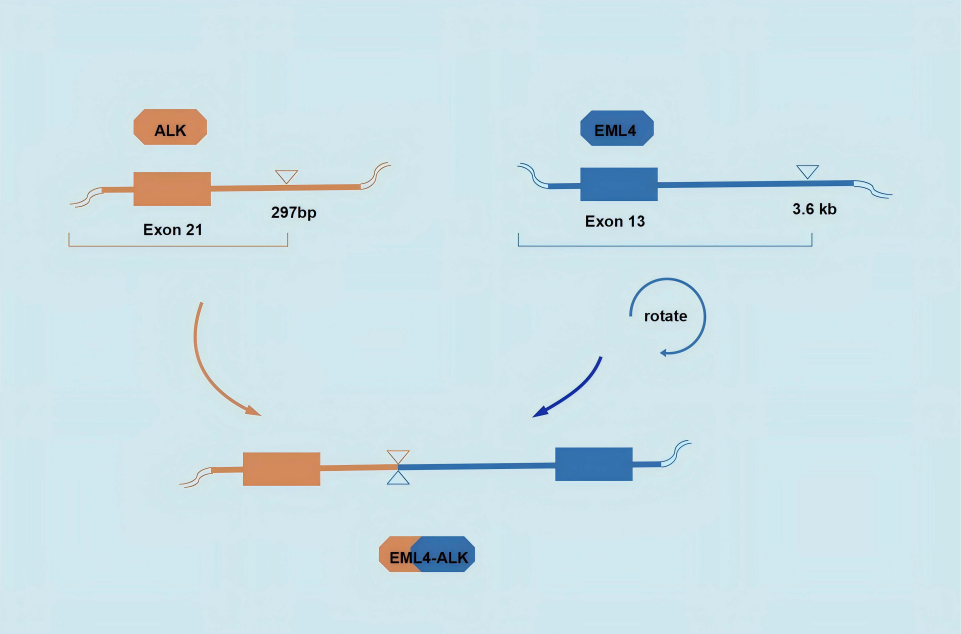

Figure 2 EML4-ALK fusion gene structure.
Note: ALK gene and EML4 gene are directed to chromosome 2p from opposite directions. 297bp upstream of exon ALK 21 is connected to 3.6kb downstream of exon EML4 13, forming EML4-ALK fusion gene (V1 variant subtype).
Abbreviation: EML4-ALK, Echinoderm microtubule associated protein like 4- anaplastic lymphoma kinase.

ALK-TKI Drug Resistance Mechanism

Despite their efficacy, resistance to ALK-TKIs remains a major challenge. This article explores both pharmacological and physiological mechanisms of drug resistance. Physiological drug resistance can be further categorized into primary and secondary drug resistance, with secondary drug resistance mainly including ALK-dependent and ALK-independent resistance mechanisms.

Pharmacological Resistance Mechanism

One important reason for crizotinib resistance is its limited ability to cross the blood–brain barrier. The accumulation of crizotinib in the intracranial space is prevented by p-glycoprotein (ABCBl/ABCG2),[21] resulting in a concentration of the drug in the blood 384 times higher than in the cerebrospinal fluid.[22] Intracranial progression after crizotinib treatment was as high as 41% in the PROFILE 1005 and PROFILE 1007 studies.[23] No pharmacokinetic-related resistance has been observed with second- and third-generation ALK-TKIs to date.

Physiological Resistance Mechanisms

Primary Drug Resistance

The mainstream view is that ALK-positive NSCLC patients with disease progression within 3–6 months of ALK-TKI treatment are considered to have primary drug resistant to ALK-TKIs.[24] Most evidence of primary drug resistance comes from case reports. Factors such as KRAS gene co-mutation,[25,26] EGFR gene co-mutation,[27] Bcl-2 interacting mediator of cell death (Bim) gene deletion polymorphism,[28] MYC copy number amplification,[29] EML4-ALK rearrangement mutation with low mutant allele fraction (MAF),[30] and etc., have all been considered to be associated with primary drug resistance. ALK fusion protein and EGFR mutation can co-exist and be expressed in the same tumor cells. Variations in protein phosphorylation levels may affect TKI response in patients with ALK/EGFR co-mutation.[28] Additionally, poor clinical outcomes were reported in seven patients with co-mutations of ALK and K-RAS after initial crizotinib treatment.[31] The traditional "rejection theory" has been challenged by the gradual detection of co-existing mutations

in NSCLC. K-RAS co-mutations, in particular, may serve as a negative predictor of TKI response in patients with ALK-positive NSCLC.[32]

High somatic coding mutation loads and DNA repair gene mutations (including TP53) were also found to be involved in primary drug resistance after crizotinib treatment, as demonstrated by Whole Exome Sequencing(WES).[32] A study of 18 primary drug-resistant patients, who had a median progression-free survival (mPFS) of only 2.2 months, was published at American Society of Clinical Oncology (ASCO).[33] Primary resistance has been believed to be associated with rare ALK fusion partners (such as ZC3H8-ALK, ALK-LOC1027238, and ALK-DTNB-ASXL2), PTEN/mTOR mutations, the ALK G3709A mutation, and KIT mutations. Paola found that mutations affecting TP53 gene, especially non-disruptive mutations, are able to affect prognosis of ALK-positive patients in NSCLC. This phenomenon is linked to the acquisition of carcinogenic gain-of-function (GOF) mutations, despite non-destructive mutations maintaining some activity of the wild-type TP53 protein.[34] Using WES and RNA sequencing data, Professor Jason demonstrated that TP53 mutations were associated with a significantly poorer PFS, though TP53 deletions did not adversely affect outcomes, indicating potential functional distinctions between TP53 deletion and mutation in tumor biology.[35] Furthermore, the loss of genes within the ALK region was linked to a shorter PFS. Kevin pointed out that the poor prognostic ALK phenotype likely represents a heterogenous population of primary resistance, early development of resistance and an aggressive disease course.[36] The addition of each poor prognostic factor is suspected to be additive or synergistic in conferring a poor prognostic ALK phenotype. The prognostic association of variant 3 is likely related to the stability of the protein and acquired ALK G1202R resistance mutations, which most commonly affect the first- and second-generation inhibitors, but not lorlatinib. Baseline mutations in TP53, cell cycle regulation, and DNA repair likely relate to higher genomic instability and predispose the cancer cell to acquire novel signaling bypass pathways. Baseline alterations in the signaling pathways also likely promote the escape. Cell cycle disruptions and other alterations in DNA repair are other co-mutations that may strongly predict early resistance and progression. Given the limited research on the mechanisms of primary drug resistance, the mechanisms of primary drug resistance are expected to be further explored through large sample studies in the future.

Secondary Drug Resistance

Based on distinct drug resistance mechanisms and corresponding clinical treatment strategies, the secondary drug resistance to ALK-TKIs can be categorized into ALK-dependent and non-ALK-dependent drug resistance. ALK-dependent drug resistance mainly includes secondary gene mutations in the kinase domain and amplification of ALK fusion gene. On the other hand, non-ALK-dependent drug resistance mechanisms primarily involves abnormal activation of bypass signal path, histological transformation, abnormal protein expression, and gene epigenetic regulation.

Secondary Gene Mutations in the Kinase Region

Secondary gene mutations in ALK kinase domain are a common mechanism of drug resistance to ALK-TKIs. These mutations lead to changes in protein conformation and the spatial conformation of the drug-kinase binding region, thus interfering with TKI binding and resulting in acquired drug resistance.[37] ALK mutations mainly occur in several areas,[38] including the ATP-binding pocket, solvent front, ribose binding pocket, N/C-terminal to the α C-helix, and Asp-Phe-Gly. Approximately 20% of patients develop drug-resistant mutations after receiving first-generation ALK-TKI therapy. The most common mutation associated with crizotinib resistance is L1196M, where a leucine residue is replaced by methionine, which has a longer thioether side chain, preventing crizotinib from binding to the ALK kinase due to steric hindrance. Subsequently, other crizotinib mutations were discovered, including the co-mutation G1202R+G1269A.

The probability of gene mutation after second-generation ALK-TKI treatment exceeds 50%. The G1202R mutation in solvent-region, where glycinate residue is substituted by the larger-volume arginine, is one of the most common gene mutations in second-generation ALK inhibitors. This mutation can disrupt the interaction between the piperidine ring in the structure of ceritinib and alectinib and the kinase domain.[39] Some mutations cause ceritinib resistance by producing P-ring fluctuations.[40,41] Alectinib, Brigatinib and Ensartinib were all detected with different drug resistance mutations, of which G1269A could be inhibited by other second-generation ALK-TKIs in addition to ensartinib.[42] Lorlatinib is primarily associated with compound resistance mutations.[43] Among them, the G1202R+L1196M mutation is currently

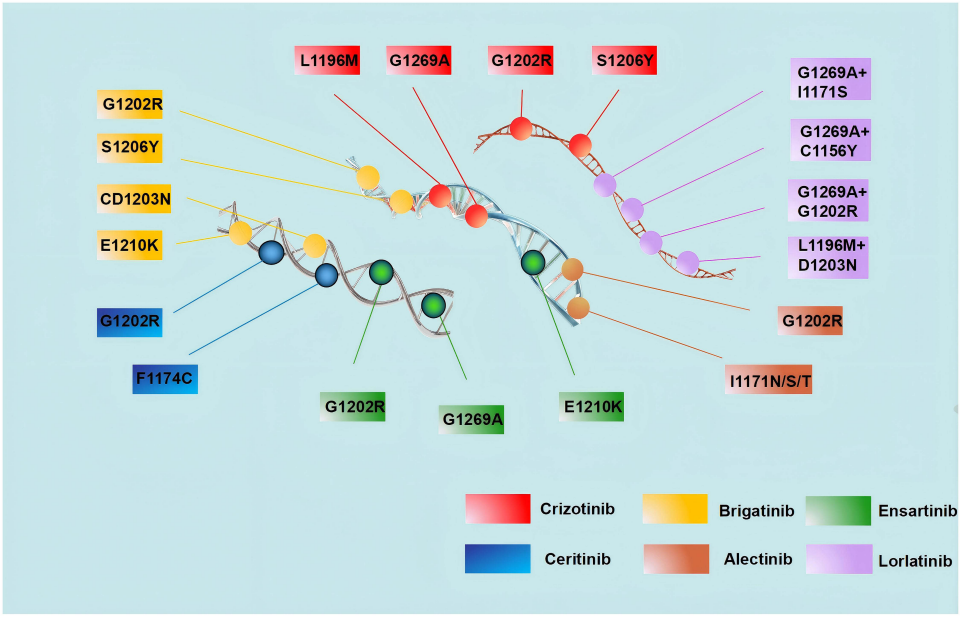

Figure 3 Secondary gene mutations to ALK-TKIs.
Note: The figure shows common gene mutations for the first/second/third-generation ALK-TKIs. Red indicates mutations frequently observed with crizotinib, yellow represents brigatinib-associated mutations, green denotes mutations common to ensartinib, blue corresponds to ceritinib-specific mutations, orange highlights alectinib-related mutations, and purple identifies compound mutations typically associated with lorlatinib.

the most resistant to lorlatinib (IC_{50} = 1000 nmol/L) and confers resistant to all ALK-TKIs.[44] Variant subtypes of EML4-ALK may have different drug resistance mutations. The V3 variant has a higher probability of secondary drug resistance mutations than V1 and V2 variants, and its mutation type tend to be more unique and complex[17,45] (Figure 3).

ALK Fusion Gene Amplification

Crizotinib-induced increased EML4-ALK copy number was first found in a drug-resistant H3122 cell line (H3122CR).[46] Subsequently, an increased copy number of the ALK gene was found in two crizotinib-resistant patients, suggesting that gene amplification may also play a role in acquired resistance.[47] A fusion between Ral GTPase activating protein catalytic subunit alpha 1 Gene (RALGAPA1) and Neuregulin-1 (NRG1) was found in patients treated with alectinib, and gene sequencing confirmed the presence of NRG1 fusion in the cell line (H3122-NRG1) binding RALGAPA1-NRG1 fusion. Moreover, H3122-NRG1 cells showed significant resistance to crizotinib.[48] Currently, only a small fraction of ALK-TKI-resistant patients have been found to have ALK amplification, and the existing data cannot identify the conditions and critical trigger values of gene amplification leading to drug resistance. Therefore, fusion gene amplification is not considered to be the dominant resistance mechanism of ALK-TKIs.

Abnormal Activation of the Bypass Signal Pathway (Table 1)

When the ALK signaling pathway is inhibited, bypass signaling pathways, such as EGFR, KIT and IGF-1R, are activated.[39] These bypass pathways circumvent the original target and activate downstream pathways, leading to ALK inhibitor resistance.[49] The main ligands of the EGF receptor are epidermal growth factor (EGF) and transforming growth factor-α (TGF-α). As a ligand of c-Met, hepatocyte growth factor (HGF) activates the transmembrane signaling pathway after binding to corresponding receptors, which can promote tumor development, metastasis, invasion and may contribute to drug resistance.[50] EGFR upregulates its ligand expression and is the most common bypass activation pathway,[51] which can cause resistance to crizotinib, alectinib, and ceritinib. Abnormal activation of EGFR with increased autophosphorylation, is also thought to contribute to crizotinib resistance.[52] In in vitro experiments, heparin-binding epidermal growth factor-like growth factor (HB-EGF) was found to activate EGFR and trigger resistance to crizotinib through Erk1/2 and Akt transduction bypass signals.[53] The abnormal P13K-AKT pathway is associated with patients with crizotinib

Table 1 Activation Pathways of Abnormal Bypass Signaling Pathways to ALK-TKIs

ALK-TKI	Bypass Signal Path	Mode	Ref
Crizotinib	EGFR	Up-regulation	[51]
Crizotinib	EGFR	Autophosphorylation increase	[52]
Crizotinib	HB-EGF	Abnormal activation	[53]
Crizotinib	P13K-AKT	Abnormal path	[54]
Crizotinib	HER2/3	Amplification	[55]
Crizotinib	PKC	Activation	[55]
Ceritinib	MAP2K1	Mutation	[56]
Ceritinib	SRC signaling	Activation	[58]
Ceritinib	ERK1/2	Activation	[59]
Alectinib	TGF-α	Unknow	[60]
Alectinib	MET	Excitation	[61]
Lorlatinib	NF2	Afunction	[62]
Lorlatinib	MiR-100-5p	Up-regulation	[63]

Abbreviations: EGFR, epidermal growth factor receptor; HB-EGF, heparin-binding epidermal growth factor-like growth factor; P13K-AKT: Phosphatidylinositol-3-kinase-AK; HER2/3: human epidermal growth factor receptor 2/3; PKC, Protein Kinase C; MAP2K1, mitogen-activated protein kinase kinase 1; SRC, sarcoma gene; ERK1/2, extracellular regulated protein kinases1/2; TGF-α, transforming growth factor-α; MET, mesenchymal to epithelial transition factor; NF2, neurofibromatosis type 2.

secondary EGFR L858R mutation resistance.[54] Ligand-mediated human epidermal growth factor receptor 2/3 (HER-2/3) activation and Protein Kinase C(PKC) activation[55] are also implicated in crizotinib resistance. In a cell model study, the MEK inhibitor smeitinib (AZD6244) combined with ceritinib was active in ALK-positive drug-resistant tumors with mitogen-activated proteinkinase kinase 1(MAP2K1)-activating mutations,[56] indicating that acquired resistance can also result from reactivation of downstream effector proteins. The RAS-MEK pathway may be a key downstream effect of EML4-ALK.[57] Activation of the sarcoma gene (SRC) signaling pathway may also contribute to ceritinib resistance.[58] SHP099, a newly discovered SHP2 small molecule inhibitor, when combined with ceritinib, prevents the growth of drug-resistant PDCs by blocking the reactivation of RAS, ERK1, and ERK2 (ERK1/2).[59] TGF-α-induced EGFR pathway activation signal transduction pathway has been observed in alectinib-resistant models. Cell sensitivity to alectinib was restored after the pathway was knocked out.[60] HGF-induced MET activation stimulates the phosphorylation of the adaptor protein Grb-2-associated binder 1 (Gab1) and activates the downstream signaling pathway, contributing to drug resistance in the alectinib bypass signaling pathway.[61] Loss of neurofibromatosis type 2 (NF2) function has been identified as a bypass resistance mechanism of Lorlatinib.[62] Additionally, the upregulation of miR-100-5p may inhibit the expression of mTOR pathway-related mRNA, thus leading to ALK-TKI drug resistance.[63]

Histological Transformation

Histological transformation is another key mechanism of ALK-TKI resistance in NSCLC. Epithelial to mesenchymal transition(EMT) is considered to be the most common morphological change, characterized by loss of epithelial tissue markers and increased expression of interstitial tissue markers, which may be related to upregulation of vimentin expression and downregulation of e-cadherin.[64] Morphological phenotypic changes were observed in artificially induced crizotinib-resistant spindle cells (H2228/CR), suggesting that EMT may be associated with crizotinib resistance.[49] Enrichment of mutated genes in crizotinib-resistant tissues revealed four pathways related to EMT, further confirming that EMT plays a role in crizotinib resistance.[65] Several cases have been reported in which patients with ALK-positive lung adenocarcinoma transformed into small cell lung cancer (SCLC) or squamous cell carcinoma (SCC) after targeted therapy, resulting in drug resistance.[66,67] Deletion of the retinoblastoma (RB) and p53 genes,[68] as well as mutations in the PTEN gene,[69] may have important status in SCLC transformation. For epithelial to EMT-mediated resistance, SRC inhibitors combined with lorlatinib are highly sensitive to patient-derived cell lines.[62]

Abnormal Protein Expression

The overexpression of P-glycoprotein (P-gp) is found in ceritinib-resistant NSCLC. After downregulation of P-gp, drug-resistant cells become sensitive to ceritinib again.[70] P-gp may lead to increased drug effects and decreased drug exposure in the central nervous system, which may provide a reference for the poor intracranial activity of ceritinib.[70] Other studies have shown that exosomes of drug-resistant cells may induce drug resistance in sensitive strains and enhance their cell migration ability.[71]

In addition to gene mutations and signaling pathway abnormalities, gene epigenetic regulation plays an important role in the resistance to ALK-TKIs. DNA methylation, one of the most important mechanisms of epigenetic regulation, has been shown that DNA methylation plays a key role in the resistance to ALK-TKIs. Kim built an in vitro model of ceritinib-resistant NSCLC and employed genome-wide DNA methylation analysis combination with single-cell RNA-seq to identify cytidine deaminase(CDA). CDA was hypomethylated and upregulated in ceritinib-resistant cells. Treatment with epigenome-related nucleosides, such as 5-formyl-2'-deoxycytidine, selectively decreased CDA-overexpressing resistant cells via accumulation of DNA damage.[72] Non-coding RNAs, such as microRNAs(miRNAs) and long non-coding RNAs (lncRNAs), play an important role in regulating gene expression and cell signaling pathways. Byoung investigated the dynamic changes in the transcriptome and enhancer landscape during development of acquired resistance to ALK-TKIs. Histone H3 lysine 27 acetylation (H3K27ac) was profoundly altered during acquisition of resistance, and enhancer remodeling induced expression changes in both miRNAs and mRNAs. The research suggests that enhancer remodeling and altered expression of miRNAs play key roles in cancer drug resistance.[73] Future research could focus on exploring the epigenetic mechanisms and provide new therapeutic targets for overcoming resistance.

Treatment Strategies to Drug Resistance

Resistance to ALK-TKIs is inevitable. The subsequent treatment strategies are different according to the progressive models. Meanwhile, novel drug molecules and combination therapies are being researched and developed (Figure 4).

Treatment of "Oligoprogression"

Patients with progressive disease characterized by ≤5 metastases or ≤2 affected organs after systemic treatment with ALK-TKI were defined as "oligoprogression".[74] Patients with oligoprogression can continue with the original TKI therapy combined with local ablation therapy (LAT), such as radiotherapy, radiofrequency ablation, cryoablation, and surgery. Stereotactic radiotherapy (SRT) is a common method used for tumor control, offering low toxicity and effective treatment for oligoradiotherapy in oncogene-driven NSCLC.[75] Crizotinib combined with radiotherapy has been shown to reduce tumor proliferation, microvascular density and perfusion, while enhancing the inhibitory effect on ALK-positive NSCLC tumor cells.[76,77] Clinical studies have demonstrated that patients with extracranial oligoprogression who were treated with crizotinib and LAT had actuarial local lesion control rates of 100% and 86% at 6 and 12 months, respectively. The median duration of crizotinib use was prolonged by local treatment (28 months vs 10 months).[78] However, a preclinical study presented an opposing view, showing that radiotherapy combined with ALK inhibitors did not significantly improve outcomes compared to radiotherapy alone, and EML4-ALK cells treated with ALK inhibitors showed no significant sensitization to radiation.[79] At present, questions about the safety, mode, and timing of local treatment for minimal progression remain to be answered by more precise prospective studies.

Management of Intracranial Progression

The incidence of brain metastases at the time of first diagnosis in patients with ALK-positive NSCLC is as high as 20%,[80] and this rate gradually increases with prolonged targeted drug therapy.[81] For patients with 1–4 localized brain metastases after ALK-TKI treatment, stereotactic radiosurgery (SRS) is widely used for its low toxicity and protection of normal brain tissue.[82] In addition, localized intracranial progression after crizotinib treatment can be managed by increasing the drug dosage.[83] Compared with crizotinib, second- and third-generation ALK-TKIs have superior blood–brain barrier penetration and intracranial activity,[84] which can improve drug resistance caused by low concentration of crizotinib in the brain. Ceritinib, alectinib, brigatinib, and lorlatinib have all been proven effective for treating localized CNS metastases after crizotinib resistance.[85–88] In patients progressed with second-generation ALK-TKI, lorlatinib readministration achieved a 63.0%

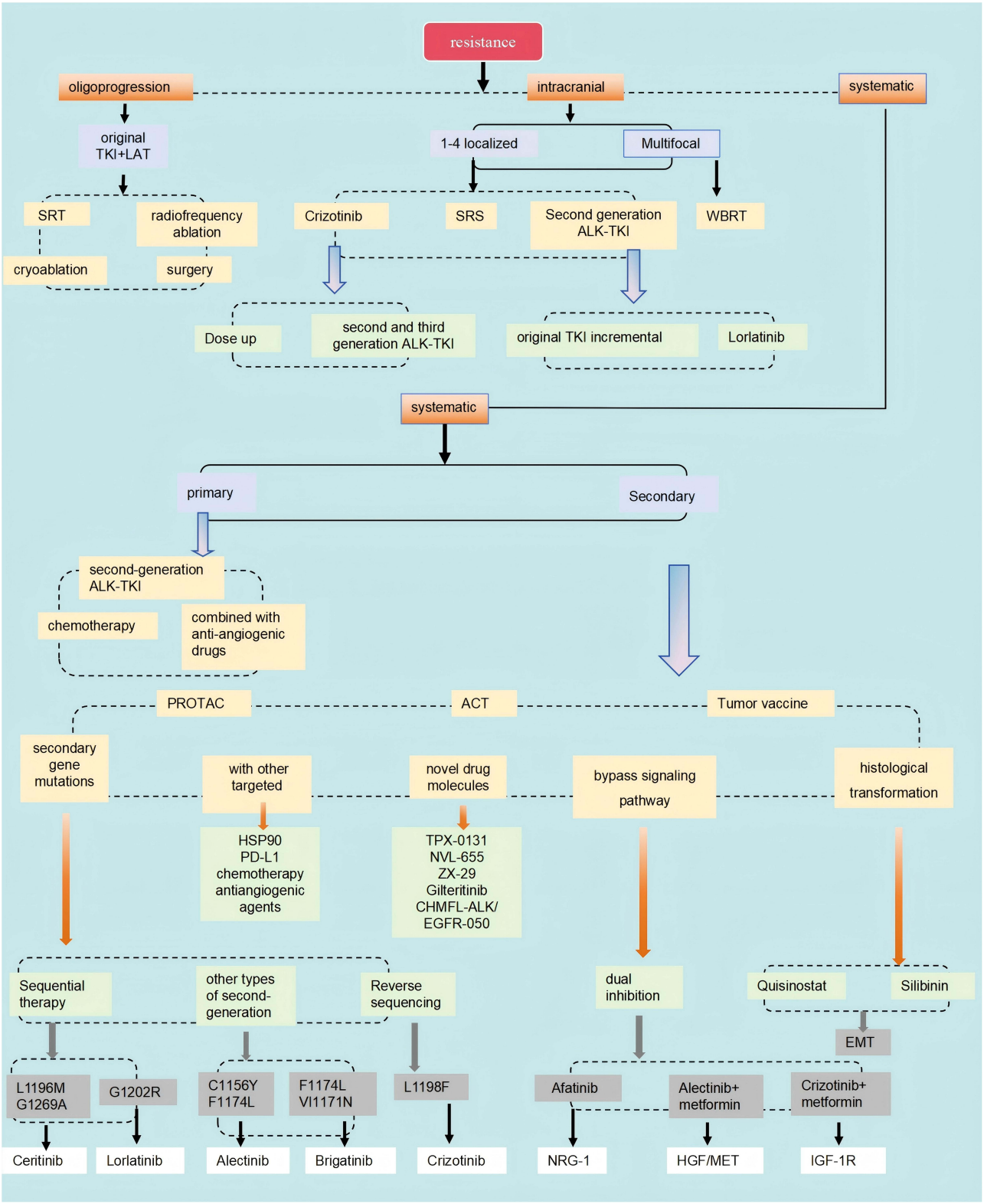

Figure 4 Summary of treatment strategies for drug resistance.
Note: This figure represents the contents of the chapter "Treatment strategies to drug resistance".

intracranial ORR.[89] Alectinib and brigatinib have also been reported to reinduce CNS disease control by dose escalation.[90,91] Therefore, for patients with intracranial progression after second-generation ALK-TKI treatment, lorlatinib or increased doses of the original TKI may be considered. For multifocal CNS progression (more than 4 intracranial lesions), whole brain radiation therapy (WBRT) can relieve symptoms in more than 50% of patients as standard treatment.[92] However, WBRT has a limited effect on survival, with the median survival extension ranging from only 4 to 6 months.[92] For patients with metastatic adenocarcinoma, combination chemotherapy has certain CNS efficacy.[93]

Treatment of Systematic Progress

Treatment of Primary Drug Resistance

Patients with EML4-ALK rearrangement who progressed after 1 month of crizotinib treatment were reported to be sensitive to chemotherapy.[30] Ceritinib considered beneficial for patients with primary crizotinib resistance.[94] ALK-positive patients with primary resistance to crizotinib can derive survival benefits from either second-generation ALK-TKIs or chemotherapy, but there is no significant difference between the two.[95] Nick has reported that dual inhibition of ALK and vascular endothelial growth factor (VEGF) may be a reasonable combined approach.[96] In addition, previous cases have shown that TKIs combined with anti-VEGF drugs can allow the drugs to reach the tumor site and overcome primary drug resistance.[97] However, more evidence is needed to support the use of anti-angiogenic therapy in ALK rearranged NSCLC, including pre-clinical, translational, and clinical data.

Treatment of Secondary Gene Mutations in the Kinase Region (Sequential Therapy and ALK Sequencing Analysis)

Sequential therapy is a common strategy to overcome resistance to ALK-TKIs secondary gene mutations, and more than 70% of patients who were resistant to crizotinib chose to continue treatment with progeny ALK-TKIs.[98] Ceritinib overcomes the common drug resistance mutations of crizotinib by binding specifically to the anterior cleavage site of ALK. The inhibitory effect of alectinib in patients who progressed after treatment with crizotinib was demonstrated in the ALTA-3 trial. Lorlatinib has a good therapeutic effect on almost all the discovered drug-resistant mutations, including high-resistance mutations such as G1202R. In clinical studies, lorlatinib demonstrated an effective rate of 39% in patients who progressed after second-generation TKI treatment, with an ORR reaching 48%.[89] In addition, after developing resistance to a second-generation ALK-TKI, it is possible to switch to another second-generation ALK-TKI. Alectinib showed high activity against F1174L (ceritinib secondary mutation) and D1203N (brigatinib secondary mutation). After alectinib resistance, I1171/N/S and V1180L mutation sites could be inhibited by Ceritinib. Brigatinib can inhibit ensartinib and alectinib secondary mutations G1269A and I1171N, and even inhibit G1202R. Brigatinib also achieved mPFS at 7 months in patients who progressed after multiline therapy (at least 2 ALK-TKIs).[99–101] The G1269A mutation developed after enshatinib treatment can be inhibited by other ALK second-generation targeting drugs (excluding enshatinib).[102]

The reverse selection of ALK inhibitors is also recognized in clinical practice. In patients who switch to alectinib after ceritinib resistance, secondary mutations in I1171T and V1180L can be overcome with ceritinib.[103] Multiple sequential treatments with ALK-TKIs can increase the probability of complex mutations, such as E1210K+D1203N and F1174C +D1203N, but both can be overcome by lorlatinib.[104,105] Some of the complex mutations after lorlatinib treatment may still be sensitive to second generation ALK-TKIs. These findings suggest that selecting different ALK-TKI combinations for sequential therapy is crucial. Even combining two different ALK inhibitors could potentially extend the survival of patients with ALK mutations.

Patients with ALK gene mutations detected by tissue testing demonstrated significantly higher ORR and PFS when treated with lorlatinib compared to those with negative mutation status (69% vs 27% and 11.0 vs 5.4 months, respectively).[106] Therefore, repeated tissue biopsy and NGS resequencing can provide a basis for clinical decision-making. For highly resistant mutations where no ALK mutation is detected, alternative therapeutic targets should be considered. Circulating tumor DNA obtained from liquid biopsy provides insight into the extent of intra-tumor heterogeneity, potentially supplementing results from re-biopsy in a non-invasive manner. The drug-resistant mutation sites and drug-resistant mutation sites that can be covered by ALK-TKIs in Table 2. Clinical studies on sequential treatment of ALK-TKIs are enrolled in Table 3.

Table 2 Table of Resistant Mutation Sites and Drug Resistance Mutation Sites to ALK-TKIs

ALK-TKI	Probability (%)	Drug	Resistant mutation site	Ref	Resistant mutation sites can be covered	Ref
First generation	20%	Crizotinib	L1196M, G1269A G1202R, S1206Y 1151Tins, L1152R C1156Y, F1174L G1202R+G1269A	[47,107–109]	L1198F	[110]
Second generation	>50%	Ceritinib	G1202R, F1174C T1151K, G1123S	[40,41,52,104]	L1196M, G1269A I1171T, S1206Y I1171/N/S, V1180L I1171N+L1196M I1171N +G1269A	[111–115]
		Alectinib	G1202R, I1171N/S/T	[105]	C1156Y, F1174L D1203N, G1269A	[102,105]
		Brigatinib	G1202R, S1206Y CD1203N, E1210K	[116]	G1202R, L1196M F1174L/V, G1269A I1171N, L1198F V1180L I1171N+L1198F I1171N+L1196M I1171N +L1256F	[86,115]
		Ensartinib	G1269A, G1202R, E1210K	[117]	F1174, C1156Y L1196M, S1206R T1151	[118]
Third generation	Unknown	Lorlatinib	G1269A+I1171S/C1156Y/ G1202 L1196M+D1203N G1202R+L1196M/F1174L	[43]	G1202R, 1151Tins I1171N, F1174L E1210K+D1203N F1174C+D1203N	[104–106]

Notes: Resistant mutation site: Secondary resistance mutations that occur after the use of the corresponding drug. Overlays of resistant mutation sites:Secondary drug resistance mutations that occur after ALK-TKIS treatment can be inhibited by corresponding drugs.

Table 3 Clinical Studies on Sequential Treatment of ALK-TKIs

Clinical trial Identifier	First-line	Sequential drug	Phase	Design	Primary endpoint	Secondary Endpoint	Status
NCT03596866	Crizotinib	Brigatinib /Alectinib	3	RCT	PFS	PFS, ORR, DOR	Active not recruiting
NCT04362072	Alectinib/ ceritinib	Lorlatinib	4	Single-Arm	OR	IC-OR, TTR DOR, PFS	Active Not recruiting
NCT04111705	Alectinib/ brigatinib	Lorlatinib	2	Single-Arm	ORR	PFS, DCR DOR, OS	Active Not recruiting
NCT02706626	Alectinib/ ceritinib	Brigatinib	2	Single-Arm	ORR	None	Terminated
NCT04074993	unknown	Brigatinib	2	Single-arm	ORR	DOR, IC-DOR	Active Not recruiting

Abbreviations: RCT, randomized Controlled Trial; PFS, progression-free survival; ORR, objective remission rate; DOR, Duration of Response; MTD, maximum tolerated dose; OR, Objective Response; IC-OR, Intracranial Objective Response; TTR, Time to Response; AEs, Incidence of Adverse events; IC-DOR, Intracranial duration of response.

Treatment of Abnormal Activation of the Bypass Signaling Pathway

To successfully overcome resistance caused by bypass signaling activation, a key therapeutic feature is the dual inhibition of both the oncogene driver and the bypass pathway. Combining ALK-TKIs with EGFR-TKIs can effectively improve drug resistance caused by activation of the downstream EGFR signaling pathway.[119] Alectinib combined with metformin may overcome alectinib resistance caused by activation of the HGF/MET signaling pathway.[120] Similarly, crizotinib combined with metformin also improves resistance mediated by the IGF-1R signaling pathway.[121] In an ALK-rearranged NSCLC cell line containing the origin of the MEK mutation, the combination of the MEK inhibitors selumetinib and

crizotinib reversed H3122CR resistance by inhibiting downstream Ras/MAPK signaling pathways.[122] Cerivastatin can induce Yes-associated protein(YAP) targeting oncogenes such as AXL, Recombinant Human Cysteine-Rich Angiogenic Inducer 61 (CYR61) and TGFβR2 in cells, providing a theoretical basis for the use of YAP in the treatment of ALK-TKI-resistant patients.[123] The combination of alectinib and cerivastatin can successfully reverse the resistance to both alectinib and lorlatinib.[124] In addition, mTOR inhibitors can overcome lorlatinib resistance caused by mutations leading to the loss of NF2 function.[62]

Treatment of Histological Transformation

Histonedeacetylase (HDAC) inhibitors, such as Quisinostat, can overcome drug resistance by inhibiting EMT through the upregulation of miR-200c.[125] When ceritinib is combined with Panobinostat,[73] it downregulates the expression of neuro-cadherin and vimentin, key markers associated with EMT. This enhances the sensitivity and inhibitory activity of ceritinib to drug-resistant cells, and exerts a strong inhibitory effect on the H3122 cell line and mouse transplanted tumors. Finally, the purpose of reversing drug resistance is achieved. Silibinin overcomes the resistance of lorlatinib and brigatinib due to EMT, restoring function through the transforming growth factor-β/drosophila mothers against deca-pentaplegic protein (TGF-β/SMAD) signaling pathway.[126]

Combination With Antitumor Drugs of Other Targets (Table 4)

Heat shock protein 90 (HSP90) is highly sensitive to the EML4-ALK fusion protein, and the use of HSP90 inhibitors can block the binding of HSP90 to ATP and promote proteasome-mediated degradation of HSP90 target proteins.[127] At present, the dual-target inhibitor of HSP90 and ALK-TKI (NCT712217) has entered phase II clinical trials and is expected to combat resistance to ALK-TKI.[128] After 5 months of nivolumab treatment, the tumor tissue disappeared completely, with a complete response lasting up to 18 months.[129] The proposed mechanism involves overexpression of the EML4-ALK fusion protein, which upregulates STAT3 protein via hypoxia-inducing factors and signal transcription. This, in turn, increases the expression of Programmed Cell Death-Ligand 1(PD-L1), leading to T-cell suppression and immune escape of tumor cells.[129] The clinical study evaluating the combination of ALK-TKIs and nivolumab for progressive NSCLC (NCT02393625) has been closed due to grade 3 or greater hepatotoxicity observed.[130] Meanwhile, the clinical study NCT02584634, which explores the combination of ALK-TKIs and Avelumab, has been transferred to a sub-study for further evaluate efficacy. Retrospective studies have shown that ALK-TKI combined with chemotherapy

Table 4 Clinical Studies to ALK-TKIs Combined With Antitumor Drugs of Other Targets

Clinical trial Identifier	ALK-TKI	Combination drug	Intervention Model	Phase	Primary endpoint	Secondary endpoint	Status
NCT02393625	Ceritinib	Nivolumab	Parallel Assignment	I	MTD, ORR	DOR, DCR TTR, PFS	Active, not recruiting
NCT03087448	Ceritinib	Trametinib	Single Group Assignment	I/II	MTD	ORR, DCR PFS, OS	Terminated
NCT03202940	Alectinib	Cobimetinib	Single Group Assignment	IB/II	MTD	ORR, PFS, OS, DOR	Recruiting
NCT02521051	Alectinib	Bevacizumab	Single Group Assignment	I/II	Recommended phase II dose Safety and tolerability	CNS-ORR CNS-DCR CNS-PFS	Unknown
NCT04005144	Brigatinib	Binimetinib	Single Group Assignment	I	Safety, tolerability	ORR, PFS, OS	Terminated
NCT04292119	Lorlatinib	Crizotinib, Binimetinib, TNO155	Parallel Assignment	1/2	MTD, ORR	PFS, DOR	Unknown
NCT04227028	Brigatinib	Bevacizumab	Single Group Assignment	1B	Incidence of AE MTD	ORR, DOR PFS, OS	Recruiting
NCT02321501	Ceritinib	Everolimus	Single Group Assignment	I/Ib	MTD	RR, PFS,	Active, not recruiting

Abbreviations: MTD, maximum tolerated dose; ORR, objective response rate; DOR, Duration of Response; DCR, disease control rate; TTR, Time to Response; PFS, progression-free survival; OS, overall survival; CNS, Central nervous system; AE, adverse events; RR, Response rate.

is a potential treatment option.[131] Additionally, a combination of ALK-TKIs with antiangiogenic agents (NLCTG1501) showed a DCR of 67% and an ORR of 8%.[132]

Novel Drugs to Overcome Drug Resistance

Fourth-Generation ALK-TKIs

TPX-0131, a fourth generation of ALK-TKI, was developed to overcome both mutations that arised from continuous ALK-TKIs use and acquired complex double mutation based on G1202R. TPX-0131 is a highly permeable macrocyclic molecule in the CNS that tightly binds to adenine sites in ATP pockets. TPX-0131 can inhibit a variety of ALK-resistant mutations, especially SFM G1202R and the complex L1196M/G1202R. The efficacy of TPX-0131 against G1202R is over 100 times greater than that of lorlatinib, but its efficacy against I1171N and G1269S is less potent.[133] TPX-0131 can effectively inhibit both wild-type ALK (IC50: 10 nmol/L) and 26 ALK mutants. In animal experiments, TPX-0131 can completely shrink tumors compared with lorlatinib, and the level of TPX-0131 in rat cerebrospinal fluid is approximately 66% of that in plasma.[133] The clinical trial for TPX-0131 (NCT04849273) is currently underway, targeting Alk-positive advanced NSCLC patients who have received less than 3 ALK-TKI treatments, and the primary outcome was ORR.

NVL-655 was designed to increase ALK selectivity and reduce CNS adverse events caused by off-target inhibition of the tropomyosin receptor kinase (TRK) family. NVL-655 effectively inhibit single and complex mutations, including solvent frontier G1202R, G1202R/L1196M, G1202R/G1269A, and G1202R/L1198F.[134] NVL-655 showed significant efficacy in Ba/F3 transplantation models of EML4-ALK V1 variant subtypes, with much higher in vivo tumor activity than lorlatinib. NVL-655 is highly selective for ALK and does not affect TrkB, so it can minimize TRK-related CNS adverse events.[135] A phase I/II clinical study of ALKOVE-1 (NCT05384626) is currently underway. The Phase I study is focused on dose escalation and safety to recommend the Phase II dose, while the Phase II study evaluates ORR and efficacy in ALK-positive lung cancer using blinded independent review committees (BICR).

Other New ALK-TKIs

ZX-29, a novel ALK-TKI, demonstrates impressive potency with IC50 values of 2.1 nM for wild-type ALK, 1.3 nM for ALK L1196M, and 3.9 nM for G1202R. ZX-29 can induce protective autophagy and apoptosis by inducing endoplasmic reticulum stress, overcoming cell resistance caused by ALK mutations, and exhibiting more powerful cytotoxicity than ceritinib.[136,137] Currently, ZX-29 is still in the preclinical development state. Gilteritinib, which acts on R/R acute myeloid leukemia, is an FM-associated receptor tyrosine kinase inhibitor.[138] Gilteritinib forms hydrogen bonds with residues such as M1199 and E1210, and overcomes single mutations and complex mutations with strong resistance, such as I1171N+L1198H and I1171N+F1174I.[139,140] Gilteritinib inhibits both wild-type and mutant ALK. Gilteritinib exerts better drug resistance activity than the previous 3 generations of ALK-TKIs by inserting into the ATP-binding site of ALK, providing additional treatment options for drug-resistant patients. Some researchers have also modified ceritinib by replacing the piperidine ring with a group of lower steric hindrance, resulting in compounds effective against both wild-type and crizotinib-resistant mutants, including the highly resistant G1202R.[141] Another reported dual-target ALK/EGFR inhibitor, CHMFL-ALK/EGFR-050, has demonstrated strong tumor suppressor activity in vivo and in vitro.[142] CEP-37440, as a dual inhibitor of ALK/FAK, has been shown to be effective against multiple ALK kinase mutations,[143] with a stronger intracranial drug dose, potentially offering greater therapeutic properties in patients with tumor brain metastases. Other new ALK-TKI candidates include WX-0593,[144] ASP3026,[145] CT-707,[146] TQ-B3139,[147] APG2449 and ZG0418 (Table 5).

PROTACs

Proteolytic targeting chimeras (PROTACs) are an emerging drug development technology that uses the ubiquitin–proteasome system (UPS) to degrade target proteins and has become a hotspot in the field of tumor therapy research.[148] PROTACs can expand the accessibility of targeted proteins, directly degrade without changing enzyme activity and eliminate all functions of the protein, and has low requirements for binding sites. The mechanism leads to the use of PROTACs at lower doses, greatly reducing off-target effects and drug resistance.[148] PROTAC molecules targeting ALK have been gradually developed. MS4077, which uses ceritinib as an ALK ligand and polyethylene glycol (PEG) as

Table 5 Clinical Studies of Novel ALK-TKIs

Drug	Clinical trial Identifier	Phase	Design	Line of therapy	Primary endpoint	Secondary endpoint	Status
TPX-0131	NCT04849273	I	Single-arm	Second line or later	DLTs	AEs	Terminated
NVL-655	NCT05384626	I/2	Single-arm	First-line	DLTs, RP2D, ORR	ORR, DOR, TTR PFS, OS, CBR	Recruiting
WX-0593	NCT04641754	2	Single-arm	Second line	ORR	PFS, DCR, DOR TTP	Unknown
ASP3026	NCT01401504	I	Single-arm	First-line	Safety and tolerability	Pharmacokinetics, ORR	Completed
APG-2449	NCT03917043	I	Single-arm	Second line / first-line	MTD, RP2D	Cmax, AUC	Recruiting
ZG0418	NCT03607188	I	Single-Arm	Second line	MTD	None	Recruiting
TQ-B3139	NCT04056572	2	Single-arm	Second line	ORR	PFS, DCR, OS	Unknown

Abbreviations: DLTs, Incidence of first cycle dose-limiting toxicities; AEs, Adverse events; RP2D, Recommended Phase 2 Dose; ORR, objective remission rate; DOR, Duration of Response; TTR, Time to Response; PFS, progression-free survival; OS, overall survival; CBR, clinical benefit rate; DCR, disease control rate; TTP, Time to Progression; MTD, Maximum Tolerated Dose; Cmax, Maximum plasma concentration; AUC, Area under the plasma concentration versus time curve.

a linked chain, can reduce the level of ALK in NCI-H2228 cells.[149] Another novel ALK PROTAC molecule TD-004[150] obtained by replacing the cereblon ligand with the von Hippel-Lindau tumor suppressor(VHL) ligand can effectively promote the degradation of the ALK-EML4 fusion protein in SU-DHL-1 and H3122 cells and inhibit the growth of H3122 xenografts. However, it should be noted that although PROTAC molecules have been partially reported in NSCLC, their poor drug formation and potential off-target toxicity still limit clinical application to a certain extent.

Immunotherapy

Programmed cell death 1 ligand 1 (PD-L1) positive patients occupy a high proportion in ALK-positive NSCLC patients, which[151] may be related to the up-regulation of ALK protein in PD-L1 expression in tumor cells.[152] Existing preclinical studies have shown that ALK driver gene positive tumors are resistant to PD-1 and PD-L1 inhibitors.[153,154] This can be explained by the immune escape of ALK and its aberrations,[155] as well as the poor immunogenicity of the tumor microenvironment in ALK-positive tumors.[156] Clinical trials investigating the combination of immune checkpoint inhibitors with ALK-TKI have yielded no clinical benefits and increased drug toxicity.[157] However, the success of the IMpower150 trial seems to provide new insights into immunotherapy in patients with ALK-positive NSCLC.[158] The combination of VEGF and PD-L1 inhibitors can overcome immunotherapy resistance to ALK-positive NSCLC.[159]

Others

Tumor vaccine is a cell fragment or fragment containing a tumor-specific antigen or tumor-associated antigen. Once entering the human body, these cell fragments can activate both fluids and cellular immunity, overcoming the immune suppression state of the body, and suppressing tumor growth. Studies have shown that the novel ALK-TKI vaccine combined with chemotherapy can significantly increase the number of $CD8^+$ and $CD4^+$ T cells in EML4-ALK mice and improve the survival rate of mice.[160] This provides a prospect for clinical application of the ALK vaccine and its combined use. Adoptive cell therapy (ACT) is a therapeutic method to improve the antitumor effect by diffuses T lymphocytes in vitro and then transfuses them back into the patient.[161] A study (NCT03215810) evaluated adoptive therapy of tumor-infiltrating lymphocytes after immunosuppressive resistance in 20 patients, with 3 of 13 patients confirming a response and 11 patients with reduced load, which may suggest a new therapeutic strategy for advanced lung cancer with ALK mutations.[162]

Discussion

Targeted drugs for ALK mutations have been extensively investigated and developed over the past few decades. A considerable number of patients can achieve the goal of five-year survival benefits. First-line use of the second

generation ALK-TKIs showed good mPFS (eg, ALESIA:41.6m,[163] eXalt3: 25.8m,[164] ALTA-1L:24.0m[165]). The third generation ALK-TKIs, when used as first-line therapy, demonstrate favorable 5-year PFS rate (60%) and powerful intracranial control effect.[166] The treatment strategy for ALK-positive patients in the first-line should be selected individually according to the specific conditions of the patient, such as tumor burden, brain metastases, genetic mutation profile, tolerance, and economic conditions.

However, resistance to ALK-TKIs remains unavoidable after first-line use. The mechanism of resistance to lorlatinib, a first-line third-generation ALK-TKI, primarily involves the activation of bypass signaling pathways and complex ALK mutations. ALK-dependent resistance is predominantly driven by secondary ALK mutations, including common complex mutations such as G1202R+L1196M and I1171N+L1196M. Some of these mutations confer high-level resistance to all ALK TKIs, while certain complex mutations may remain sensitive to first- and second-generation TKIs. ALK-independent resistance mechanisms encompass the activation of bypass signaling pathways (35%, eg, MAPK, PI3K/mTOR/PTEN, RTK pathways), MET amplification or rearrangement (22%), and epithelial-mesenchymal transition (EMT). In the Phase III CROWN trial, follow-up treatment options for patients who developed resistance to lorlatinib mainly comprised sequential ALK TKI therapy (61%) and chemotherapy with or without anti-angiogenic agents (34%). Certain complex mutations, such as G1202R+L1196M, can be addressed with dual inhibitors like AG-957/adaphostin. The mechanisms of resistance to second-generation ALK TKIs primarily encompass ALK-dependent mutations (such as G1202R, L1196M) and ALK- independent mechanisms (including bypass activation, MET amplification, and EMT). Approximately 50–60% of these mutations occur within the ALK kinase domain. Lorlatinib effectively inhibits a wide range of ALK-resistant mutations, including G1202R and complex mutations, and addresses central nervous system metastasis. Sequential treatment strategies can prolong the utility of lorlatinib, preserving it as a critical option for later-line therapy. However, the adverse effects of lorlatinib, such as hyperlipidemia and CNS reactions, may limit its long-term use. Sequential approaches can help to balance efficacy and safety. First-line treatment should be individualized based on tumor burden, presence of brain metastasis, mutation profile, drug tolerance, and economic considerations. Upon developing resistance, biopsies should be conducted to determine the underlying resistance mechanism.

Mechanism of ALK-TKIs resistance is gradually becoming clear, and primary drug resistance typically occurs within 3–6 months of treatment. Previous reports revealed that mutations affecting TP53 gene and the poor prognostic ALK phenotype are able to affect prognosis of ALK-positive patients in NSCLC. Given the limited research on the mechanisms of primary drug resistance, there is currently a lack of effective treatment strategies and large-scale clinical study data. The mechanisms of primary drug resistance are expected to be further explored through large sample studies in the future.

Acquired drug resistance mechanisms, such as secondary gene mutation, bypass activation, and EMT, have been gradually recognized, and multiple therapeutic strategies targeting these resistance mechanisms have been developed. For example, the new generation of ALK-TKIs and bypass signaling pathway inhibitors have been targeted and applied in clinical practice, effectively improving the prognosis of patients. Sequential therapy remains a key strategy to overcome the resistance of secondary ALK-TKI gene mutations, but it may change the resistance mechanism of patients. For example, the ALK G1269A and L1196M mutations are the most common mutations in crizotinib-resistant patients, while the second-generation ALK-TKI resistance is mainly driven by ALK G1202R mutations. Multiple resistance mutations often occur after lorlatinib treatment. Repeated biopsies for drug-resistant patients to obtain a drug resistance profile are particularly important in clinical decision-making, and liquid biopsies have the advantage of being noninvasive. Patients treated multiple times with different ALK-TKIs are more easily have coactivation of ALK and bypass signaling pathways. Therefore, developing more long-lasting ALK-TKIs and exploring other targets to provide effective second hits, alongside the use of bypass pathway inhibitors, is critical in delaying drug resistance. While promising, all strategies of addressing drug resistance have shortcomings. The rapid development of new ALK inhibitors is encouraging, such as TPX-0131 and NVL-655, which have obtained amazing data in clinical studies. ZX-29, gilteritinib and other novel TKI preclinical data are also promising. However, the lengthy development cycle, high costs, and the inability to meet urgent clinical needs remain challenges. Combination therapy may offer a solution to enhance the efficacy of ALK-TKIs. For example, other targeted therapies, such as Hsp90, mTOR, and PD-L1, can help counteract the downstream pathway, enhance tumor growth inhibition, and reduce tumor survival and the ability to

adapt to TKI monotherapy by bypassing secondary mutations and signaling. However, the combination of drugs may lead to potential interactions, pharmacokinetic properties of different drugs, and even enhance toxicity and reduce efficacy. The potential of targeted protein-degrading drugs developed by PROTAC technology has also attracted much attention. However, the PROTAC molecule has some problems, such as an excessively large structure, poor water solubility and serious off-target toxicity.

In the future, a deeper understanding of ALK's roles in tumor biology, as well as the mechanisms underlying tumorigenesis and drug resistance, will be essential for overcoming current limitations. Continued exploration of new therapeutic approaches will be key to advancing chronic disease management for ALK-positive NSCLC patients.

Conclusion

The development of ALK-TKIs has significantly prolonged the survival of ALK-positive patients. Although resistance to ALK-TKIs is inevitable, appropriate subsequent therapies can still provide significant clinical benefits. Repeated biopsies are crucial for elucidating the mechanisms of drug resistance in these patients, enabling informed clinical decision-making. The treatment to resistance should be considered on the basis of the resistance mechanisms, the progressive models, drug availability, and therapeutic efficacy. In summary, with ongoing discoveries in resistance mechanisms and advancements in drug development, lung cancer is anticipated to become a manageable chronic condition.

Data Availability Statement

Data Availability Statements are available in section "MDPI Research Data Policies" at https://www.mdpi.com/ethics.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, No applicable for studies not involving humans or animals.

Informed Consent Statement

"Not applicable." for studies not involving humans.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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