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 oncogenetic 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 oncogenetic 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.^{3,6}

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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.^{7–9}

Importantly, ALK inhibition showed remarkable anti-tumor 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 (TKI), such as crizotinib, alectinib, and ceritinib, demonstrated remarkable antitumor efficacy and improvement of prognosis in patients with *ALK*-rearranged NSCLC.^{10–15} Unfortunately, despite these promising results, most patients relapsed on TKI therapy within a few years because of acquired resistance.^{13,15–18} There are two main resistance mechanisms to ALK inhibitors: *ALK* dominant or *ALK* nondominant.^{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.²⁰

Another major concern is metastasis to the central nervous system (CNS), considered a sanctuary site owing to the blood–brain barrier (BBB).²¹ A limitation of the first-generation ALK inhibitor crizotinib was that relapse in the brain after treatment was commonly reported.^{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.²¹ In a Phase I/II trial of alectinib (AF-002JG), the CNS response rate was 52%.²³ 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.^{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.^{28,29} Lorlatinib, was developed by Pfizer to specifically inhibit TKI-resistant *ALK* mutants with optimal brain penetration.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.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 $C_{21}H_{19}FN_6O_2$ 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-*h*][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile (Figure 1).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).^{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.²⁹

Figure 1 The structure of crizotinib and lorlatinib.

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.²⁹ 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.²⁹

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-time of lorlatinib ranges from 19.0 to 28.8 hours across doses of 10, 50, 75, 100, and 200 mg.³³ 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.²⁹ 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.²⁹ 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 carbon¹¹- and fluorine¹⁸-labeled lorlatinib and initial positron emission tomography imaging in a nonhuman primate model.³⁴

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.³³ 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 edema (21 [39%] of 54 patients), and 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.³⁰ 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.³⁰ 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.^{15,16,30,39}

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

Table I Clinical outcomes of Phase II studies of ALK inhibitors used after crizotinib with or without chemotherapy

Clinical trials and cohorts	Ceritinib ³⁹	Alectinib ¹⁶	Brigatinib ¹⁵	Lorlatinib ³⁰	
	Phase II study	Phase II global study	Phase II study	Phase II study	
	(ASCEND-2)		180 mg cohort	ALK-positive cohorts	
Previous treatment	Crizotinib + chemo	Crizotinib ± chemo	Crizotinib ± chemo	Crizotinib ± chemo	Treatment naïve
Number of patients	n=140	n=138	n=110	n=59	n=30
Systemic response					
ORR (%)	39	50	54	69	90
95% CI	(31%–47%)	(41%–59%)	(43%–65%)	(NA)	(NA)
Median PFS (months)	5.7	8.9	12.9	(NA)	(NA)
95% CI	(5.4–7.6)	(5.6–11.3)	(11.1–NR)	(NA)	(NA)
Intracranial efficacy (measurable baseline CNS metastases)					
Number of patients	n=20	n=35	n=18	n=37	n=8
Intracranial ORR (%)	45	57	67	68*	75*
95% CI	(23%–69%)	(39%–74%)	(41%–87%)	(NA)	(NA)

Note: *The information whether ORR was calculated from measurable baseline CNS metastases was not available.

Abbreviations: ALK, anaplastic lymphoma kinase; CNS, central nervous system; NA, not available; NR, not reached; ORR, overall response rates; PFS, progression-free survival.

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.^{33,35} 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.^{13,14,16,23,36–40} 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 pneumonitis 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.⁴¹ 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.⁴² 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.^{43,44}

Recently, the mechanisms of lorlatinib resistance have been described by screening accelerated mutagenesis in vitro and sequencing 20 lorlatinib-resistant biopsy specimens from patients.⁴⁵ 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.⁴⁵

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

	Crizotinib			Ceritinib			Alectinib			Brigatinib			Lorlatinib	
	Phase I ³⁶	Phase II ³⁷	Phase I ³⁸	Phase II ³⁹	Phase I/II ²³	Phase II ¹⁶	Phase I/II ⁴⁰	Phase I/II ³³	Phase I/II ⁴⁰	Phase I/II ³³	Phase I/II ³³			
Patients (n)	144	1,066	246	140	47	138	137	54						
Major AEs ^a	All grades (%)	Grade 3–4 (%)	All grades (%)	Grade 3–4 (%)	All grades (%)	Grade 3–4 (%)	All grades (%)	Grade 3–4 (%)	All grades (%)	Grade 3–4 (%)	All grades (%)			
Gastrointestinal disorders	56	–	51	83	6	81	6	–	53	–	11			
	50	–	47	86	6	80	6	–	41	–	–			
	28	–	35	30	–	29	–	33	23	–	22			
	39	–	47	61	4	63	4	–	21	–	–			
General disorders														
Fatigue	24	–	21	43	5	36	6	–	43	4	15			
Peripheral edema	30	–	–	–	–	–	–	25	13	–	39			
Nervous system disorders														
Cognitive disturbance	– ^b	–	–	–	–	–	–	–	–	–	24			
Peripheral neuropathy	–	–	–	–	–	–	–	–	–	–	39			
Headache	–	–	–	19	–	–	–	16	33	–	–			
Respiratory disorders														
Cough	–	–	–	29	–	21	–	–	31	–	–			
Dyspnea	–	–	–	21	4	21	6	–	23	6	–			
Others														
Hypertension	–	–	–	–	–	–	–	–	15	5	–			
Myalgia	–	–	–	15	–	–	–	23	–	–	–			
Weight increase	–	–	–	–	–	–	–	–	–	–	11			
Pneumonitis/ILD ^c	3	2	2	4	3	1	<1	0	2	2	0			
Eye disorders	64	–	58	–	–	–	–	–	–	–	–			
Representative abnormal laboratory values														
Neutropenia	–	–	21	–	–	–	–	4	–	–	–			
Increased AST	10	4	30	33	10	32	5	–	13	–	13			
Increased ALT	12	3	–	44	27	44	17	4	11	–	–			
Increased γ-GTP	–	–	–	–	–	18	12	–	–	–	–			
Increased CPK	–	–	–	–	–	–	–	–	–	–	–			
Increased creatine	–	–	–	17	–	–	–	–	–	–	–			

(Continued)

Table 2 (Continued)

Patients (n)	Crizotinib			Ceritinib			Alectinib			Brigatinib			Lorlatinib		
	Phase I ³⁶			Phase II ³⁷			Phase II ³⁹			Phase II ¹⁶			Phase I/II ⁴⁰		
	All grades (%)	Grade 3–4 (%)	Grade 3–4 (%)	All grades (%)	Grade 3–4 (%)	Grade 3–4 (%)	All grades (%)	Grade 3–4 (%)	Grade 3–4 (%)	All grades (%)	Grade 3–4 (%)	Grade 3–4 (%)	All grades (%)	Grade 3–4 (%)	Grade 3–4 (%)
Major AEs ^a	144	1,066	246	140	47	138	137	54							
Increased amylase	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Increased lipase	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Hypercholesterolemia	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Hypertriglyceridemia	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

Notes: ^aMajor AEs were selected from common AEs ($\geq 10\%$ of frequency). ^b“–” in All grades: $<10\%$ or not available. ^c“–” in Grade 3–4: $<3\%$ or not available. ^dPneumonitis/ILD were included as major AEs as critical side effects in using ALK inhibitors.

Frequency of AEs: ■, ■, ■, ■.

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; ILD, interstitial lung disease; γ -GTP, γ -glutamyltransferase.

metastasis.²⁹ Based on Phase I/II trial data, lorlatinib may represent an effective therapeutic strategy for ALK-TKI-resistant mutant NSCLC as well as progressive CNS metastases after ALK-TKI treatment.³³ A Phase III trial (NCT03052608) comparing the efficacy of lorlatinib with crizotinib as a first-line treatment for patients with advanced *ALK*-positive NSCLC is currently ongoing. As with alectinib and ceritinib, lorlatinib is expected to show superior efficacy to crizotinib in treating *ALK*-positive NSCLC.^{46,47} If so, the question is which ALK inhibitor should be used for the first-line treatment of *ALK*-positive NSCLC: lorlatinib, alectinib, or ceritinib.

Recently, osimertinib, a third-generation EGFR-TKI, has shown superior efficacy to standard EGFR-TKI therapy (gefitinib) in treating *EGFR*-mutant NSCLC.⁴⁸ In April 2018, the FDA approved osimertinib as a first-line treatment for *EGFR*-mutant NSCLC. Like osimertinib, lorlatinib may become standard-of-care first-line treatment for *ALK*-positive NSCLC. Then, can we say that lorlatinib is the best for first-line therapy which prolongs PFS and OS?

At this point, the optimal treatment strategy using lorlatinib remains unclear. First-line use of lorlatinib, the effect of which on PFS remains unknown, can be followed by crizotinib treatment if lorlatinib resistance is mediated by the L1198F-containing double mutation conferring sensitivity to crizotinib.^{41,45} What, then, about the sequential use of alectinib or ceritinib followed by lorlatinib? Although the significance of alectinib or ceritinib treatment after lorlatinib remains unclear, preclinical studies demonstrated that ceritinib and alectinib were also resistant to a lorlatinib-resistant mutation.⁴⁵ Considering that most *ALK* secondary mutations for alectinib and ceritinib can be overcome using lorlatinib, sequential therapy of lorlatinib after alectinib or ceritinib might prolong PFS and OS compared with using lorlatinib as a first-line therapy. The outcome of the Phase III CROWN study (NCT03052608) and a retrospective study on the sequential use of lorlatinib followed by alectinib or ceritinib may verify the value of this strategy. Brigatinib also joins this complex sequential therapy, contributing to a median OS of 5 years among *ALK*-rearranged patients, which is a landmark in the treatment of advanced NSCLC.

A recent meta-analysis of alectinib showed that ALK inhibitor-naïve patients tended to have a higher ORR than crizotinib-pretreated patients (87%; 95% CI 81%–92% vs 52%; 95% CI 46%–58%).⁴⁹ Furthermore, the recent Phase III ALUR study (NCT02604342; alectinib vs chemotherapy in crizotinib-pretreated patients) has reported a median PFS of 9.6 months (95% CI 6.9–12.2) and 1.4 months (95% CI 1.3–1.6) with alectinib and chemotherapy, respectively.⁵⁰ In the J-ALEX trial, the median PFS of ALK inhibitor-

Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Wild type	S	S	S	S	S
L1196M	R	S	S	S	S
G1202R	R	R	R	R?	S
G1202R/L1196M	R	R	R	R?	R
G1202R/L1198F	R	R	R	R?	R
L1196M/L1198F	S	R	R	R	R

S	Sensitive: IC ₅₀ ≤50 nM
R	Resistant: IC ₅₀ >50 nM
R?	Resistant: IC ₅₀ >50 nM

?: It remains controversial whether brigatinib is resistant or not to these mutation statuses.

Figure 2 Sensitivity of Ba/F3 cells expressing *EML4-ALK* variant 1, either wild type or mutant, to ALK inhibitors.

Abbreviation: ALK, anaplastic lymphoma kinase.

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).⁵¹ 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.⁵¹ 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.^{12,52} 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.⁵³ At present, several clinical trials of ICIs with ALK-TKI are ongoing.⁵⁴ 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.⁵⁵ 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.⁴⁵

Recently, specific *ALK* fusion variants were shown to be associated with clinical outcome.⁵⁶ *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.^{29,33} 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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Author contributions

Takaki Akamine wrote the manuscript and designed figures with support from Gouji Toyokawa who was in charge of overall direction. Takashi Seto and Tetsuzo Tagawa supervised the revising of the manuscript. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

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