Article published online: 2022-09-02

Lung Cancer

Long-Term Outcomes of Crizotinib Treated ALK-Positive Lung Cancer Patients: A Retrospective Audit of Prospective Data from Resource-Constrained Settings

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South Asian J Cancer 2023;12(2):179–184.

Abstract

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Purpose Crizotinib has been one of the standard treatment options for the treatment of anaplastic lymphoma kinase (ALK) rearranged non-small cell lung cancer (NSCLC) based on higher progression-free survival (PFS) and objective response rates in phase III clinical trials. However, real-world data about the long-term efficacy and toxicity of crizotinib is limited.

Methods A retrospective analysis of all patients with ALK-positive NSCLC, treated with crizotinib between March 2014 and December 2016, was performed. The main outcomes measured were PFS, overall survival (OS), and adverse effects.

Results One hundred and eighty-eight patients treated with crizotinib during this period were included in this study. The median age was 50 years (range: 24–74) with a majority being males (73.2%) and 80.3% with a performance status of 0 to 1. The median duration of follow-up was 49.4 months (range: 3.4–86.3%). The median PFS of crizotinib was 17.3 months (95% confidence interval [CI], 13.0–21.6) and 12.8 months (95% CI, 8.1–17.6) when used in first line or subsequent lines, respectively. The median OS was 38.3 months (95% CI, 28.4–48.2). The patients who received crizotinib in the first line had a median OS of 45.5 months (95% CI, 29.6–61.4) as compared with 29.7 months (95% CI, 22.2–37.2) for those who received in subsequent line (hazard ratio, 0.6, 95% CI, 0.4–0.9, $p = 0.022$). The most

Keywords
- crizotinib
- ALK-positive
- lung cancer
- long-term outcomes

DOI https://doi.org/10.1055/s-0042-1753478 ISSN 2278-330X

How to cite this article: Kapoor A, Noronha V, Patil V, et al. Long-Term Outcomes of Crizotinib Treated ALK-Positive Lung Cancer Patients: A Retrospective Audit of Prospective Data from Resource-Constrained Settings. South Asian J Cancer 2023;12(2):179–184.

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

common all grade toxicities include transaminitis, anemia, fatigue, and corrected QT prolongation.

Conclusion This real-world study confirms the long-term beneficial effects of crizotinib in ALK rearranged NSCLC with favorable toxicity profile like that of the registration studies, in resource constrained settings.

Introduction

The use of anaplastic lymphoma kinase (ALK) inhibitors in ALK-positive non-small cell lung cancer (NSCLC) patients is one of the poster boys for personalized treatment in cancer.[1] In resource-constrained settings, crizotinib and ceritinib, which are first- and second-generation ALK inhibitors, respectively, remain the first choice because of cost and various available support programs for these drugs. It should be noted that even these drugs are not available to all the patients representing a significant limitation and disparity in cancer care in low-middle income countries (LMICs) and developed countries.[1] The safety and efficacy of crizotinib have been established in randomized controlled trials (RCTs).[2,3] However, the real-world data on long-term outcomes and safety outside clinical trials is sparingly available. Such data are important to understand the benefits of ALK inhibitors when the cost of the testing and treatment limits their widespread use.

Patients and Methods

This study is a retrospective audit of a prospectively collected database at the Department of Medical Oncology, Tata

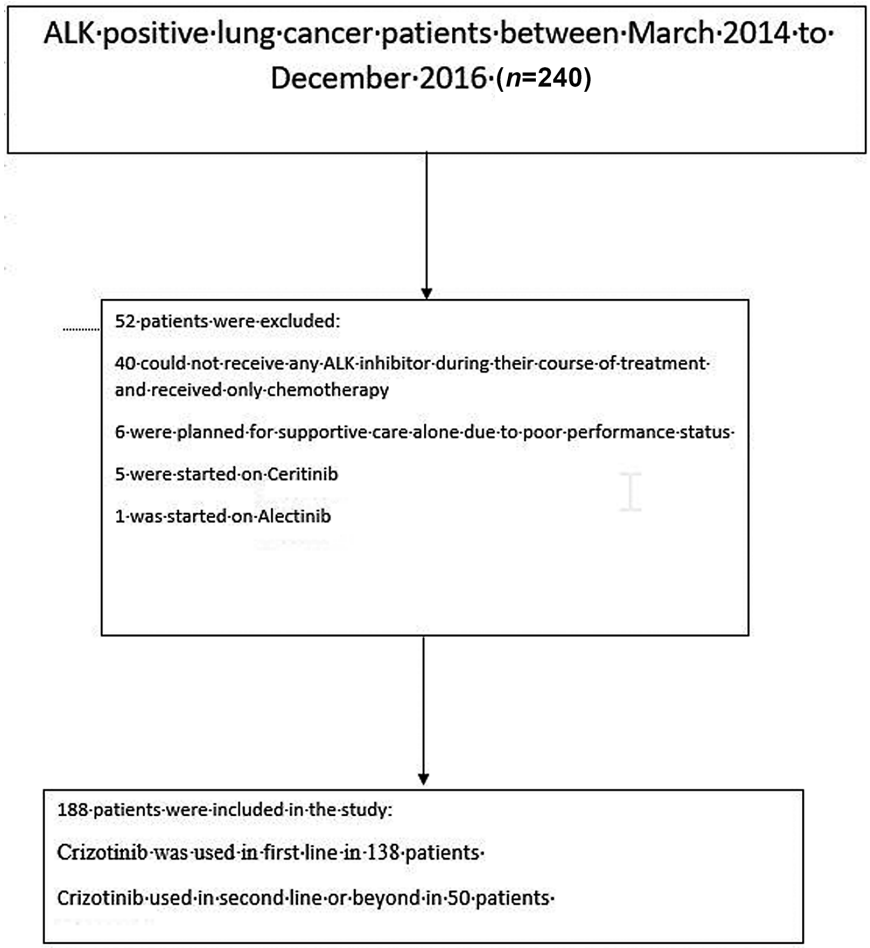


Fig. 1 Flow diagram of the study. ALK, anaplastic lymphoma kinase.

Memorial Hospital, Mumbai, India. Consecutive ALK-positive NSCLC patients who were started on crizotinib from March 2014 till December 2016 were included in this study. The prospective database is a part of institutional lung audit in which the patients provide written informed consent for the capture of prospective data. The study was conducted according to ethical guidelines established by the Declaration of Helsinki and other guidelines like Good Clinical Practice Guidelines and those established by the Indian Council of Medical Research.

Immunohistochemistry (IHC) or break-apart fluorescence in situ hybridization (FISH) was used to identify ALK fusion. The monoclonal antibody D5F3 (Ventana Medical Systems, Tucson, Arizona, United States) was used for IHC for ALK, while the FISH analysis was performed with the "Abbot Molecular" platform. One-hundred nuclei were scored to determine the final percentage of ALK positivity. A cutoff of 15% was used to denote samples as positive or negative for ALK.

Patients underwent a complete history and physical examination and routine blood testing (complete hemogram, renal and liver function test) prior to therapy. Demographic data, including smoking status and tobacco use, were collected. Tumor staging was performed by a contrast-enhanced computed tomography of the chest and upper abdomen (CECT) or whole body fluorodeoxyglucose-positron emission tomography-contrast-enhanced computed tomography . Electrocardiograms were performed for monitoring QTc (corrected QT interval using Bazett's formula) for patients receiving crizotinib at 8 to 12 weeks interval or as and when required. Dose reductions were performed as per the standard recommendations. Radiological response assessment was performed every 8 to 12 weeks or at symptomatic progression using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria. The treatment was modified at disease progression or intolerable side effects. The adverse events were evaluated using the Common Terminology Criteria for Adverse Events version 4.02 (CTCAE v 4.02). At progression, further therapy was considered based on standard recommendations.

Progression-free survival (PFS) was measured as the duration in months between the date of start of crizotinib till the date of progression, or death without progressive disease or change in treatment. Overall survival (OS) was computed in months from the date of diagnosis of advanced-stage disease until death. Kaplan–Meier method was used to calculate PFS and OS, while Cox proportional hazard model was used for calculating hazard ratio (HR). All statistical calculations were performed using SPSS version 20 (Armonk, New York, United States).

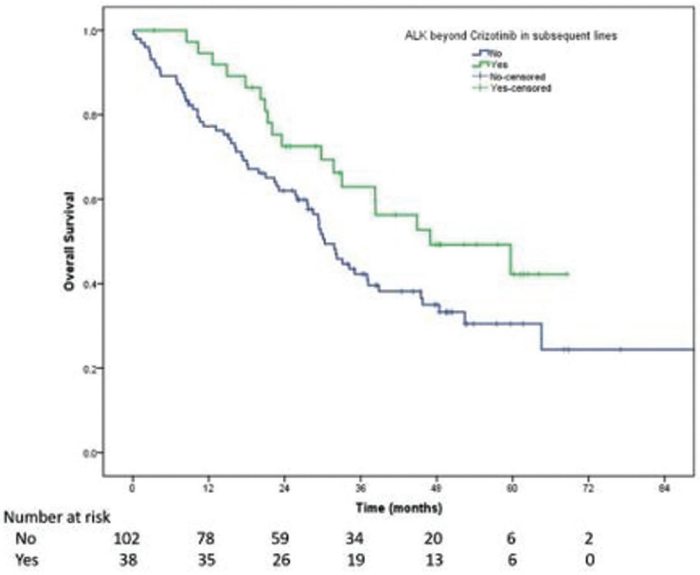
Table 1 Baseline characteristics of the patients

Characteristics	Number (percentage)
Age	Median: 50 years
	Range: 24–74 years
Gender	
Male	120 (63.8)
Female	68 (36.2)
Histology	
Adenocarcinoma	180 (95.7)
Adenosquamous	8 (4.3)
ECOG PS	
0–1	151 (80.3)
2–4	37 (19.7)
Smoking	
Ever smoker	28 (14.8)
Never smoker	160 (85.2)
Stage	
III	15 (7.9)
IV	173 (92.1)
Comorbidities	
None	103 (54.8)
Hypertension	32 (17.0)
Diabetes mellitus	29 (15.4)
COPD or emphysema	6 (3.2)
Prior tuberculosis	6 (3.2)
Others	11 (5.8)
Multiple comorbidities (>1)	10 (5.3)
Location of disease	
Intrathoracic only	132 (70.2)
Extrathoracic metastasis	81 (43.0)
Both intra and extrathoracic metastases	46 (24.4)
Site of metastasis	
Contralateral lung	64 (34.0)
Pleural effusion	89 (47.3)
Bone	54 (28.7)
Liver	28 (14.8)
Brain	28 (14.8)
Others	5 (2.6)

Abbreviations: COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; PS, performance score.

Results

A total of 188 patients of ALK-positive NSCLC received crizotinib between March 2014 and December 2016. ►Fig. 1 shows the flow diagram of the study. The median follow-up duration was 49.4 months (range: 3.4–86.3). The baseline characteristics of the patients is depicted in ►Table 1. The median age was 50 years (range: 24–74) with 38 (20.2%) having age more than 60 years; 68 (36.2%) were females, 37 (19.7%) had Eastern Cooperative Oncology Group performance status of 2 to 4, while rest ($n = 151$, 80.3%) had PS of 0 to 1. The histology was adenocarcinoma in 180 (95.7%), while it was adenosquamous in the rest; 85 (45.2%) had comorbidities, hypertension being the most



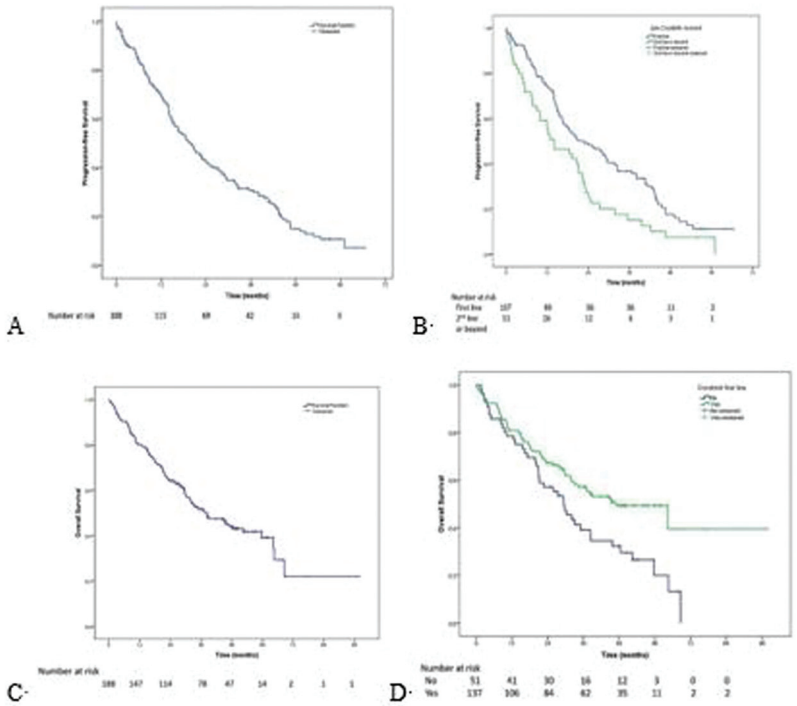
Next-generation ALK inhibitors post Crizotinib	*n* (%)	OS in months (95% CI)	HR (95 % CI)	*p*-value
No	102 (72.8)	30.3 (26.7-33.9)	Reference	-
Yes	38 (27.2)	46.9 (20.7-73.3)	1.6 (1.0-2.8)	0.054

Fig. 2 Kaplan–Meier curve of overall survival of patients who could receive next-generation anaplastic lymphoma kinase inhibitors who progressed on crizotinib versus those who could not. CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

common in 32 (17%) followed by diabetes in 29 (15.4%) of the patients. Extrathoracic metastases were present in 81 (43.1%) of the patients at baseline with bone, liver, and brain metastasis in 54 (28.7%), 28 (14.9%), and 21 (11.2%) patients, respectively. The method for ALK detection was IHC in 133 (70.7%), FISH in 39 (20.7%), and both in 16 (8.5%) patients.

Crizotinib was used in first-line in 138 (73.4%) of the patients; it was used in second and third in 33 (17.6%) and 11 (5.8%) of the patients, respectively, while in fourth and fifth line in three (1.6%) patients each. Out of 188 patients on crizotinib, 125 (66.5%) had progressed; the most common site of progression was brain in 57 (45.6%), followed by loco-regional in 47 (37.6%) of the patients. The median PFS on crizotinib was 16.4 months (95% CI, 12.7–20.1); it was significantly higher when used in first-line 17.3 months (95% CI, 13.0–21.6) as against 12.8 months (95% CI, 8.1–17.6) when used in second-line or beyond (HR, 1.51 95% CI, 1.07–2.12, $p = 0.018$, ►Fig. 2A, B). The median OS was 38.3 months (95% CI, 28.4–48.2), with 5 years survival being 40% (►Fig. 2C). The patients who received crizotinib in the first line had a median OS of 45.5 months (95% CI, 29.6–61.4) as compared with 29.7 months (95% CI, 22.2–37.2) for those who received in subsequent line (HR, 0.6, 95% CI, 0.4–0.9, $p = 0.022$, ►Fig. 2D). Out of 188 patients, 125 (66.5%) had progression on crizotinib and 38 of these patients could receive next-generation ALK inhibitors. These included 24 (63.1%) patients receiving ceritinib, 7 (18.4%) lorlatinib, 6 (15.8%) alectinib, and 2 (5.2%) received ceritinib followed by lorlatinib. The median OS for patients who could receive next-generation ALK inhibitors was 46.9 months (95% CI, 20.7–73.3) as against 30.3 months (95% CI, 26.7–33.9) for those who could not (HR, 1.6, 95% CI, 1.0–2.8, $p = 0.054$, ►Fig. 3).

The most common grade 1/2 toxicity on crizotinib was transaminitis in 101 (53.7%) of the patients, while grade 3/4 transaminitis occurred in 9 (4.8%). Other common grade 1/2 toxicities included anemia in 80 (42.5%), fatigue in 64 (34%), raised creatinine in 29 (15.4%), QTc prolongation in 41 (21.8%), and visual disturbance in 23 (12.2%) of the patients. Grade 3 QTc prolongation occurred in eight (4.2%), while nine (4.8%) patients had renal cyst formation while on crizotinib. Permanent discontinuation of crizotinib because of uncontrolled toxicities was required in 5 (2.7%) of the patients, while in two (1.1%) patients, financial issues precluded the continued use of crizotinib.



Crizotinib used in first line	n (%)	PFS in months (95% CI)	HR (95 % CI)	p-value
Yes	137 (72.8)	22.7 (14.4-31.1)	Reference	
No	51 (27.1)	14.1 (6.8-21.3)	1.7 (1.2-2.4)	0.005

Crizotinib used in first line	n (%)	OS in months (95% CI)	HR (95 % CI)	p-value
Yes	137 (72.8)	45.5 (29.6-61.4)	0.6 (0.4-0.9)	
No	51 (27.1)	29.7 (22.2-37.2)	Reference	0.022

Fig. 3 (**A**) Progression-free survival (PFS) of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer patients treated with crizotinib. (**B**) PFS of patients treated with crizotinib in first-line versus second-line or beyond. (**C**) Overall survival (OS) of patients treated with crizotinib. (**D**) OS of patients treated with crizotinib in first-line versus second-line or beyond. CI, confidence interval; HR, hazard ratio.

Discussion

RCTs of crizotinib have showed significant benefit in PFS and OS. However, the real-world data of efficacy and toxicity of crizotinib is limited, especially from India.[4] A combined analysis of Asian population in the two randomized trials PROFILE 1007 and PROFILE 1014 showed that the PFS and OS was maintained with comparable incidence of toxicities among Asian and non-Asian population.[5]

To the best of our knowledge, this is the largest single-center data from India that highlights the long-term survival outcomes of the patients treated with Crizotinib for ALK-positive lung cancer. Also, in our study, the benefit was more in first line than when given in subsequent lines. The outcomes are encouraging and closely resemble that of PROFILE 1014 that reported 4-year survival probability of 56.6%.[3] In our study, the PFS was nearly double of that reported in the pivotal randomized trials, this might be due to comparatively better tolerance of crizotinib in Indian patients that leads to continuation of treatment in a larger proportion of the patients. Also, the frequency of response assessment in real-world is usually different from that of RCTs; for example, in our study, most of the patients underwent scan at 12-week interval as against 8 weeks in RCTs. Another real-world data from China has reported higher PFS as compared with RCTs.[4]

They postulated that this could be implicated to the higher proportional discontinuance of crizotinib treatment in response to the adverse effects in the RCTs. A multicenter study from India of 250 patients showed a median PFS and OS of 11.3 and 24.7 months, respectively, for all patients treated with crizotinib irrespective of the line of treatment with a low incidence of grade 3 or 4 toxicities.[6] On comparison, the possible reasons for the higher PFS and OS in our study could be due to higher percentage of patients receiving first-line crizotinib (73.4 vs. 64.8%) and lower prevalence of baseline brain metastasis (11.2 vs. 34.8%). A study by Del Valle et al on real-world experience from Singapore reported a median PFS of 15 months that was similar to our study, while the median OS was not reached.[7] In another real-world study from North America, a median PFS of 9.5 months and median OS of 23.4 months were reported, which are more similar to the PROFILE studies.[8]

In our study, only 27% of the patients treated with crizotinib could receive second- or third-generation ALK inhibitors. This reflects the real-world scenario where the cost constraints have significant bearing on the selection of drugs. The limitations of our study include its retrospective design, and data from a single center that is expected to have its inherent bias.

Conclusion

Our study reveals that crizotinib is well tolerated in Indian patients and the toxicity profile matches with that of the randomized trials except for a higher incidence of all grade transaminitis. However, the rate of grade 3 or 4 elevation in transaminases was lower. Large real-world data are an essential supplement to the randomized studies and our study confirms the long-term survival outcomes in ALK-positive lung cancer patients treated with crizotinib.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

None.

Conflict of Interests

V.N. reports research grants from Dr. Reddy's Laboratories Inc, Amgen, Sanofi India Ltd., Intas Pharmaceuticals and Astra Zeneca Pharma India Ltd., outside the submitted work. K.P. reports grants from Biocon Ltd, grants from Dr. Reddy's Laboratories Inc, grants from Fresenius Kabi India Pvt Ltd, grants from Alkem Laboratories, grants from Natco Pharma Ltd, grants from BDR Pharmaceuticals Intl Pvt Ltd, grants from Roche Holding AG, outside the submitted work. All grants were paid to the institution. None of the other authors have anything to declare that may be considered as potential competing interest.

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