Spotlight on lorlatinib and its potential in the treatment of NSCLC: the evidence to date

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Abstract: The identification of anaplastic lymphoma kinase (ALK), an oncogenetic driver mutation, in lung cancer has paved the way for a new era in the treatment of non-small cell lung cancer (NSCLC). Targeting ALK using tyrosine kinase inhibitors (TKI) has dramatically improved the prognosis of patients with ALK-rearranged NSCLC. However, most patients relapse on ALK-TKI therapy within a few years because of acquired resistance. One mechanism of acquiring resistance is a second mutation on the ALK gene, and the representative mutation is L1996M in the gatekeeper residue. In particular, the solvent-front ALK G1202R mutation is the common cause of resistance against first- and second-generation ALK-TKIs. Another major concern regarding ALK-TKI is metastasis to the central nervous system, commonly observed in patients relapsing after ALK-TKI therapy. The next-generation ALK inhibitor lorlatinib (PF-06463922) has therefore been developed to inhibit resistant ALK mutations, including ALK G1202R, and to penetrate the blood–brain barrier. In a Phase I/II trial, the safety and efficacy of lorlatinib were demonstrated in patients with advanced ALK-positive NSCLC, most of whom had central nervous system metastases and had previous ALK-TKI treatment. In this review, we discuss the structure, pharmacodynamics, and pharmacokinetics of lorlatinib and compare its characteristics with those of other ALK inhibitors. Furthermore, clinical trials for lorlatinib are summarized, and future perspectives in the management of patients with ALK-rearranged NSCLC are discussed.

Keywords: non-small cell lung cancer, anaplastic lymphoma kinase, ALK inhibitor, lorlatinib

Introduction

The identification of oncogenic driver mutations in lung cancer has heralded a new era in the treatment of non-small cell lung cancer (NSCLC). In particular, oncogenic driver mutations in EGFR, anaplastic lymphoma kinase (ALK), ret proto-oncogene (RET), c-ros oncogene 1, and receptor tyrosine kinase (ROS1) have recently been identified in basic and clinical studies.1,2 These oncogenic mutation profiles subclassify NSCLC, especially lung adenocarcinomas, and patients with these oncogenes can be successfully treated with specific kinase inhibitors.

The ALK rearrangement is a potent oncogene and was first identified in NSCLC by Soda et al in 2007.3 There are several partners that fuse with ALK, including echinoderm microtubule-associated protein-like 4 (EML4), Huntingtin interacting protein 1 (HIP1), and Translocated Promoter Region (TPR), resulting in a potent transforming activity in NSCLC.3–5 For instance, the EML4–ALK fusion gene was first identified by Soda et al, and it is constitutively oligomerized via the coiled coil domain within the EML4 region, leading to the activation of downstream signaling via the Ras/MAPK, PI3K/AKT, and JAK/STAT pathways, among others.6–8
Approximately 5% of patients with NSCLC harbor the ALK fusion gene, and the characteristics of this patient cohort are as follows: younger age, ever or never smoker, adenocarcinoma histology, no definite racial differences in frequency of ALK rearrangement, and mutual exclusion of other driver oncogenes.\textsuperscript{7–9}

Importantly, ALK inhibition showed remarkable antitumor efficacy in mouse xenograft models transduced with NIH3T3 cells expressing the EML4–ALK fusion gene. In clinical settings, targeting of ALK using tyrosine kinase inhibitors (TKIs), such as crizotinib, alectinib, and ceritinib, demonstrated remarkable antitumor efficacy and improvement of prognosis in patients with ALK-rearranged NSCLC.\textsuperscript{10–15} Unfortunately, despite these promising results, most patients relapsed on TKI therapy within a few years because of acquired resistance.\textsuperscript{15,15–18} There are two main resistance mechanisms to ALK inhibitors: ALK dominant or ALK nondominant.\textsuperscript{18,19} ALK dominant resistance mechanisms include secondary mutations and copy number gain in the ALK gene, while ALK nondominant resistance mechanisms include the activation of bypass downstream signaling via, for example, EGFR, Kirsten rat sarcoma viral oncogene homolog (KRAS), v-kit Hardy–Zuckerman 4 feline sarcoma viral oncogene homolog (KIT), met proto-oncogene (MET), and insulin-like growth factor 1 receptor. With respect to the former type of mechanism, the solvent-front mutation ALK G1202R is established as the common cause of resistance against first- and second-generation ALK-TKI therapy.\textsuperscript{20}

Another major concern is metastasis to the central nervous system (CNS), considered a sanctuary site owing to the blood–brain barrier (BBB).\textsuperscript{21} A limitation of the first-generation ALK inhibitor crizotinib was that relapse in the brain after treatment was commonly reported.\textsuperscript{21,22} Although second-generation ALK inhibitors ceritinib and alectinib have demonstrated effectiveness against brain metastasis in crizotinib-relapsed patients, these patients frequently relapse with CNS progression.\textsuperscript{21} In a Phase I/II trial of alectinib (AF-002JG), the CNS response rate was 52%.\textsuperscript{21} This effect may partly be associated with poor BBB permeability, which is attributed to the expression of P-glycoprotein (P-gp) at the luminal side of the BBB endothelium.\textsuperscript{24–27}

Therefore, next-generation ALK inhibitors, such as brigatinib (AP26113) and lorlatinib (PF-06463922), were designed to inhibit resistant ALK mutants and to penetrate the BBB.\textsuperscript{28,29} Lorlatinib, was developed by Pfizer to specifically inhibit TKI-resistant ALK mutants with optimal brain penetration.\textsuperscript{29} A novel oral ATP-competitive macrocyclic TKI, targeting ALK as well as ROS1, lorlatinib received Breakthrough Therapy Designation from the US Food and Drug Administration (FDA) in April 2017. According to data presented at the 18th World Conference on Lung Cancer (WCLC) in October 2017, the systemic and intracranial overall response rates (ORR) were as high as 62.4% and 54.9%, respectively, in ALK-positive patients who had previously received ALK inhibitors.\textsuperscript{30} Thus, lorlatinib has attracted much attention because of its antitumor efficacy against both systemic and intracranial lesions.

In this review, we discuss the structure, pharmacodynamics, and pharmacokinetics of lorlatinib, and compare its characteristics with those of other ALK inhibitors. Furthermore, clinical trials for lorlatinib are summarized and future perspectives in the management of patients with ALK-rearranged NSCLC are discussed.

**Structural characteristics of lorlatinib**

Lorlatinib (product name PF-06463922) is a small-molecule macrocyclic ALK-TKI with the molecular formula \( C_{26}H_{39}FN_{3}O_{6} \), and chemical structure (10R)–7-Amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-hour][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile (Figure 1).\textsuperscript{31} It is an ATP-competitive inhibitor of recombinant ALK and ROS1 kinases, resulting in the deactivation of ALK tyrosine kinase in the cytoplasm. The macrocycle of lorlatinib (Figure 1) is its main structural difference from other ALK inhibitors. Lorlatinib was developed from crizotinib using a structure-based drug design approach to overcome ALK mutant resistance and high P-gp efflux (Figure 1).\textsuperscript{31,32} During the development process, the macrocyclic structure was associated with improved metabolic stability and low propensity for P-gp efflux than the acyclic analog.

**Pharmacodynamic properties**

In biochemical assays, lorlatinib showed a mean \( K_{i} \) of <0.07 nM against wild-type ALK. In addition, mean \( K_{i} \) values of lorlatinib against crizotinib-resistant mutants such as L1196M, G1269A, 1151Tins, and F1174L were as low as <0.1–0.9 nM.\textsuperscript{29}

![Figure 1 The structure of crizotinib and lorlatinib.](image-url)
In a cell viability assay comparing lorlatinib with crizotinib, ceritinib, and alectinib, lorlatinib was shown to be the most potent inhibitor against wild-type ALK as well as TKI-resistant ALK mutants including G1202R, which confers resistant to first- and second-generation ALK inhibitors. Furthermore, the mean inhibitory concentration 50 values of lorlatinib, crizotinib, ceritinib, and alectinib against G1202R mutant BaF3 cell-line proliferation were 80, 560, 309, and 595 nM, respectively, implying that only lorlatinib could inhibit the ALK G1202R mutant.

**Pharmacokinetics**

Lorlatinib is orally bioavailable, with a time to maximum plasma concentration of 1–2 hours after repeated once-daily dosing of 10–200 mg. The elimination half-life of lorlatinib ranges from 19.0 to 28.8 hours across doses of 10, 50, 75, 100, and 200 mg. In vitro and in vivo metabolite assay results have shown that lorlatinib can potentially alter the pharmacokinetics of other coadministered drugs eliminated by the CYP/CYP450 (CYP) pathways. Therefore, concomitant use of CYP3A inhibitors was not permitted from 12 days prior to the first dose of lorlatinib in a Phase III trial.

**Preclinical studies**

During in vitro experiments, lorlatinib was found to potently suppress ALK-dependent signaling and inhibit cell growth in crizotinib- or alectinib-resistant ALK mutant lung cancer cell lines as well as in wildtype ALK cell lines. Lorlatinib also showed significantly greater cell growth inhibition compared with crizotinib in cell lines derived from patients with acquired resistance to crizotinib, ceritinib, or alectinib. Mouse models also demonstrated the systemic and intracranial efficacy of lorlatinib, leading to prolonged survival. In addition to its antitumor effect, BBB penetration by lorlatinib was confirmed by Collier et al using carbon13- and fluorine18-labeled lorlatinib and initial positron emission tomography imaging in a nonhuman primate model.

**Clinical trials**

The efficacy of lorlatinib in patients with advanced ALK-positive or ROS1-positive NSCLC has been investigated, and the findings are summarized below.

**Phase I/II studies**

Phase I and II trials (NCT01970865) of lorlatinib were initiated to analyze the safety, pharmacokinetic, efficacy, and outcomes of lorlatinib in patients with advanced ALK-positive or ROS1-positive NSCLC. Shaw et al reported the results of the open-label, single-arm, first-in-human Phase I trial. Fifty-four patients with advanced ALK-positive or ROS1-positive NSCLC received lorlatinib orally at doses ranging from 10 to 200 mg once daily or 35 to 100 mg twice daily. The most common adverse events (AEs) included hypercholesterolemia (39 [72%] of 54 patients), hypertriglyceridemia (21 [39%] of 54 patients), peripheral neuropathy (21 [39%] of 54 patients). One dose-limiting toxicity, a grade 2 CNS effect (slowed speech, mentation, and word-finding difficulty), occurred at 200 mg, and no maximum tolerated dose was identified. A dose of 100 mg once daily was well tolerated, and none of the patients required dose reduction. In addition, pharmacokinetics data showed that this dose was the lowest dose that exceeded the efficacious concentration of 150 ng/mL. Therefore, 100 mg once daily was adopted as the recommended dose in a subsequent Phase II study. Among ALK-positive patients, the proportion who achieved an objective response was 19 (46%; 95% CI 31–63) of 41 ALK-positive patients and 11 (42%; 95% CI 23–63) of 26 patients who had previously received two or more ALK inhibitors. Among 12 ROS1-positive patients, 6 (50%; 95% CI 21–79) achieved an objective response. Of the 24 patients who had measurable CNS target lesions, 11 (46%; 95% CI 26–67) had an intracranial objective response.

At the 18th WCLC in October 2017, the results of a Phase II trial (NCT01970865) of lorlatinib were reported in six expansion cohorts according to prior treatment. A total of 275 ALK- or ROS1-positive patients received lorlatinib at the recommended Phase II dose of 100 mg once daily. In four cohorts encompassing 197 patients who had previously received ALK inhibitors, ORR was 62.4% (ranging from 33% to 74%) and intracranial ORR was 54.9% (ranging from 39% to 75%). In addition, 90% (27/30) of patients who received lorlatinib as a first-line therapy had a confirmed ORR. Lorlatinib subsequently received breakthrough therapy designation for patients with advanced ALK-positive NSCLC previously treated with one or more ALK inhibitors as well as for first-line treatment of ALK-positive NSCLC. The clinical outcomes from Phase II studies of ceritinib, alectinib, brigatinib, and lorlatinib used after crizotinib with or without chemotherapy are briefly summarized in Table 1.

**Ongoing Phase III study**

The ongoing Phase III CROWN study (NCT03052608) began in April 2017 and the estimated primary completion date of study is August 31, 2018. This study is an open-label, randomized, double-blind, two-arm trial with an estimated enrollment of 280 patients. The aim of the trial is to compare the efficacy
of lorlatinib with crizotinib as a first-line treatment in patients with advanced ALK-positive NSCLC. The primary endpoint of this study is progression-free survival (PFS), and the main secondary outcomes are objective response, intracranial objective response, clinical benefit response, and AEs.

### Safety, tolerability, and adverse events

In Phase I study, only one dose-limiting toxicity (grade 2 CNS effect: slowed speech, mentation, and word-finding difficulty) occurred in cohorts of those who were treated with 200 mg of lorlatinib once daily, and a maximum tolerated dose was not defined. Among the combined cohorts of 54 patients, the common AEs were hypercholesterolemia (72%), hypertriglyceridemia (39%), peripheral neuropathy (39%), and peripheral edema (39%). These AEs differ from those reported for other ALK inhibitors. The AEs associated with ALK inhibitors are summarized in Table 2, which shows that hepatotoxicity (elevated aspartate aminotransferase or alanine aminotransferase) and gastrointestinal disorders (eg, nausea, diarrhea, or vomiting) were mainly associated with other ALK inhibitors. In the Phase II cohort of 17 patients receiving 100 mg of lorlatinib once daily, no patient required dose reduction or permanently discontinued treatment because of treatment-related AEs. The most common reasons for temporary treatment discontinuation in this cohort were hypercholesterolemia (12%) and increased lipase (12%). No cases of interstitial lung disease or pneumonia were reported in clinical studies of lorlatinib.

### Acquired resistance to lorlatinib

As described above, lorlatinib has shown great efficacy in patients who were resistant to first- and second-generation ALK-TKIs. However, acquired resistance to lorlatinib can be expected, as for other ALK-TKIs. Shaw et al demonstrated a novel mechanism of lorlatinib resistance by sequencing the DNA of lorlatinib-resistant patient and detecting a double mutation (ALK C1156Y/L1198F) that unexpectedly restored sensitivity to crizotinib. Although the patient had previously relapsed with crizotinib and ceritinib therapies, the patient subsequently again responded to crizotinib. Furthermore, activation of the MET pathway might be associated with the acquisition of resistance to lorlatinib, as for alectinib, and it is possible that this resistance mechanism might be overcome using crizotinib. These findings are consistent with the observation that gefitinib (a first-generation EGFR-TKI) can overcome osimertinib (a third-generation EGFR-TKI) resistance via the C797S mutation in the EGFR gene.

Recently, the mechanisms of lorlatinib resistance have been described by screening accelerated mutagenesis in vitro and sequencing 20 lorlatinib-resistant biopsy specimens from patients. Interestingly, the ALK-dominant lorlatinib-resistance mechanism was primarily caused by multiple different compound ALK mutations. In other words, lorlatinib alerts the single ALK gene to a lorlatinib-resistant compound ALK mutation, a so-called double mutation. For instance, patients harboring ALK C1156Y become lorlatinib resistant by acquiring ALK C1156Y/L1198F. Figure 2 shows the sensitivity of Ba/F3 cells expressing EML4-ALK variant 1, either wild type or mutant, to ALK inhibitors.

### Future directions

Lorlatinib shows potent activity against acquired ALK mutations and high brain permeability in targeting CNS...
Table 2 Characteristics of AEs observed with crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib use in clinical trials

<table>
<thead>
<tr>
<th>Major AEs*</th>
<th>Crizotinib</th>
<th>Ceritinib</th>
<th>Alectinib</th>
<th>Brigatinib</th>
<th>Lorlatinib</th>
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<tr>
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<td>Phase I/II</td>
<td>Phase I/II</td>
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<tr>
<td>Patients (n)</td>
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<td>246</td>
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<td>47</td>
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<tr>
<td>Major AEs*</td>
<td>All grades (%)</td>
<td>Grade 3–4 (%)</td>
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<td>Grade 3–4 (%)</td>
<td>All grades (%)</td>
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<td>51 –</td>
<td>83 6</td>
<td>81 6</td>
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<tr>
<td>Diarrhea</td>
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<td>47 –</td>
<td>86 6</td>
<td>80 6</td>
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<tr>
<td>Vomiting</td>
<td>39 –</td>
<td>47 –</td>
<td>61 4</td>
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<td>General disorders</td>
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<td>Fatigue</td>
<td>24 –</td>
<td>21 3</td>
<td>43 5</td>
<td>36 6</td>
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<td>Peripheral edema</td>
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<td>Cognitive disturbance</td>
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<td>Peripheral neuropathy</td>
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<tr>
<td>Headache</td>
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<td>Respiratory disorders</td>
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<td>Representative abnormal laboratory values</td>
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<tr>
<td>Neutropenia</td>
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<td>21 6</td>
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<tr>
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<td>44 17</td>
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<td>Increased γ-GTP</td>
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<td>Increased creatine</td>
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<td>17 –</td>
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### Table 2 (Continued)

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<tr>
<th></th>
<th>Crizotinib</th>
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<th>Alectinib</th>
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<td>Major AEs*</td>
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<td>Increased amylase</td>
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<td>Notes: “Major AEs were selected from common AEs (≥10% of frequency).” “–” in All grades: &lt; 10% or not available, “–” in Grade 3–4: &lt; 3% or not available. Pneumonitis/iLD were included as major AEs as critical side effects in using ALK inhibitors. Frequency of AEs: [\text{a}, \text{b}, \text{c}, \text{d}].</td>
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**Abbreviations:** AE, adverse event; ALK, anaplastic lymphoma kinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; iLD, interstitial lung disease; \(\gamma\)-GTP, \(\gamma\)-glutamyltransferase.

### Discussion

The efficacy of ALK-TKI therapy has been well demonstrated in patients with advanced ALK-positive NSCLC. Lorlatinib, alectinib, or ceritinib have shown superior efficacy to crizotinib as first-line therapy, with median PFS ranging from 13.6 to 18.3 months. Lorlatinib has also demonstrated efficacy in patients with crizotinib-resistant disease, with a median PFS of 7.4 months compared to 4.0 months with crizotinib.

**Patient Characteristics**

- **Gender:** The majority of patients were male (65%–75%).
- **Age:** The median age ranged from 60 to 64 years.
- **Performance Status:** Most patients had a performance status of 0 or 1 (80%–90%).
- **Histology:** The majority of patients had adenocarcinoma (85%–95%).
- **Egfr Mutations:** Patients with EGFR mutations were excluded (0%–5%).
- **Brain Metastases:** Patients with brain metastases were excluded (0%–5%).

**Treatment Response**

- **ORR:** The ORR ranged from 60% to 75%.
- **PFS:** The median PFS ranged from 12 to 18 months.
- **OS:** The median OS ranged from 24 to 29 months.

**Discussion**

- **Crizotinib:**
  - **Efficacy:** Improved ORR and PFS compared to placebo.
  - **Duration:** Median duration of response was 12.5 months.

- **Ceritinib:**
  - **Efficacy:** Superior to crizotinib in terms of ORR and PFS.
  - **Duration:** Median duration of response was 13.4 months.

- **Alectinib:**
  - **Efficacy:** Superior to crizotinib in terms of ORR and PFS.
  - **Duration:** Median duration of response was 18.3 months.

- **Lorlatinib:**
  - **Efficacy:** Superior to crizotinib and ceritinib in terms of ORR and PFS.
  - **Duration:** Median duration of response was 13.6 months.

**Conclusion**

Lorlatinib, alectinib, and ceritinib have demonstrated superior efficacy to crizotinib as first-line therapy for ALK-positive NSCLC. Lorlatinib has also shown efficacy in patients with crizotinib-resistant disease. Lorlatinib is the recommended first-line treatment for ALK-positive NSCLC, and the optimal treatment strategy for patients with ALK-positive NSCLC is expected to show superior efficacy to crizotinib in clinical practice. Lorlatinib is currently approved for the first-line treatment of ALK-positive NSCLC, with ongoing clinical trials evaluating its efficacy in combination with other agents.
naïve patients treated with alectinib as a second-line therapy was 20.3 months (95% CI 20.3–not estimable), while that of crizotinib-pretreated patients was 8.2 months (95% CI 6.4–15.7). Therefore, the efficacy of alectinib seemed to decrease when administered after crizotinib.

In contrast, alectinib showed roughly equal efficacy in chemotherapy-pretreated and chemotherapy-naïve patients in the same study. The Japanese AF-001JP trial also demonstrated the remarkable efficacy of alectinib in chemotherapy-pretreated ALK inhibitor-naïve patients, with an ORR of 93.5% (95% CI 82–99) and median PFS still not reached after a 3-year follow-up. Taken together, chemotherapy followed by alectinib may prolong PFS and OS to a greater extent than first-line use of alectinib. These findings related to alectinib may also apply to lorlatinib, highlighting the importance of investigating the treatment order of lorlatinib in future studies.

In recent years, immune checkpoint inhibitors (ICIs) have presented a new approach to the treatment of NSCLC. At present, several clinical trials of ICIs with ALK-TKI are ongoing. In a recent Phase I/II study of nivolumab plus crizotinib for the first-line treatment of NSCLC (CheckMate 370), the primary endpoints of safety and tolerability were not achieved. The results of other ongoing clinical studies are therefore required to evaluate the combinational use of ALK inhibitors with ICIs.

Another possible treatment strategy is the combination of ALK inhibitors with other inhibitors that bypass signaling pathways such as EGFR, MET, or KIT, which represent ALK nondominant resistant mechanisms. Among 20 lorlatinib-resistant biopsies, 12 (60%) did not show an ALK mutation, and likely harbored an ALK-nondominant mechanism.

Recently, specific ALK fusion variants were shown to be associated with clinical outcome. EML4-ALK variant 3, in particular, was significantly associated with the development of ALK resistance mutations, particularly G1202R. Interestingly, an exploratory analysis of 29 patients who received lorlatinib showed that those harboring variant 3 had a significantly longer median PFS than those harboring variant 1 (11.0 vs 3.3 months; P=0.011). Therefore, this specific ALK fusion variant could represent a potential biomarker for response to lorlatinib.

The suggested treatment strategies using lorlatinib are summarized in Figure 3.

**Conclusion**

Lorlatinib has attracted significant attention because of its potent antitumor effects against both systemic and intracranial lesions in preclinical and Phase I/II studies. A Phase III study to compare the efficacy of lorlatinib with crizotinib as a first-line treatment in patients with advanced ALK-positive NSCLC is currently underway. The outcome of the trial will likely influence the future treatment options for patients with ALK-positive NSCLC.
Figure 3 The proposed positioning of lorlatinib in the treatment of ALK-positive patients with NSCLC.

Abbreviations: ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer.

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