Drug Evaluation

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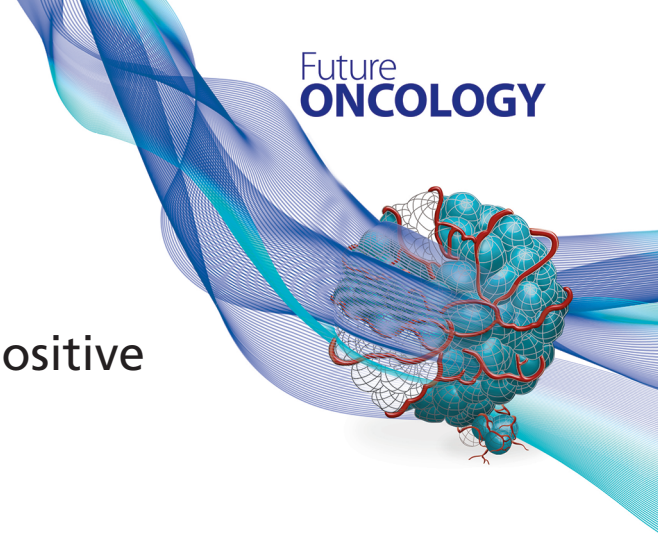

Lorlatinib as a treatment for ALK-positive lung cancer

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Lorlatinib, a third-generation ALK tyrosine kinase inhibitor, has been approved as a treatment for ALK-positive lung cancer. This review provides information regarding the pharmacology and clinical features of lorlatinib, including its efficacy and associated adverse events. Pivotal clinical trials are discussed along with the current status of lorlatinib as a treatment for ALK-positive lung cancer and future therapeutic challenges.

Plain language summary: Lorlatinib has been approved as a new standard treatment for lung cancer with gene alteration known as ALK fusion. This review provides information regarding the characteristics of lorlatinib, including its efficacy and the unexpected medical problems that occur during treatment. Today, treatment of ALK-positive lung cancer is more complicated because of the active development of drugs like lorlatinib. This review demonstrates the logic of including lorlatinib as part of the treatment plan and sheds light on the future of treatment for ALK-positive lung cancer.

First draft submitted: 20 February 2022; Accepted for publication: 20 June 2022; Published online: 4 July 2022

Keywords: brain metastasis • pharmacodynamics • pharmacokinetics • real-world data • resistance • treatment sequence

Lung cancer is the world's leading cause of cancer-related death [1]. Approximately 35–39% of patients with non-small-cell lung cancer (NSCLC) are diagnosed with the disease after it has metastasized or progressed, at which point the 5-year survival rate is only 7%, although this is gradually improving [2–4].

Genetic abnormalities in lung cancer need to be considered in the context of signaling pathways, and these pathways can be therapeutic targets. A number of drugs have already been developed in this regard. Some of these drugs, including EGFR and ALK inhibitors, have become first-line alternatives to cytotoxic chemotherapy. Of the tyrosine kinase inhibitors (TKIs), ALK inhibitors have achieved the longest survival times in patients undergoing treatment for lung cancer [5,6]. Median overall survival for ALK-positive lung cancer can already exceed 80 months [7].

Rearrangement of the ALK gene by fusion with another gene can promote the growth of tumors [8]. The EML4-ALK fusion gene was discovered in some NSCLC patients in 2007 [9–11]. Epidemiological data suggest that ALK rearrangement occurs in approximately 4–5% of NSCLC patients [12].

The success of crizotinib, a drug developed as a c-Met inhibitor and commercialized as an ALK inhibitor, has led to further development of therapies for ALK-positive lung cancer [13]. Subsequent TKIs (e.g., ceritinib, alectinib, brigatinib and lorlatinib) have been almost globally approved for the management of ALK-positive NSCLC [14]. However, these treatments consistently lead to the development of resistance, which facilitates disease progression. The second-generation ALK-TKI alectinib exhibits a safety profile that allows its use for longer periods [5,6]; however, its use has also been associated with the development of drug resistance [15]. Further improvements in ALK testing and treatment are thus needed to successfully diagnose and treat the diverse manifestations of ALK-positive lung cancer [16].

Lorlatinib, an oral small-molecule inhibitor of ALK and ROS1 kinase, has been developed as a third-generation ALK-TKI to address drug resistance and improve brain penetration in patients with ALK-positive NSCLC. Based on the results of a phase I/II study [17], lorlatinib was approved for the treatment of ALK-positive NSCLC in Japan

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in September 2018 and in the USA in November of the same year [18]. In addition, the US FDA and regulatory authorities in Japan and Europe expanded lorlatinib approval to first-line treatment in patients with metastatic NSCLC whose tumors are ALK-positive [19–21]. This review discusses the current status of lorlatinib as a therapeutic agent for ALK-positive lung cancer as well as future therapeutic challenges.

Pharmacology

During its development, lorlatinib was known as PF-06463922. It features a macrocyclic structure [22,23] and was devised through structure-based drug design, with an emphasis on lipophilic efficiency and optimization of other biochemical properties. Lorlatinib exhibits good absorption, distribution, metabolism and excretion; it also demonstrates a low tendency for efflux via *P*-glycoprotein and good passive permeability [24].

The major pathways for lorlatinib metabolism in humans are oxidation and glucuronide conjugation. *In vitro* studies have shown that lorlatinib metabolites are mainly generated via CYP3A and UGT1A4; CYP2C19, CYP2C8 and UGT1A3 exhibit only minor involvement. The plasma protein binding rate of lorlatinib has been reported as 66% [25]. When a single 100-mg oral dose of lorlatinib was administered to 27 healthy adults on an empty stomach after a high-fat meal, the area under the curve extrapolated to infinity and maximum plasma concentration (postprandial/fasting) values were 104.7 and 90.9%, respectively.

Lorlatinib has good oral bioavailability. In non-clinical studies by pharmacological inhibition of CYP3A4 with oral ritonavir, as was the simultaneous inhibition of *P*-glycoprotein using oral elacridar,these inhibitory interactions resulted in a 16-fold increase in absolute lorlatinib brain concentration with no apparent toxicity, which might be useful for optimizing the clinical application of lorlatinib [26,27]. Another study also showed that daily concomitant use of rifampin, a potent CYP3A inducer, significantly reduced plasma concentration compared with a single dose of lorlatinib [28]. In addition, all healthy participants had severe but self-limiting elevations of transaminase levels. Baseline ALB level and total daily dose of lorlatinib are significantly associated with lorlatinib clearance, whereas the use of proton pump inhibitors is significantly associated with decreased lorlatinib absorption rate constant; however, these factors do not have clinically meaningful effects on lorlatinib plasma pharmacokinetics [29].

With respect to pharmacodynamics, tumor growth inhibition was assayed in nude mice that had been subcutaneously transplanted with the NCI-H3122 cell line (derived from human non-small-cell lung cancer [NSCLC]) and NIH3T3 cell line (derived from mouse fibroblasts) harboring ALK fusion proteins with L1196M, G1269A, I1171T and G1202R mutations, which are resistant to existing ALK tyrosine kinase inhibitors (TKIs; e.g., crizotinib, alectinib and ceritinib) [24,30]. In biochemical assays, PF-06463922 inhibited the catalytic activity of recombinant human wild-type ALK, with a mean Ki level <0.07 nM. In addition, use of PF-06463922 against crizotinib-resistant ALK mutations (e.g., L1196M, G1269A, 1151Tins, F1174L, C1156Y, L1152R and S1206Y) was associated with mean Ki values ranging from <0.1 to 0.9 nM. Thus, this third-generation TKI is effective against most known resistant mutants that arise after treatment with first- or second-generation ALK-TKIs. With respect to the pharmacokinetic–pharmacodynamic relationship, associations among systemic exposure, target modulation and antitumor effect of PF-06463922 were reported in mice that had been transplanted with H3122 NSCLC cells expressing the crizotinib-resistant ALK L1196M mutation or NIH3T3 cells expressing the CD74-ROS1 mutation [31,32].

In a phase I/II study, plasma concentrations of PF-06463922 increased in a dose-dependent manner with single doses of 10–200 mg; a slightly more than dose-dependent increase was observed with multiple doses [33]. The area under the plasma concentration–time curve over the dosing interval of PF-06895751 (a nonactive metabolite of benzoic acid resulting from the cleavage of amide and aromatic ether bonds of PF-06463922) from time 0 to τ (dosing interval) increased by approximately 80% compared with multiple doses of PF-06463922, indicating that lorlatinib clearance increased with multiple doses compared with a single dose. Furthermore, there were no apparent differences in lorlatinib pharmacokinetic parameters between Asian and non-Asian individuals for single or multiple doses.

In an early trial, 11 healthy male participants (mean age: 37.6 years) received one of two treatment regimens: a single 100-mg oral dose of lorlatinib followed by a 50-mg intravenous dose or intravenous lorlatinib followed by oral lorlatinib [34]. The adjusted geometric mean of the absolute oral bioavailability was 80.78% (95% CI: 75.73–86.16). The estimated mean plasma half-lives for lorlatinib elimination were 25.5 h for the oral dose and 27.0 h for the intravenous dose.

In a phase I study (NCT03542305) of patients with severe renal dysfunction (n = 5), moderate or mild renal dysfunction (n = 8 each) or normal renal function (n = 8), the effects of renal dysfunction on lorlatinib safety and

pharmacokinetics were evaluated [35]. The area under the curve extrapolated to infinity of the plasma concentration–time profile of lorlatinib increased by 4, 19 and 41% in the mild, moderate and severe renal impairment groups, respectively, compared with the normal renal function group; however, no serious adverse events (AEs) were reported. Thus, no adjustment in lorlatinib dose was recommended for patients with mild to moderate renal impairment, whereas a reduction in the starting dose of lorlatinib (from 100-mg, once daily to 75-mg, once daily) was recommended for patients with severe renal impairment. Several detailed reviews have been published with regard to the pharmacology of lorlatinib [36–39].

Pivotal clinical trials

In the phase I portion of a phase I/II lorlatinib study (NCT01970865), 55 patients with advanced NSCLC were enrolled, with 54 receiving treatment and 53 with confirmed ALK or ROS1 status (i.e., 41 ALK-positive patients and 12 ROS1-positive patients) being analyzed [40]. Twenty-eight patients had previously been treated with two or more ALK-TKIs and 39 had brain metastases. Patients received lorlatinib orally at doses from 10 to 200 mg once daily or 35–100 mg twice daily. During treatment with 200-mg, once daily, one patient with brain metastases was unable to receive 16 of the 21 planned doses of lorlatinib because of grade 2 CNS effects (delayed speech, decreased consciousness and anomic aphasia). These symptoms resolved 48 h after discontinuation of lorlatinib. Among patients receiving low doses of lorlatinib, all three in the 35-mg, twice daily cohort tolerated treatment but discontinued lorlatinib because of disease progression at the time of first tumor evaluation. Furthermore, the 75- and 100-mg, twice daily treatments were poorly tolerated, with all four patients in the 100-mg, twice daily cohort requiring dose reductions. Thus, no maximum tolerated dose was established; however, based on comparisons of safety profiles among doses as well as ease of administration and predicted plasma concentrations of lorlatinib that inhibit the resistant ALK G1202R mutation, 100-mg, once daily was selected as the recommended dose.

Of the 54 patients receiving treatment in the aforementioned clinical trial, grade 3 AEs were observed with regard to five patients with hypercholesterolemia, three with hypertriglyceridemia, one with cognitive impairment, two with increased lipase, three with weight gain and one with an increased AST level [40]. There were also two patients with grade 4 and none with grade 5 hypercholesterolemia. The objective response rates (ORRs) were 46% in ALK-positive patients and 42% in patients with ALK-positive tumors who had received two or more TKIs. Responses were also observed in patients with acquired mutations to prior ALK-TKI and those with brain metastases.

The efficacy of lorlatinib was confirmed in the global phase II portion of a phase I/II study (NCT03052608) involving patients with ALK- or ROS1-positive advanced NSCLC [17]. This study enrolled patients with an Eastern Cooperative Oncology Group performance status of 0–2 and adequate organ function regardless of CNS metastases. Patients were enrolled in one of six expansion cohorts (EXPs) based on ALK and ROS1 status as well as prior therapy. Patients received lorlatinib 100 mg orally once daily. The primary end points were ORR and response of intracranial (IC) metastasis. Patients (n = 276) were enrolled in one of the following groups: ALK-positive, treatment-naive (EXP1: n = 30); ALK-positive, pretreated with crizotinib without chemotherapy (EXP2: n = 27); ALK-positive, pretreated with crizotinib and chemotherapy (EXP3A: n = 32); ALK-positive with one prior ALK-TKI other than crizotinib with or without chemotherapy (EXP3B: n = 28); ALK-positive and pretreated with two ALK-TKIs with or without chemotherapy (EXP4: n = 65); ALK-positive and pretreated with three ALK-TKIs with or without chemotherapy (EXP5: n = 46); and ROS1-positive and pretreated with or without chemotherapy (EXP6: n = 47). One patient in EXP4 was excluded from the safety analysis because he died before receiving lorlatinib. In untreated ALK-positive patients (EXP1), ORR was 90% and IC responses were observed in two of three (67%). In patients who had received at least one prior ALK-TKI (EXP2–5: n = 198), ORR was 47% and IC responses were observed in 51 of 81 (63%). In patients who had previously received crizotinib only (EXP2–3A), ORRs were observed in 20 of 23 (87%) and IC responses were observed in 41 of 51 (69.5%). In patients who had previously received one ALK-TKI therapy other than crizotinib (EXP3B), ORRs were observed in five of nine (55.6%) and IC responses were observed in nine of 28 (32.1%). In patients who had previously received two or more ALK-TKI therapies (EXP4–5), ORRs were observed in 26 of 49 (53.1%) and IC responses were observed in 43 of 111 (38.7%). Among patients with measurable brain metastases, IC responses were observed in 82% (95% CI: 57–96), extracranial (EC) responses were observed in 23% (95% CI: 5–54) and 71% of patients treated with lorlatinib had a complete IC response.

Partitioned survival models for cost–effectiveness analysis utilizing data from a phase I/II study have suggested that lorlatinib is a cost-effective alternative to chemotherapy as second- or third-line treatment for ALK-positive

NSCLC [41]. In another study, the cost–effectiveness analysis of lorlatinib was performed using a microsimulation model from the US payer perspective and showed that lorlatinib was not cost-effective compared with crizotinib at its current price when administered as first-line treatment [42].

The CROWN trial (NCT03052608) is a randomized phase III trial comparing lorlatinib with crizotinib as first-line treatment in 296 patients with untreated advanced ALK-positive NSCLC [43]. Stratification factors include brain metastasis status and ethnicity, and patients are randomized at a 1:1 ratio to the two treatment groups. The primary end point of the study is progression-free survival (PFS), as determined by a blinded independent central review. Secondary end points include ORR, IC response rate, overall survival (OS) and safety. In the interim analysis, the median follow-up time was 18.3 months in the lorlatinib group and 14.8 months in the crizotinib group. The median duration of treatment (DoT) was 9.6 months in the crizotinib group and has not been reached in the lorlatinib group. Baseline characteristics were comparable between the two arms and similar to those in prior phase III studies of second-generation ALK-TKIs. IC metastases were present at baseline in 26 and 27% of patients in the lorlatinib and crizotinib groups, respectively. According to a blinded independent central review, the median PFS was 9.3 months in the crizotinib group (hazard ratio [HR]: 0.28; 95% CI: 0.19–0.41; $p < 0.001$) and has not been reached in the lorlatinib group. The percentage of patients alive without disease progression at 12 months was 78% in patients receiving lorlatinib and 39% in patients receiving crizotinib. According to a blinded independent central review, ORRs were 76% in the lorlatinib group and 58% in the crizotinib group, with an odds ratio (OR) of 2.25 (95% CI: 1.35–3.89). The median duration of response was 11 months in the crizotinib group and has not been reached in the lorlatinib group. The IC response rates (monitored by blinded independent central review) in patients with measurable brain metastases at baseline were 82% with lorlatinib and 23% with crizotinib. The IC progression rates at 12 months were 2.8% in the lorlatinib group and 33.2% in the crizotinib group. The EC progression rates at 12 months were 15.4% in the lorlatinib group and 44.3% in the crizotinib group. The median OS has not been reached in either group at the time of interim analysis. Moderate to severe toxicity (grade 3/4 AEs) has occurred in 72% of patients in the lorlatinib group and 56% of those in the crizotinib group, and fatal toxicities have occurred in 5% of patients in both groups.

In summary, the interim analysis of the CROWN trial demonstrated longer PFS, improved IC response and better disease control in patients with untreated advanced ALK-positive NSCLC who received lorlatinib compared with those who received crizotinib [43]. In addition to second-generation ALK-TKIs, lorlatinib is now the first-line therapy of choice in all major geographic regions, and in the CROWN trial, lorlatinib demonstrated the highest IC activity rate reported to date, with a 61% IC complete response rate, including measurable and nonmeasurable brain metastases. In patients without baseline brain metastases, the IC control rate with lorlatinib was 97% at 12 months, which is also superior to data from previous randomized trials of second-generation agents.

Efficacy in treating brain metastasis

Patients with ALK gene rearrangements have a higher risk of developing brain metastases. It has been reported that the cumulative incidence of brain metastases in ALK-rearranged NSCLC patients was 23.8% initially and 23.8, 45.5 and 58.4% after 1, 2 and 3 years, respectively [44]. Brain metastases develop in up to 74% of patients treated with crizotinib [45]. Second-generation TKIs more readily penetrate the blood–brain barrier and inhibit brain metastases compared with crizotinib. In the ALEX trial, the IC response rate for alectinib in previously untreated brain metastases was 81% compared with 50% for crizotinib [6]. In addition, among patients who relapsed after first-line treatment with crizotinib, a high IC response rate was achieved with both ceritinib (45%) and brigatinib (42–67%). IC-ORR of second-generation ALK-TKIs is reportedly two- to threefold higher than IC-ORR of the first-generation TKI crizotinib, positioning second-generation ALK-TKIs as first-line treatment for NSCLC patients with brain metastases. In patients who relapsed after first-line crizotinib, lorlatinib demonstrated a 42–48% IC response rate [40].

IC and EC responses, regardless of previously administered TKIs, are strengths of lorlatinib [46]. According to a report regarding the current activities of systemic agents against CNS metastases in NSCLC as well as the potential mechanisms of action of these small and large molecules [47], lorlatinib was developed with a focus on improved CNS penetration and potent inhibition of resistance mutations in the ALK kinase domain, especially G1202R [24]. Indeed, PET studies using radiolabeled lorlatinib in preclinical models, including nonhuman primates, demonstrated the high brain permeability of this compound [48–50]. In addition, pharmacokinetic analysis performed in four patients treated in the phase I portion of the phase I/II lorlatinib study who underwent lumbar puncture showed a mean

ratio of cerebrospinal fluid to plasma concentration of 0.75, demonstrating high penetrance of lorlatinib in the CNS [40].

In a pooled EXP analysis of the phase II portion of the phase I/II trial, 139 patients received at least one second-generation ALK-TKI pretreatment (EXP3B–5) [17,51]. Of these patients, 28 received one second-generation ALK-TKI pretreatment (EXP3B), 65 received two ALK-TKI pretreatments (EXP4) and 46 received three ALK-TKI pretreatments (EXP5). In EXP3B–5, ORR (95% CI) was 39.6% (range: 31.4–48.2%), IC-ORR was 56.1% (range: 42.4–69.3%), EC-ORR was 36.7% (range: 28.7–45.3%), median duration of response was 9.6 months (range: 5.6–16.7), IC duration of response was 12.4 months (range: 6.0–37.1), EC duration of response was 9.7 months (range: 6.1–33.3), median PFS was 6.6 months (range: 5.4–7.4) and median OS was 20.7 months (range: 16.1–30.3). In EXP3B, ORR was 42.9% (range: 24.5–62.8%), IC-ORR was 66.7% (range: 29.9–92.5%) and EC-ORR was 32.1% (range: 15.9–52.4%). In EXP4–5, ORR was 38.7% (range: 29.6–48.5%), IC-ORR was 54.2% (range: 39.2–68.6%) and EC-ORR was 37.8% (range: 28.8–47.5%). The plasma concentration of lorlatinib was not significantly associated with ORR or IC-ORR.

In a phase II study in China (NCT03909971) in patients who had prior crizotinib treatment and ≥1 nonirradiated EC target lesion before lorlatinib administration, the primary end point was objective response [52]. A total of 47 of 67 (70.1%; 95% CI: 57.7–80.7) patients in the cohort achieved an overall objective response.

Carcinomatous meningitis is a complication of NSCLC with variable clinical manifestations and limited efficacy of existing therapies. In an ALK-positive lung cancer patient with brain metastases and meningeal dissemination, appropriate sequential administration of first-, second- and third-generation ALK-TKIs led to survival for more than 90 months [53]. A response to lorlatinib has also been reported in patients with meningeal carcinomatosis resistant to alectinib and brigatinib [54], including patients with swallowing difficulty because of impaired consciousness due to CNS lesion. In one case, nasogastric administration of lorlatinib alleviated consciousness changes within 3 days, and the patient survived [55]. After lorlatinib treatment for 1 week, clinical improvements (e.g., better mental status, reduced headache and greater leg strength) were observed in a patient with brain metastases from ALK-positive lung cancer involving dissemination from the cerebellum throughout the spinal cord [56]. Furthermore, pretreated patients with EML4-ALK-rearranged NSCLC (including inflammatory myofibroblastic sarcoma patients) reportedly achieved robust remission in association with sequential administration of next-generation ALK-TKIs, including rechallenge, particularly when the CNS was the site of progression [57–62].

According to a network meta-analysis of 11 randomized controlled trials (2687 patients with NSCLC and 991 with brain metastasis), for PFS for brain metastasis patients, compared with platinum doublet chemotherapy, lorlatinib (HR: 0.01; 95% CI: 0.001–0.12), alectinib (HR: 0.05; 95% CI: 0.01–0.21) and brigatinib (HR: 0.07; 95% CI: 0.007–0.76) [63]. Although no individual treatment was superior to chemotherapy in terms of OS in NSCLC patients, alectinib (HR: 0.29; 95% CI: 0.03–1.68), lorlatinib (HR: 0.41; 95% CI: 0.04–4.13) and ceritinib (HR: 0.63; 95% CI: 0.10–4.25) were more effective therapies. In a network meta-analysis of six ALK-TKIs and platinum-based cytotoxic agents, no significant differences were observed in PFS (HR: 0.742; 95% CI: 0.466–1.180) or OS (HR: 1.180; 95% CI: 0.590–2.354) between lorlatinib and alectinib [64]. In the Asian subgroup, there was no significant difference in PFS between lorlatinib and alectinib. In the non-Asian subgroup, lorlatinib was significantly superior to alectinib in terms of PFS (HR: 0.388; 95% CI: 0.195–0.769). The incidence of grade 3 treatment-related AEs (TRAEs) in all patients was significantly higher with lorlatinib than alectinib (relative risk: 1.918; 95% CI: 1.486–2.475). According to a Bayesian network meta-analysis of nine randomized controlled trials involving 2484 ALK-positive lung cancer patients, lorlatinib was more beneficial in terms of PFS and risk of CNS progression than other first-line therapies in patients with advanced ALK-positive NSCLC [65]. Notably, lorlatinib had higher toxicity and increased the risk of grade 3 AEs compared with alectinib (OR: 4.26), whereas alectinib caused the fewest grade 3 AEs.

Overall, lorlatinib has been determined to be a superior treatment for patients with brain metastasis [63–69]. A summary of the efficacy of 100 mg lorlatinib once daily (phase II and III studies) is included in Table 1.

Toxicity

Characteristic TRAEs of lorlatinib include hypercholesterolemia and hypertriglyceridemia. The following AEs were recorded in phase I and II studies: hypercholesterolemia (72/81.5%), hypertriglyceridemia (39/60.4%), peripheral neuropathy (39/29.8%) and peripheral edema (39/43.3%) [17,40]. Significant correlations were identified between plasma lorlatinib concentration and risk of grade ≥3 hypercholesterolemia (OR: 5.256) and TRAEs (OR: 3.214). Baseline cholesterol and treatment duration are associated with the likelihood of grade ≥3 hypercholesterolemia [70].

Table 1. Results of phase II and III lorlatinib trials.

Lorlatinib trial												
Phase	Prior treatment	Patients (n)	ORR, % (95% CI)	Duration of response, months (95% CI)	Intracranial response, % (95% CI)	Duration of intracranial response, months (95% CI)	Time to tumor response, months (95% CI)	PFS, months (95% CI)	1-year survival rate, % (95% CI)	Discontinuation by AE, % (95% CI)	Trial ID	Ref.
II	None	30	90.0 (73.5–97.9)	NR (10.0–NR)	66.7 (9.4–99.2)	NR (NR–NR)	1.4 (1.3–2.7)	NR (11.4–NR)	–	–	NCT01970865	[17]
	Crizotinib w/wo chemo	59	69.5 (56.1–80.8)	NR (11.1–NR)	87.0 (66.4–97.2)	NR (8.4–NR)	1.4 (1.3–2.6)	NR (12.5–NR)	–	–		
	SG ALK-TKI w/wo chemo	28	32.1 (15.9–52.4)	NR (4.1–NR)	55.6 (21.2–86.3)	NR (4.1–NR)	1.4 (1.4–2.7)	5.5 (2.7–9.0)	–	–		
	≧2 prior ALK-TKI w/wo chemo	111	38.7 (29.6–48.5)	NR (5.5–NR)	53.1 (38.3–67.5)	14.5 (8.4–14.5)	1.4 (1.4–2.9)	6.9 (5.4–9.5)	–	–		
II	Crizotinib	67	70.1 (57.7–80.7)	NA (9.7–NA)	80.6 (64.0–91.8)	NA (NA–NA)	1.4 (0.6–11.1)	NA (NA–NA)	–	–	NCT03909971	[48]
	Other than crizotinib	42	47.6 (32.0–63.6)	11.2 (2.9–NA)	47.6 (25.7–70.2)	NA (5.6–NA)	1.4 (1.2–5.6)	5.6 (2.9–9.7)	–	–		
III	None	149	76 (68–83)	NE (NE–NE)	82 (57–96)	NE (NE–NE)	1.9 (1.8–3.7)	NR (NR–NR)	78 (80–84)	7	NCT03052608	[40]

AE: Adverse event; chemo: Chemotherapy; NA: Not applicable; NE: Not evaluated; NR: No response; ORR: Objective response rate; PFS: Progression-free survival; SG: Second-generation; TKI: Tyrosine kinase inhibitor; w/wo: With/without.

Changes in cognitive function (24/23%), mood (19/22%) and speech (15/8%) have been recorded as CNS effects [17]. Weight gain (17/18.2%), fatigue (15/13.1%), diarrhea (<10/10.5%) and arthralgia (<10/10.2%) have also been recorded. In two (0.7%) patients in a phase II study (NCT01970865), the most common severe AE was cognitive impairment [71]. Treatment was discontinued, and the symptoms were reversible. A risk of severe hepatotoxicity has been reported when lorlatinib is used concomitantly with strong CYP3A inducers, resulting in a contraindication [72]. TRAEs in a global phase III trial were similar to those in phase I and II trials: grade 3 or 4 TRAEs (primarily changes in lipid levels) occurred in 72% of patients, but the TRAE-related overall permanent discontinuation rate was only 7%, which is lower than that observed in patients receiving crizotinib [43]. Hyperlipidemia has been found to be manageable with lipid-lowering therapy. In one study, more than 80% of patients received at least one lipid-lowering agent, with more than 20 and 30% of patients requiring two or more agents for hypercholesterolemia and hypertriglyceridemia, respectively [71].

The differences in TRAE profiles among ALK-TKIs are described in the following sections. According to AE reports in the FDA Adverse Event Reporting System database, liver failure (e.g., hepatic failure, fulminant hepatitis and hepatic necrosis) is reported more frequently in association with ceritinib, crizotinib and alectinib than with lorlatinib [73]. In addition, according to FDA Adverse Event Reporting System records from 2012 to 2020, there are significant safety signals with regard to metabolic disorders (specifically hypercholesterolemia) in association with lorlatinib (proportional reporting ratio: 3.34; reporting OR: 3.53) [74].

An observational and retrospective analysis of spontaneous reports to the FDA Adverse Event Reporting System of psychiatric AEs associated with ALK-TKIs approved for NSCLC (e.g., crizotinib, ceritinib, alectinib, brigatinib and lorlatinib) up to 2020 showed that, among ALK-TKIs that may cause psychosis-like reactions, the rate for lorlatinib was high (2.8%) [75]. The incidences of heart failure, supraventricular tachycardia and ventricular arrhythmia, calculated through analysis of data from VigiBase, a WHO pharmacovigilance database, were compared among EGFR inhibitors (e.g., erlotinib, gefitinib, afatinib and osimertinib), BRAF inhibitors (e.g., dabrafenib), MEK inhibitors (e.g., trametinib) and ALK ± ROS1 inhibitors (e.g., alectinib, brigatinib, ceritinib, crizotinib and lorlatinib). ALK and ROS1 inhibitors were associated with increased odds of conduction disease (reporting odds ratio = 12.95, 99% CI: 10.14-16.55), but lorlatinib had lower odds of conduction disease relative to other ALK inhibitors (reporting odds ratio = 0.21, 99% CI: 0.07–0.69) [76].

A systematic review showed that the drug-induced lung damage rate among 170 patients who received lorlatinib was 1.8% [77]. During recovery from alectinib-related drug-induced interstitial lung disease with metastatic ALK-rearranged NSCLC, patients tolerated lorlatinib, and no relapses of drug-induced interstitial lung disease were observed [78]. Although lorlatinib induces interstitial lung disease in 1.8% of patients (a lower rate than that observed among patients receiving brigatinib), cross reactivity-related pulmonary toxicity has been reported after its administration as sequential therapy in one patient who had brigatinib-related pneumonia [79]. In a patient with alectinib hepatotoxicity that could not be managed by dose reduction, a successful outcome was achieved by switching to lorlatinib [80]. However, grade 4 hypertriglyceridemia and acute pancreatitis were reported in a patient who received lorlatinib [81].

Proteinuria induced by lorlatinib treatment has been reported in a dose-dependent manner [82]. In one case, a patient was treated with lorlatinib, and the dose was reduced to 75 mg per day because of weight gain, metabolic abnormalities (i.e., dyslipidemia and elevated hemoglobin A1c), fatigue, confusion and depression [83]. The dose was then reduced to 50 mg per day and combined with statin administration. The patient responded to treatment and the antitumor effect was maintained at the last follow-up, 13 months after initiation of lorlatinib.

According to FDA data regarding preclinical models, the effects of lorlatinib on male reproductive organs are reversible. Female patients of reproductive age should be advised to use effective nonhormonal contraception during treatment with lorlatinib and for at least 6 months after the last dose. Importantly, lorlatinib may render hormonal contraceptives ineffective. In addition, based on genotoxicity findings, male patients with female partners of reproductive age are recommended to use effective contraception during treatment with lorlatinib and for at least 3 months after the last dose. The carcinogenicity of lorlatinib has not been explored.

Patient-reported outcomes & quality-of-life

Patient-reported outcomes and quality-of-life from a phase I/II study demonstrated that lorlatinib treatment provides clinically meaningful improvements in quality-of-life as well as physical, emotional and social function and that these improvements are maintained over time [84]. In addition, Mazieres *et al.* reported that for symptoms of fatigue, nausea, vomiting, insomnia, anorexia and constipation, there was a statistically significant difference for

lorlatinib but no clinically significant difference [85]. For diarrhea, there was a clinically meaningful and statistically significant difference in favor of lorlatinib. Lung cancer symptoms improved from baseline in both the lorlatinib and crizotinib groups, with clinically meaningful improvement in cough as early as cycle two that was maintained through cycle 18. Time to treatment deterioration for the composite end point of lung cancer symptoms (cough, dyspnea or chest pain) was similar between these groups (HR: 1.09; 95% CI: 0.82–1.44; p = 0.5415). Median time to worsening global quality-of-life was 24.0 months for lorlatinib and 12.0 months for crizotinib (HR: 0.92; 95% CI: 0.65–1.29).

Physician–patient communication is particularly important during treatment with lorlatinib. A clear explanation (e.g., using plain language and examples) of the potential for specific AEs along with reassurance that such events are generally minor and can be alleviated with appropriate medication will facilitate AE monitoring and management [86]. Because of the unique AEs associated with the use of lorlatinib, a practical reference tool has been created for clinicians and basic researchers [87,88]. There is also a support site for ALK-positive cancer patients, especially those with lung cancer (www.alkpositive.org/).

Resistance & treatment sequences

Lorlatinib has demonstrated activity in patients resistant to first- and second-generation inhibitors, but the molecular characteristics of acquired resistance to lorlatinib are heterogeneous and complex, and platinum/pemetrexed chemotherapy (not only targeted therapy) is still an effective treatment option for patients exhibiting resistance to lorlatinib [89]. The clinical manifestations of ALK-positive NSCLC vary widely among patients, and differences in the molecular events underlying crizotinib resistance are the main reason for heterogeneity [90]. Available ALK-TKIs must be used carefully as part of individualized treatment strategies tailored to prevent disease progression, with consideration of clinical and cost limitations [91]. It is important to determine the most effective sequence and combination of ALK inhibitors for individual patients [92].

Resistance can involve acquired ALK mutations or bypass-driven resistance or, in some cases, both. Approximately half of patients have mutations that render them resistant to ALK-TKIs, whereas in the other half different mechanisms underlie resistance; such tumors are unlikely to respond to lorlatinib. The major problems associated with ALK-positive NSCLC are acquired resistance and control of CNS metastases [93]. Secondary mutations in ALK are a common resistance mechanism to second-generation ALK inhibitors that is predictive of sensitivity to lorlatinib [94]. Next-generation sequencing analysis of autopsy tumor samples from the lung, liver and kidney of a patient with advanced ALK-positive lung cancer who developed resistance to alectinib within 3 months of treatment initiation showed that the tumor mutation burden was high and the tumor evolution was heterogeneous [95]. Lorlatinib reduced the growth of such tumors both *in vitro* and *in vivo*. Notably, progression from second- to third-generation agents is not the only available treatment strategy. For example, in rare instances, crizotinib shows antitumor effects in tumors that do not respond to alectinib [96]. Moreover, brigatinib has been shown to elicit a good response in a patient with resistance to alectinib who had a previously unreported ALK mutation (p.A1200_G1201delinsW) [97]. When subsequent resistance involving a KRAS off-target mutation (p.Q61K) occurred, lorlatinib had only a limited effect, whereas chemoimmunotherapy was sufficient to achieve tumor control. Sequential treatment and molecular profiling are needed.

Mutations in the ALK gene are detected in approximately 40% of ALK inhibitor-resistant patients [98]; thus, there is a need to continue genomic profiling of resistance associated with ALK mutations. Genotyping of tumors with ALK mutations after failure of second-generation TKIs may help identify patients who could benefit clinically from lorlatinib [99]. Long-term studies of detailed molecular profiles based on tumor biopsies and ctDNA as well as the adaptive mechanisms that confer resistance to this targeted agent have been made possible by the development of patient-derived xenografts and cell lines [100,101].

Approximately 12 mutations in the catalytic domain of the ALK fusion protein have been found to confer crizotinib resistance; there is no single gatekeeper mutation [102]. Sequential administration of ALK-TKIs is presumed to promote the acquisition of ALK-resistant mutations and lead to compound ALK mutations resistant to treatment [103,104]. Although compound ALK mutations after lorlatinib exposure have been observed in *in vitro* studies [105], the success of rechallenge in patients taking other kinase inhibitors after resistance to lorlatinib remains under investigation. It is currently unknown whether selected subpopulations may benefit from upfront lorlatinib versus sequential use of next-generation ALK inhibitors (e.g., alectinib or brigatinib followed by lorlatinib). A randomized phase II trial that assigned pretreated patients with or without resistance mutations to treatment groups

according to individual or combinations of resistance mutations has been initiated, and the results will be published in 2026 at the earliest (ALK master protocol: NCT03737994) [106].

Here the authors review the phenomenon of resistance in ALK-positive lung cancer, including the use of lorlatinib to overcome resistance to other treatments, resistance to lorlatinib and implementation of sequential treatment. In cases of severe disease progression, timely rebiopsy and biological redefinition may be beneficial [107]. A recent report also suggested that tumor genotyping may identify the patients most likely to benefit from lorlatinib [99].

With regard to clinically significant mutations, an analysis of repeat biopsies of lorlatinib-refractory patients revealed compound ALK mutations in 35% [105]. Whole-genome sequencing of three patients confirmed stepwise accumulation of ALK mutations during sequential dosing. ALK-TKIs promote the emergence of compound ALK mutations that confer robust resistance to ALK-targeted therapy, suggesting that identification of these compound ALK mutations is important for the development of effective therapeutic strategies.

The L1198F mutation in ALK has been reported to cause structural changes in the inhibitory site, thus modulating the binding affinity of ALK to crizotinib and lorlatinib; the L1198F mutation also affects ALK autoactivation [108]. The T1151Sins mutation in ALK was detected in tumors resistant to ceritinib but not in those responsive to lorlatinib. *In vitro* evaluation confirmed that ALK with the T1151Sins mutation was resistant to ceritinib but sensitive to lorlatinib. MET amplification was also present in tumors resistant to lorlatinib [109]. A good response to lorlatinib was reported in a patient with a novel ALK resistance deletion p.(Q1188_L1190del) who had shown a lack of sensitivity to ceritinib, alectinib and brigatinib despite a previously identified ALK deletion (G1202del); these findings were consistent with preclinical evidence [94,110]. The C1156Y/G1269A compound mutation maintained sensitivity to lorlatinib, suggesting that coexisting off-target resistance mechanisms may drive disease progression even in the presence of compound mutations. Similar to the L1196M/G1202R mutation, the L1196M/D1203N mutation conferred high lorlatinib resistance, and the combined G1202R/F1174L mutation was reportedly less resistant to lorlatinib compared with the G1202R mutation alone because Ba/F3 cells expressing EML4-ALKG1202R/F1174L required a slightly higher concentration of lorlatinib to induce cell death compared with cells expressing EML4-ALKG1202R (IC_{50}: 83 nM) [101].

In a Japanese study of 112 consecutive biopsy samples from 32 ALK-positive patients, secondary mutations (G1202R, G1269A, I1171T, L1196M, C1156Y and F1245V) were found in 75% of samples after failure of crizotinib [111]. Mutations in G1202R and I1171N were detected in approximately half of the samples after alectinib failure. After ceritinib treatment, G1202R, F1174V and overexpression of *P*-glycoprotein were observed in approximately half of the samples. After lorlatinib treatment, a L1196M/G1202R compound mutation was detected in one sample. The I1171S/G1269A compound mutation in ALK, found in clinical samples resistant to lorlatinib, is expected to be overcome by ceritinib and brigatinib [112]. Among lorlatinib-resistant patients, two of 12 with circulating tumor cells had compound mutations in ALK, some of which were consistent with tumor biopsy findings [113]. Other samples had G1202R/T1151M compound mutations not detected by tumor biopsy. These results demonstrate the genetic heterogeneity of circulating tumor cells that may be useful for identifying treatment-resistant mutations in patients treated with ALK-TKIs. The clinical usefulness of this evaluation requires further investigation.

Compound mutations such as I1171N/F1174I and I1171N/L1198H are resistant to all currently approved ALK-TKIs. However, gilteritinib, a TKI approved for the treatment of relapsed and refractory FLT3-positive acute myeloid leukemia, is effective in inhibiting ALK-TKI-resistant single mutants and I1171N compound mutants both *in vitro* and *in vivo* [114]. In terms of the conformational dynamics of the ALK kinase domain, I1171N compound mutations significantly inhibited the energetically and structurally conserved hydrogen bonding interaction between hinge residues Glu1197 and Met1199 in the lorlatinib-bound state; however, such compound mutations did not have an obvious negative effect on the binding affinity or stability of the gilteritinib-bound state [115].

A patient resistant to brigatinib had the ALK R1192P mutation, which was sensitive to brigatinib during *in vitro* studies; however, it coexisted with the G1202R mutation in the *cis* configuration, which led to resistance and the need to switch to lorlatinib [116]. *In silico* modeling predicted that the ALK G1202K mutation may serve as a novel resistance mechanism to alectinib, and clinical findings validated this prediction [117]. Lorlatinib has shown efficacy in the treatment of ALK with the G1202L mutation after the failure of crizotinib and brigatinib [118]. In a patient with metastatic ALK-positive NSCLC who exhibited disease progression despite treatment with crizotinib and ceritinib, the T1151K mutation in ALK was reported, and salvage treatment with alectinib or lorlatinib was possible [119]. The L1196M/G1202R mutation can arise against brigatinib in patients with NSCLC; this double mutation also confers resistance to lorlatinib. In addition, a patient with ALK-rearranged lung cancer exhibited

progression despite lorlatinib treatment, and that tumor converted to neuroendocrine carcinoma and demonstrated L1196M acquisition [120,121]. ALK-rearranged NSCLC harboring crizotinib-resistant 1151Tins exhibited lorlatinib sensitivity in both *in vitro* and clinical studies [122]. Multiple compound mutations in ALK promoting lorlatinib resistance and a single mutation in L1256F have also been reported [123]. A response to lorlatinib was observed in a patient with crizotinib-resistant ALK harboring the C1156Y mutation [124]. Upon disease recurrence, a second mutation in ALK (L1198F) was found. Paradoxically, the L1198F substitution led to crizotinib resensitization, enabling subsequent treatment with crizotinib.

In addition, in targeted sequencing analysis of patients with EML4-ALK-rearranged malignant pleural mesothelioma treated with alectinib (first-line therapy) and lorlatinib (fourth-line therapy), the I1171N and L1196M mutations appeared after alectinib failure, whereas the I1171N, L1196M and G1202R mutations were identified after lorlatinib failure [125]. L1196M was located in the *cis* configuration relative to G1202R, suggesting that this position effect may have acted synergistically to promote resistance to both alectinib and lorlatinib. In a patient with relapsed neuroblastoma harboring the F1174L mutation and amplification, lorlatinib was administered in a compassionate use program and showed some efficacy.

Two non-EML4-ALK rearrangements, LOC388942-ALK and LINC00211-ALK, were simultaneously identified in the cerebrospinal fluid of a patient whose CNS metastases had become resistant to alectinib [126]. ALK inhibitor resistance in the CNS was reportedly overcome by increasing the dose of alectinib to 600 mg twice daily and then switching to lorlatinib. With regard to non-EML4-ALK fusions, the HIP1-ALK (H21:A20) variant has been associated with better outcomes [127]. One patient treated with first-line lorlatinib achieved a partial response over 26.5 months.

Serial ALK-TKI use may also result in a higher frequency of ALK-independent or 'fusion-extrinsic' resistance. These resistance mechanisms include EGFR/MAPK pathway activation and epithelial–mesenchymal transition (EMT) upregulation [94,101,128] rather than secondary ALK mutations that develop after the administration of first- and second-generation TKIs. Although mutations in the ALK gene are detected in approximately 40% of ALK inhibitor-resistant patients, EMT upregulation (a mechanism of resistance to various targeted agents) was detected in a single crizotinib-resistant lesion in a patient with relapsed ALK NSCLC [98]. The ALK mutant L1196M and EMT upregulation were detected simultaneously in a single crizotinib-resistant lesion in a patient with relapsed ALK lung cancer. Digital PCR analysis combined with immunohistochemistry staining of EMT markers showed that ALK L1196M was mainly present in epithelial-type tumor cells, indicating that the mesenchymal phenotype and ALK mutations can coexist as independent mechanisms underlying ALK inhibitor resistance in lung cancer. Preclinical experiments showed that EMT upregulation combined with decreased expression of miR-200c and increased expression of ZEB1 leads to cross-resistance to next-generation ALK inhibitors (e.g., alectinib, ceritinib and lorlatinib) and that pretreatment with the histone deacetylase inhibitor xinostat could overcome this resistance by restoring normal EMT *in vitro* and *in vivo*. EMT proteins and matrix metalloproteinases have important roles in brain metastasis that involve regulation of the blood–brain barrier. Treatment with alectinib and lorlatinib significantly reduces the mRNA and protein levels of EMT markers while inhibiting cell viability and migration of target cells in a dose- or time-dependent manner. These findings suggest that alectinib and lorlatinib may inhibit NSCLC metastasis by downregulating matrix metalloproteinase activity and EMT activation [129]. EMT upregulation is a major problem associated with rapid disease progression and a poor response to continued ALK inhibition [130].

Src signaling has been identified as a resistance mechanism for alectinib, and combination therapy with ALK and Src inhibitors can inhibit the growth of other ALK NSCLC cell lines, including ceritinib- and lorlatinib-resistant cells, by effectively inhibiting receptor tyrosine kinase activity and downstream PI3K/AKT signaling through Src inhibition [131]. Several ALK-resistant patient-derived cell lines have been reported to be sensitive to combination of ALK and Src inhibition. [101,132]. Moreover, Src inhibition can partially restore EMT-associated E-cadherin expression in cells in lorlatinib-resistant patient-derived mesenchymal cells, whereas FGF receptor inhibitors can sensitize ALK-rearranged EMT cell lines to lorlatinib *in vitro*. In addition, a patient with ALK-positive lung adenocarcinoma exhibited acquired resistance to lorlatinib during treatment for brain metastasis; the tumor showed histological transformation to squamous cell carcinoma with MET amplification [133]. When tumors grow after lorlatinib administration, readministration of crizotinib results in tumor shrinkage, suggesting that resistance to lorlatinib and the response to readministration of crizotinib after lorlatinib administration may be partially related to activation of the MET pathway [134]. Treatment with third-generation ALK inhibitors, especially

as first-line therapy, may result in MET-induced resistance; in such instances, it may be clinically beneficial to target both ALK and MET in patients with acquired MET alterations [135].

A rare instance of CNS metastasis was observed in a patient with advanced ALK-positive NSCLC harboring the G1202R mutation in ALK after failure of ceritinib and alectinib [136]. The tumor exhibited transformation to small cell lung cancer along with an inactivating Rb1 mutation (C706Y) and the loss of exons 1–11 in p53 after a CNS response to lorlatinib. The coexistence of a solvent front mutation and transformation can be evaluated by genomic profiling. A BRAF V600E mutation also contributes to lorlatinib resistance [137]. A925L/AR cells, which are resistant to various ALK-TKIs (e.g., alectinib, crizotinib, ceritinib and lorlatinib), acquire resistance via EGFR activation through the overexpression of amphiregulin, which is in turn caused by decreased expression of miRNA-449a. *In vivo* analysis showed that combined treatment with alectinib and EGFR TKIs (e.g., erlotinib and osimertinib) could inhibit the progression of leptomeningeal carcinomatosis [138]. In a sequencing analysis of cfDNA performed at relapse after a response to lorlatinib in neuroblastoma with the F1174L mutation in ALK, amplifications of CDK4 and FGFR1 were observed along with the Q61K mutation in NRAS [139]. Ceritinib and brigatinib can overcome the I1171S/G1269A compound mutation in ALK, which is resistant to lorlatinib [112].

A total of 31 cancer tissues and 90 cfDNA samples from 88 patients were analyzed in a multicenter targeted next-generation sequencing study of cfDNA and cancer tissues from NSCLC patients who progressed after treatment with ALK-TKIs [140]. In 32 crizotinib-resistant cancers, five (16%) ALK mutations (L1196M × 2, I1171T, D1203N and G1269A/F1174L) and three possible bypass mutations (NRAS G12V, EGFR R108K and PIK3CA E545K) were found. In 18 ceritinib-resistant cancers, four ALK mutations (G1128A, G1202R, G1269A and I1171T/E1210K) and three possible bypass mutations (KIT D820E, MET E1012* and EGFR P265_C291del) were found. In 24 alectinib-resistant cancers, four ALK mutations (G1202R × 2, W1295C and G1202R/L1196M) and one possible bypass mutation (EGFR P753S) were found. In 18 lorlatinib-resistant cancers, two (11%) ALK mutations (G1202R and G1269A) and two possible bypass mutations (BRAF V600E and MET D1246N) were found. Notably, in an analysis of 20 patients, mutations were identified in nine (45%) and six (30%) tissue and cfDNA samples, respectively, with a concordance rate of 45%.

EML4-ALK tumors exhibit some genetic variants. Compared with patients with EML4-ALK variant 1 fusions, patients with EML4-ALK variant 3 fusions are more likely to develop secondary mutations (e.g., ALK G1202R) regardless of whether they are treated with second-generation ALK inhibitors [141]. In addition, variant 3 fusions are associated with significantly longer PFS than variant 1 fusions (HR: 0.31; 95% CI: 0.12–0.79; p = 0.011). The G1202R/S1206Y double mutation in EML4-ALK variant 3 was also detected in the *cis* configuration in an ALK-positive NSCLC patient whose disease progressed after sequential treatment with crizotinib, alectinib and lorlatinib [142]. Among patients with EML4-ALK-rearranged lung squamous carcinoma, OS was 11 months despite switching to lorlatinib [143]. After the emergence of drug resistance, genetic analysis revealed an EML4-ALK fusion with V3(V3a/b) variants. By contrast, a Russian single-center study reported ALK-rearranged variants in 28 patients [144]. There were no significant differences in OS or PFS between patients with variant 1 and 3 rearrangements. The role of the EML4-ALK variant remains incompletely understood.

The use of biopsy tissue during exacerbations is not limited to genomic profiling. In a patient with brain and leptomeningeal disease showing a complete response to consecutive treatment with crizotinib, brigatinib, ceritinib and lorlatinib for more than 5 years, sarcoid-like granulomatous lymphadenitis was diagnosed during lorlatinib treatment; thus, lorlatinib was continued [145]. In a patient with ALK-positive lung cancer that showed no response to alectinib therapy and metastasized to the gastrocnemius muscle, there was also no response to two cycles of second-line therapy with pemetrexed; however, the patient responded to lorlatinib [146].

According to a retrospective analysis of data from a phase II study (NCT01970865) in which patients who received lorlatinib for at least 3 weeks achieved the best overall response (complete response, partial response or stable disease), the median OS after disease progression was not reached (95% CI: 21.4 to not reached) and 14.6 months (95% CI: 11.2–19.2), respectively, in patients who previously received crizotinib alone and those who received at least one prior treatment with a second-generation ALK-TKI [147]. Given the current treatment options, continued lorlatinib treatment after progression is still of value. With regard to the role of cytotoxic therapy in the treatment of ALK-positive lung cancer, platinum/pemetrexed chemotherapy showed moderate efficacy (ORR: 29.7%; 95% CI: 15.9–47.0) in 37 patients with advanced ALK-positive NSCLC refractory to one or more second-generation ALK-TKIs who received platinum/pemetrexed-based chemotherapy [148]. Continued ALK-TKIs may increase efficacy (median PFS: 6.8 vs 3.2 months; HR: 0.33; p = 0.025), indicating that continued ALK-TKI treatment may be useful.

Real-world data

There remain minimal real-world data regarding the impact of ALK-TKI treatment sequence and clinical features on ALK-positive NSCLC patients, including with regard to lorlatinib, although a few reports have been published. The Global Lorlatinib for ALK(+) and ROS1(+) Retrospective Study (GLASS) was based on an early access program conducted in Turkey, Switzerland, Russia, Israel, Germany, France and the USA [149]. The GLASS study recruited 106 ALK-positive and 17 ROS1-positive patients between March 2015 and January 2019. In the ALK-positive cohort, 50% of the patients were male, 73% were never-smokers and 68% had brain metastases. EC-ORR and IC-ORR were 60 and 62%, respectively, and EC and IC disease control rates were 91 and 88%, respectively. The median DoT was 23.9 ± 1.6 months, whereas the median OS was 89.1 ± 19.6 months. The most common AEs of any grade were peripheral edema (48%), hyperlipidemia (47%), weight gain (25%) and fatigue (30%). CNS AEs (e.g., grade 1–2 cognitive impairment) were reported in 18% of patients. Lorlatinib showed outstanding EC/IC efficacy in previously treated ALK- and ROS1-positive NSCLC. The median OS of 89 ± 19 months in ALK-positive NSCLC was consistent with previous findings.

According to early or expanded access programs in Hong Kong, Singapore, South Korea, Taiwan, Thailand and the USA (n = 76), ORR for lorlatinib in ALK patients who had received two or more prior ALK-TKIs was 35% (vs 38.7% in a phase II study), whereas the median PFS for ALK patients who had used two or more ALK-TKIs was 11.2 months (vs 6.9 months in a phase II study) [150]. In patients who had received three or more previous TKIs, ORR, disease control rate, median DoT and median PFS were 18 and 65% (4.8 and 6.5 months), respectively. The response to lorlatinib based on prior ALK-TKI therapy was similar between Asians and non-Asians in early and expanded access programs. Furthermore, patients had a lower incidence of AEs than that reported in the phase II trial, which might have been related to differences in local AE management practices rather than selection bias within the programs.

A retrospective study involving 121 patients diagnosed with stage IV ALK-rearranged NSCLC was conducted in Switzerland and Italy between 2011 and 2016 [151]. The median OS from diagnosis of stage IV disease was 48.0 months, and the use of multiple ALK-TKI lines was positively correlated with OS (p = 0.016) and the use of alectinib or lorlatinib (rather than crizotinib ± ceritinib) in any line of treatment (p = 0.022). In a retrospective study of 51 patients (37 ALK-positive and 14 ROS1-positive) in Austria who received lorlatinib as second-line (or later) treatment, the median follow-up and DoT in ALK-positive patients were 25.3 and 4.4 months, respectively, and ORR was 43.2% [152]. The median OS in the ALK-positive group from the start of lorlatinib treatment was 10.2 months. Most AEs did not significantly affect the symptom burden, which is important for late-line treatment. Only one patient permanently discontinued treatment because of AEs. Nineteen patients received brigatinib as the last line of treatment, with ORR of 32.6% and DoT of 3.5 months. No significant differences were observed in DoT, OS or ORR according to the line or sequence of treatment. Lorlatinib was the best choice as both early- and late-line treatment as well as for treatment after second-generation TKIs.

In a Korean study, 12 patients had previous first- or second-generation ALK-TKI therapy, and two ALK-positive patients and one ROS1-positive patient had G1202R and G2032R mutations, respectively [153]. ORR was 64% and the disease control rate was 91%. Of the three ALK-positive patients with IC target lesions, one (33%) had a complete response and two (67%) had a partial response, yielding an IC-ORR of 100%. The most common AE was hypercholesterolemia (83%), and no AE-related dose reductions or treatment discontinuations were reported. In a report of lorlatinib treatment in heavily pretreated Caucasian patients, ORRs for patients who had received only one second-generation ALK-TKI (n = 20) and those who had received multiple second-generation TKIs (n = 17) were 50 and 35%, respectively [152]. There were no differences among patients according to prior TKIs, and lorlatinib was active when administered after brigatinib. In a cohort study conducted in the UK, 42 patients received an ALK-TKI as first-line treatment after brigatinib, and of these, 34 (>80%) received lorlatinib [154]. With respect to safety and efficacy, any TKI (including alectinib and brigatinib) can be used as late-line treatment regardless of which was used as first-line treatment.

In a retrospective study conducted in Germany, the overall ALK-TKI discontinuation rate was approximately 25–30%, and there were no significant differences in discontinuation rates between second-generation ALK inhibitors after crizotinib or systemic chemotherapy and lorlatinib after second-generation TKIs or systemic chemotherapy [155]. Additional treatment with either TKI was associated with significantly longer survival, with median OS rates of 59 and 41 months, respectively, suggesting that patients with early TKI discontinuation and good general condition may benefit from treatment that includes systemic chemotherapy. A total of 22 ALK-positive

patients were included in a retrospective study conducted in Taiwan [156]. The ORR and disease control rate with lorlatinib were 35.7 and 64.3%, respectively, and the median PFS was 6.2 months. A total of 94.7% of patients developed dyslipidemia (grade 3 or 4 in 21.1%), but none of these patients discontinued treatment because of it.

Conclusion

Lorlatinib has emerged as a new option for ALK tyrosine kinase inhibitor therapy. The treatment of ALK-positive lung cancer is expected to become more sophisticated and precise. Effective sequences of ALK tyrosine kinase inhibitors and cytotoxic agents can be increasingly complex and detailed, but this is still a narrow path. The continuous development of target-driven treatment is expected to provide further treatment options, but this may require many years of drug development and clinical validation.

Future perspective

The successful development of lorlatinib is a milestone in the treatment of ALK-positive NSCLC that will have long-term impacts. Lorlatinib is expected to positively contribute to the prolonged survival already observed in patients with ALK- and ROS1-positive NSCLC. There is a need to continue current efforts to improve patient prognosis through molecular approaches. Overcoming acquired resistance to this new drug is the logical (and inevitable) next step [157]. Here the authors summarize future perspectives.

Re-examination of tissues and plasma in the event of disease progression has become important for individualized and optimized patient management. Although approximately half of all ALK patients will acquire resistant mutations, those with off-target resistance (e.g., MET, HER2 and KRAS) will require different treatment strategies, including participation in early-phase clinical trials and off-label administration of targeted agents. When multiple tests are required, invasiveness and cost are important considerations. Minimally invasive monitoring techniques, such as ctDNA measurement by liquid biopsy, may allow planning of kinase inhibitor treatment before clinical resistance develops or patients become symptomatic. High-throughput studies of the genome, transcriptome and proteome can reveal the various mechanisms by which multiple tumor types develop resistance to the third-generation ALK TKI lorlatinib [128]. As a laboratory test, an optimal protocol has been reported for single-cell sequencing of floating tumor cells in pleural fluid [158]. Enriched floating tumor cells are subjected to whole-genome amplification followed by genomic sequencing. In the exploratory study, somatic mutations in floating tumor cells were consistent with mutations detected in tissue samples. This protocol can also be applied to analysis of circulating tumor cells in peripheral blood, thus expanding the potential for molecular profiling in cancer treatment. Indeed, complete concordance has been demonstrated between ALK fusions detected in tissue and plasma during disease progression [159]. The ALK mutation profile in plasma is presumably dependent on the specific TKI administered, such that ALK G1202R is the most frequent plasma mutation detected after progression with treatment with second-generation TKIs. This mutation is consistently suppressed by treatment with lorlatinib.

Biologically favorable ALK fusion tumors have a mean tumor mutation burden of less than 3 mut/Mb and currently have the longest survival rates of all NSCLCs [160]. In patients with lung cancer, the tumor mutation burden is a useful marker for predicting the outcome of PD-1 pathway blockade therapy. Therefore, an immune checkpoint inhibitor response may be absent or appear late in ALK-positive lung cancer treatment. In that context, the main concern may be the poor efficacy of late-line immune checkpoint inhibitor therapy as well as the side effects of combined TKI and immune checkpoint inhibitor treatment. Notably, ALK fusion has distinct effects on TKIs depending on the variant [161]. The presence of EML4-ALK fusion variant 3 and/or TP53 mutations indicates high-risk cases that are likely to exhibit early treatment failure, thus requiring more aggressive surveillance and treatment strategies [162–165].

Extensive investigations are ongoing regarding the clinical utility of longitudinal ctDNA assays for early detection of disease progression as well as improved treatment strategies for patients with progression. Among 29 patients who relapsed on lorlatinib, plasma genotyping detected ALK mutations in 22 (76%), of whom 14 (48%) had two or more ALK mutations [103]. The most common ALK mutation combinations were G1202R/L1196M and D1203N/1171N. Compared with second-generation ALK-TKIs, two or more ALK mutations were detected in significantly more patients who relapsed on lorlatinib (48 vs 23%; $p = 0.017$). Serial analysis of plasma revealed that eight of 15 (53%) patients who received lorlatinib after a second-generation TKI acquired one or more new ALK mutations with lorlatinib. The results of the next-generation sequencing analysis using plasma tissue that will be conducted in the SPACEWALK prospective cohort study (recruiting completed in February 2021) should provide further guidance (NCT03833934).

The next major pharmacological challenges in this area are the development of more potent fourth-generation TKIs as well as effective immuno-oncological interventions, such as ALK-directed cell therapies, which are essential for further enhancement of survival and curative treatments for ALK-positive tumors [166]. With regard to the development of combination therapies, patients with symptomatic CNS disease who had received heavy pretreatment with a third-generation ALK-TKI, chemotherapy or radiation therapy were administered a combination of bevacizumab and lorlatinib, and these patients exhibited disease control that persisted for 5–9 months, which was significantly longer than that observed for prior lorlatinib monotherapy [167]. In patients who progress during treatment with lorlatinib, the combination of lorlatinib and bevacizumab may avoid both on- and off-target resistance [103].

An shRNA screen of 1000 genes in multiple ALK inhibitor-resistant patient-derived cells was performed to identify genes conferring sensitivity to ALK inhibitors [168]. SHP2, a nonreceptor protein tyrosine phosphatase, was identified in multiple patient-derived cells. A small-molecule inhibitor of SHP2 was able to stop the growth of resistant patient-derived cells.The combination of a synthetic miRNA inhibitor with crizotinib or lorlatinib by Locked Nucleic Acid was associated with resistance to miR-100-5p, providing a new therapeutic target for drug resistance. [169]. The FAM179A gene was identified as a novel fusion partner for ALK in plasma cfDNA from NSCLC patients, but the response to ALK inhibitors has not been determined among NSCLC patients harboring the FAM179A-ALK fusion gene [170].

In 2021, the CLIP1-LTK fusion gene was discovered in lung adenocarcinoma [171]. CLIP1 is a member of the microtubule plus-end tracking protein family. LTK and ALK constitute the ALK/LTK subfamily of receptor-type tyrosine kinases, which share approximately 80% identity in their respective kinase domains. In cell viability assays using Ba/F3-CLIP1-LTK cells, lorlatinib was tenfold more efficient than other ALK inhibitors, with an IC_{50} of 1.1 nM, which suggests that lorlatinib could be a highly effective treatment for tumors induced by CLIP1-LTK fusion.

Executive summary

Pharmacology
- Lorlatinib has good oral bioavailability.
- No apparent differences were observed in lorlatinib pharmacokinetic parameters between Asian and non-Asian individuals.

Pivotal clinical trials
- Four clinical trials have been conducted thus far: a phase I/II study series, the phase III CROWN study and a Chinese phase II study.
- These trials showed similar efficacy, such as good penetration for CNS metastasis and characteristic adverse effects.

Efficacy in treating brain metastasis
- Lorlatinib was determined to be a superior treatment for patients with brain metastasis.

Toxicity
- Lorlatinib has some characteristic adverse effects, but most are well tolerated.
- Changes in cognitive function, mood and speech have been reported.
- Hypercholesterolemia, hypertriglyceridemia and weight gain have also been reported.

Patient-reported outcomes & quality-of-life
- Patient-reported outcomes and quality of life from a phase I/II study showed that lorlatinib treatment provides clinically meaningful improvements.
- Physician–patient communication is particularly important during treatment with lorlatinib.

Resistance & treatment sequences
- It is important to determine the most effective sequence and combination of ALK inhibitors for individual patients.
- There is a need to continue genomic profiling of resistance associated with ALK mutations.

Real-world data
- Real-world data have confirmed the efficacy and safety of the prospective studies.

Author contributions

K Baba and Y Goto declare authorship and acknowledge that both authors have made significant contributions to and are in agreement with the content of the manuscript. Authorship is based on substantial contributions to the conception or design of the work or the acquisition, analysis or interpretation of data for the work; drafting the work or revising it critically for important

intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Company review disclosure

In addition to the peer-review process, with the authors' consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the authors at their discretion and based on scientific or editorial merit only. The authors maintained full control over the manuscript, including content, wording and conclusions.

Financial & competing interests disclosure

Y Goto reports consulting or advisory roles with Eli Lilly, Chugai Pharmaceutical, Taiho Pharmaceutical, Boehringer Ingelheim, Pfizer, Novartis, AstraZeneca, GlaxoSmithKline, MSD, Guardant Health, Daiichi Sankyo, Kyorin Pharmaceutical, Illumina, Thermo Fisher Scientific and Johnson and Johnson. Y Goto is also on the speakers' bureau for AstraZeneca, Eli Lilly, Chugai Pharmaceutical, Taiho Pharmaceutical, Boehringer Ingelheim, Ono Pharmaceutical, Bristol Myers Squibb, Pfizer, MSD, Shionogi, Novartis, Merck and Johnson and Johnson. Y Goto reports institutional research funding from AbbVie, Eli Lilly, Taiho Pharmaceutical, Bristol Myers Squibb, Ono Pharmaceutical, Daiichi Sankyo, Pfizer, Novartis, Kyorin Pharmaceutical, Chugai Pharmaceutical and Guardant Health. All of the aforementioned roles and funding are outside the submitted work. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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