Article published online: 2025-02-25

Safety of Lorlatinib in Patients with Unresectable Advanced *ALK*-Positive Non-Small-Cell Lung Cancer Previously Treated with ALK Inhibitors: A Single-Arm, Open-Label, Phase IV Study in India

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Ind J Med Paediatr Oncol 2025;46:422–426.

Abstract

Lorlatinib is approved in India for patients with previously treated anaplastic lymphoma kinase (*ALK*)–positive advanced or recurrent non-small-cell lung cancer (NSCLC). Owing to the limited number of Indian patients in phase I/II and III studies, a postapproval study was conducted to report the safety and efficacy of lorlatinib in this patient population. In this phase IV study, patients with unresectable advanced and/or recurrent *ALK*-positive NSCLC resistant or intolerant to $\geq$1 prior ALK inhibitor were treated with lorlatinib. The primary endpoint was investigator-assessed incidence of treatment-related adverse events (TRAEs). Secondary endpoints were investigator-assessed objective response rate (ORR), intracranial ORR, duration of response (DOR), and intracranial DOR. Among the 100 patients enrolled, the most frequently reported TRAEs were hypertriglyceridemia (57%), hypercholesterolemia (57%), and weight increase (38%). The confirmed ORR and intracranial ORR by the investigator were 41% (95% confidence interval [CI]: 31.9–50.8%) and 36% (95% CI: 24.5–48.8%), respectively. The median systemic and intracranial DORs were not reached. The safety profile of lorlatinib was consistent with that reported in the phase I/II study. Lorlatinib

Keywords
- ALK tyrosine kinase inhibitor
- lorlatinib
- non-small-cell lung cancer
- safety

article published online
February 25, 2025

DOI https://doi.org/10.1055/s-0045-1801883.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

showed a clinically meaningful improvement in ORR and intracranial ORR in patients with unresectable advanced *ALK*-positive NSCLC. These results support the use of lorlatinib in India for patients with previously treated *ALK*-positive advanced NSCLC. ClinicalTrials.gov identifier: NCT04541706.

Introduction

Rearrangements of the anaplastic lymphoma kinase (*ALK*) gene are found in 3 to 5% of non-small-cell lung cancers (NSCLCs) and show high sensitivity to therapy with ALK tyrosine kinase inhibitors (TKIs).[1,2] Recently, the standard treatment of patients with advanced *ALK*-positive NSCLC has undergone a shift from sequential first-generation ALK TKIs followed by more potent second-generation or third-generation ALK TKIs to front-line second-generation ALK TKIs.[3] Although most patients derive clinical benefit from second-generation ALK TKIs, ultimately, they end up with progressive disease, including central nervous system (CNS) progression, due to acquired resistance.[1]

Lorlatinib is a third-generation, reversible, macrocyclic TKI of ALK and ROS1 designed to be CNS penetrant and to overcome known secondary resistance mutations in the ALK tyrosine kinase domain.[4,5] Preclinical studies have shown that lorlatinib is more potent than first- and second-generation TKIs against nonmutant *ALK* and against most known ALK domain resistance mutations.[3,4,6]

In a single-arm, phase I/II, multicenter study, treatment with lorlatinib showed durable response in patients with *ALK*-positive NSCLC who had previously received at least one ALK TKI, including the first-generation drug crizotinib and second-generation drugs ceritinib and alectinib, with or without chemotherapy.[1] In patients with *ALK*-positive NSCLC previously treated with ALK TKIs, the objective response rate (ORR) was 47.0% (95% confidence interval [CI]: 39.9–54.2%) and the intracranial ORR was 63.0% (95% CI: 51.5–73.4%).[1] The overall median duration of response (DOR) was not reached (NR; 95% CI: 11.1 months–NR), and the median intracranial DOR was 14.5 months (95% CI: 8.4–14.5 months).[1] Based on these findings, lorlatinib received marketing authorization in India for the treatment of patients with unresectable advanced *ALK*-positive NSCLC who had previously received ALK TKIs. Due to the lack of Indian patients in the pivotal phase I/II study and the limited number in the subsequent global phase III CROWN (NCT03052608) study, this postapproval study was conducted to obtain additional safety and efficacy data of lorlatinib in patients with pretreated unresectable advanced and/or recurrent *ALK*-positive NSCLC in India. Here, we report the final results from this study.

Materials and Methods

Study Design and Patients

This was a phase IV (NCT04541706), open-label, multicenter, nonrandomized, prospective, single-arm study in patients with unresectable advanced and/or recurrent *ALK*-positive NSCLC who had previously received at least one ALK TKI. The study was conducted over approximately 1 year and 11 months, from August 2020 through July 2022. The patients were adults (aged $\geq$18 years) with evidence of histologically or cytologically confirmed diagnosis of unresectable advanced and/or recurrent NSCLC that carries an *ALK* rearrangement and disease progression or intolerance of one previous treatment with ALK TKI; prior chemotherapy for advanced and/or recurrent disease was allowed. Asymptomatic CNS metastases were permitted. Additionally, all patients were required to have a baseline Eastern Cooperative Oncology Group performance status of 0, 1, or 2 and adequate hematologic, renal, liver, and pancreatic function. Patients were excluded if they had radiation therapy within 2 weeks of study enrollment; major surgery within 4 weeks prior to enrollment; known prior or suspected severe hypersensitivity to study drug; or active and clinically significant bacterial, fungal, or viral infection.

Treatment and Study Endpoints

Lorlatinib was administered as a tablet at a dose of 100 mg once daily orally, with or without food. Treatment continued until investigator-assessed disease progression, unacceptable toxicity, or patient's refusal or loss to follow-up. The end of study was defined as 1 year after the last patient's first visit date. Dose interruptions and reductions were allowed to manage toxicities per investigator discretion. Visits were scheduled to occur on day 1 of a 28-day cycle and at the end of the study. Follow-up visits were scheduled to take place at 28 to 35 days post treatment.

All patients underwent baseline tumor imaging, including computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, and pelvis and MRI scans of the brain. CT and MRI scans were done every 12 weeks until the end of treatment. For all tumor assessments, the method of assessment used at screening was the same as the one used throughout the study. Tumor assessments were repeated at the end of treatment if more than 6 weeks had passed since the last evaluation. Moreover, radiological tumor assessments were conducted whenever disease progression was suspected.

Safety assessments were performed in all patients at baseline and at every subsequent visit. Adverse events (AEs) were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 and were assessed from the beginning of treatment until $\geq$28 to $\leq$35 days post treatment. The primary endpoint was the incidence of treatment-related adverse events (TRAEs).

Secondary endpoints were ORR, intracranial ORR, DOR, and intracranial DOR, as assessed by the investigator using the Response Evaluation Criteria in Solid Tumors version 1.1.

The study was conducted in accordance with legal and regulatory requirements and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), the Declaration of Helsinki (World Medical Association 1996 and 2008), and Schedule Y, Drug and Cosmetics Act of 1940 and Rules of 1945.

Statistical Analysis

Analyses of activity and safety in this study were based on the safety analysis set, which includes all patients who received at least one dose of lorlatinib. Patients with CNS metastases at baseline measurable by the investigator were included in the intracranial activity analyses. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients who experienced TRAEs of any grade, grade 3, and grade 4 were summarized. The 95% CIs for ORR and DOR were estimated using the Wilson score method and Brookmeyer and Crowley method, respectively. Due to the small number of patients with progressive disease after a complete or partial response, there was a high number of censored observations, precluding the use of the Kaplan–Meier method. Consequently, the DOR data were summarized using number (%) of patients with events, with data provided for the $\geq$6 months DOR category.

Ethical Approval

The study was conducted in accordance with legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 and 2008) and Schedule Y, Drug and Cosmetics Act 1940 and Rules 1945.

Results

A total of 111 patients were screened across 11 sites in India. Of them, 10 patients failed the screening, and 1 did not receive lorlatinib. Overall, 100 patients were enrolled and treated with lorlatinib. At the data cutoff of August 19, 2022, 45 (45%) patients discontinued the study, mostly due to disease progression (33%), and 55 (55%) patients completed the study. The median age was 49 years, 60% were males, 81% had measurable disease at baseline, 92% had adequate baseline assessment, 56% had baseline brain metastases, 54% had a primary diagnosis of adenocarcinoma, and 88% had stage IV disease (►**Supplementary Table S1**, available in the online version only). Overall, 57% of patients received one prior anticancer therapy, and 43% received more than one anticancer therapy. Most patients (95%) were treated for advanced/metastatic disease, 4% received adjuvant therapy, and 1% received neoadjuvant therapy. One patient had been previously treated for locoregional disease or recurrence prior to receiving treatment for advanced/metastatic disease. All patients received prior ALK TKI regimens, except 1 patient who received gefitinib as prior cancer therapy.

The median duration of treatment was 60 weeks (range, 0.7–89.1 weeks), and the median relative dose intensity was 100% (range, 65.5–109.3%). All-causality AEs of any grade occurred in 94%, and grade 3 or 4 AEs occurred in 45% of patients (►**Supplementary Table S2**, available in the online version only). Any-grade TRAEs occurred in 89% of patients, and grade 3 or 4 TRAEs occurred in 41% of patients; no grade 5 TRAEs were reported (►**Table 1**). The most frequently reported TRAEs, occurring in $\geq$20% of patients, were hypertriglyceridemia (57%), hypercholesterolemia (57%), weight increase (38%), peripheral edema (28%), anemia (21%), and hyperlipidemia (20%). TRAEs led to dose interruptions in 15 (15%) patients, dose reductions in 6 (6%) patients, and permanent discontinuation in 1 (1%) patient. The patient who permanently discontinued from the study died due to acute respiratory distress, which was not considered to be related to treatment.

The ORR by the investigator was 41% (95% CI: 31.9–50.8%) with lorlatinib treatment. Seven patients (7%) achieved a complete response, 34 (34%) achieved a partial response, and 6 (6%) had progressive disease (►**Table 2**). The patient who received gefitinib had stable disease as their best overall response. The median DOR was NR (95% CI: NR–NR), and 33 of 41 responders (80%) had a response that lasted for $\geq$6 months. In patients with baseline brain metastases, the intracranial ORR by investigator assessment was 36% (95% CI: 24.5–48.8%). Four (7%) patients achieved a complete response, 16 (29%) patients achieved a partial response, and 1 (2%) patient had progressive disease. The median intracranial DOR was NR (95% CI: 11.1–NR), and 18 of 20 (90%) patients had a response that lasted for $\geq$6 months.

Discussion

In this postapproval phase IV study in India, lorlatinib showed a tolerable safety profile and clinically relevant activity in patients with unresectable advanced and/or recurrent *ALK*-positive NSCLC who had previously received at least one ALK TKI. The safety profile of lorlatinib in the present study was consistent with that reported in the phase I/II clinical trial,[1] with no new safety signals reported. Lorlatinib was generally safe and tolerable, as shown by the low frequency of TRAEs leading to dose interruptions, reductions, or permanent discontinuations. There were no treatment-related deaths. Similar to other studies with lorlatinib, hypercholesterolemia and hypertriglyceridemia were the most common AEs associated with lorlatinib.[1,7] These AEs can be easily managed with appropriate dose interruptions or modifications and lipid-lowering therapy with statins.[1,7,8]

Table 1 TRAEs recorded in ≥5% of patients by the MedDRA system organ class and preferred term

	Any grade	Grade 3	Grade 4
Any TRAE, *n* (%)	89 (89)	35 (35)	6 (6)
Hypercholesterolemia	57 (57)	3 (3)	2 (2)
Hypertriglyceridemia	57 (57)	8 (8)	3 (3)
Weight increased	38 (38)	11 (11)	0
Edema peripheral	28 (28)	0	0
Anemia	21 (21)	8 (8)	0
Hyperlipidemia	20 (20)	3 (3)	0
Hyperglycemia	16 (16)	2 (2)	0
Edema	7 (7)	0	0
Cognitive disorder	6 (6)	2 (2)	0
Dyslipidemia	6 (6)	0	0
Hypomagnesemia	6 (6)	0	0
Arthralgia	5 (5)	1 (1)	0
Hyperamylasemia	5 (5)	0	0
Hyperkalemia	5 (5)	1 (1)	0
Hypoalbuminemia	5 (5)	0	0
Peripheral swelling	5 (5)	0	0

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TRAE, treatment-related adverse event.

Table 2 Objective response rate and duration of response in patients treated with lorlatinib

	All patients ($N = 100$)	Patients with baseline brain metastases ($n = 56$)
Best overall response, *n* (%)		
CR	7 (7)	4 (7)
PR	34 (34)	16 (29)
Stable disease	24 (24)	19 (34)
Non-CR/non-PD	11 (11)	8 (14)
PD	6 (6)	1 (2)
Not evaluable	18 (18)	8 (14)
Objective response rate, % (95% CI)	41 (31.9–50.8)	36 (24.5–48.8)
Median duration of response (95% CI), mo	NR (NR–NR)	NR (11.1–NR)
Duration of response ≥6 mo, *n*/*N* (%)	33/41 (80)	18/20 (90)

Abbreviations: CI, confidence interval; CR, complete response; NR, not reached; PD, progressive disease; PR, partial response.

Lorlatinib showed a clinically meaningful improvement in ORR (41%). A similar ORR (47%) was reported in the phase I/II study of patients with advanced *ALK*-positive NSCLC who were previously treated with at least one ALK TKI therapy.[1] These ORRs are slightly higher than those reported for platinum/pemetrexed chemotherapy (29.7%) in patients with advanced *ALK*-positive NSCLC refractory to second-generation ALK TKIs.[9] Although this study did not compare lorlatinib with chemotherapy, these findings are clinically relevant given that lorlatinib or platinum/pemetrexed-based chemotherapy is a standard treatment option after failure of second-generation ALK TKI therapy in patients with *ALK*-positive NSCLC.[9]

Brain metastases are frequent in patients with *ALK*-positive NSCLC and are associated with a poor prognosis.[1] In this study, baseline brain metastases were present in over half (56%) of the patients. This was similar to the phase I/II study, in which 67% of patients who had received at least one previous ALK TKI therapy had baseline brain metastases.[1] Lorlatinib exhibited considerable intracranial activity, consistent with its ability to cross the blood–brain barrier shown in preclinical models.[4] The intracranial ORR was 36% in this study compared with 63% in the original phase I/II trial.[1] Although the intracranial ORR was lower in the current study, lorlatinib still showed considerable antitumor activity in patients with baseline brain metastases. Moreover,

complete responses were reported in 7% of all patients and in 7% of patients with baseline brain metastases, demonstrating substantial systemic and intracranial antitumor activity with lorlatinib.

A limitation of this study was that it was a single-arm study without randomization to standard treatment. One patient did not receive ALK TKI as their prior therapy but was included in the study; the lack of prior ALK TKI treatment may have affected the efficacy of lorlatinib. In addition, the results provided are descriptive and exploratory in nature. Nevertheless, the results presented in this study support the use of lorlatinib in this patient cohort in India.

Conclusion

In summary, the results of this study indicate that lorlatinib has meaningful antitumor activity and an acceptable safety profile in patients with *ALK*-positive unresectable advanced NSCLC. Lorlatinib also showed intracranial activity in patients with baseline brain metastases. Based on the robust antitumor activity and safety profile of lorlatinib, the results obtained in this study support the use of lorlatinib in patients with resistance to or intolerance of prior ALK TKI therapy for advanced or metastatic *ALK*-positive NSCLC in India.

Data Availability Statement

Upon request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Authors' Contributions

U.B., V.G.G., N.R., T.P., H.P., N.G., A.P., C.D., S.B., M.J., and B.B. collected the data. C.R.R., Sh.P., S.P., F.T., and H.T. contributed to the study concept and design and analyzed the data. C.R.R. performed the statistical analysis. All the authors contributed to the interpretation of the data and to the development and approval of the manuscript. This manuscript has been read and approved by all the authors, the requirements for authorship have been met, and each author states that the manuscript represents honest work. This manuscript, including related data and tables, has not been published previously and is not under consideration elsewhere.

Patient's Consent

Written informed consent was obtained from all the patients.

Funding

The study was sponsored by Pfizer.

Conflict of Interest

V.G.G. has received honoraria/speaker fees from Pfizer. C. D. reports consulting fees/honoraria from Pfizer, Merck-Serono, Roche, and Novartis and has participated on Data Safety Monitoring/Advisory Boards for CBCC Global and Zydus. C.R.R., Sh.P., S.P., F.T., and H.T. are employees and own stocks at Pfizer. B.B. reports research grants from Pfizer, Novartis, AstraZeneca, Roche, IQVIA, and Johnson & Johnson. The remaining authors declare that they have no known competing interest.

Acknowledgments

The authors would like to thank the participating patients and their families, investigators, subinvestigators, research nurses, study coordinators, and operations staff. Editorial and medical writing support was provided by Manqoba Zungu, PhD, of Nucleus Global and was funded by Pfizer.

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