ORIGINAL ARTICLE

Clinical Profile, Practice Pattern, and Outcomes With First-Line Therapy in ALK-Positive Lung Cancer: Real-World Data From Resource-Constrained Settings

Akhil Kapoor, MD, DM,[a] Vanita Noronha, MD, DM,[b] Vijay Patil, MD, DM,[b] Nandini Menon, MD, DNB,[b] Amit Joshi, MD, DM,[b] Amit Kumar, MD, DM,[c] Ajay Kumar Singh, MD, DM,[b] Abhishek Mahajan, MD,[d] Amit Janu, MD,[d] Rajiv Kumar, MD,[e] Trupti Pai, MD,[e] Anuradha Chougule, MD,[f] Omshree Shetty, MD,[f] Kumar Prabhash, MD, DM, ECMO[b,*]

[a]*Department of Medical Oncology, Mahamana Pandit Madan Mohan Malviya Cancer Center and Homi Bhabha Cancer Hospital (A Unit of Tata Memorial Centre, Mumbai), Varanasi, India*
[b]*Department of Medical Oncology, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, India*
[c]*Department of Medical Oncology, Homi Bhabha Cancer Hospital (A Unit of Tata Memorial Centre, Mumbai), Muzaffarpur, India*
[d]*Department of Radiology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, India*
[e]*Department of Pathology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, India*
[f]*Department of Molecular Pathology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, India*

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ABSTRACT

Introduction: ALK inhibitors are one of the success stories in precision medicine for treating patients with advanced ALK-positive NSCLC. Nevertheless, developing countries have substantial constraints in using ALK inhibitors, with limited data from India.

Methods: An audit of a prospectively collected database of patients with advanced ALK-positive NSCLC treated from January 2013 to March 2018 was conducted. The SPSS version 20.0 was used for statistical analysis.

Results: A total of 441 patients were available for analysis; 62.5% were males, median age was 50 (range: 19–75) years, and 78.3% had Eastern Cooperative Oncology Group performance status of 0 to 1. When all the lines of therapies were included in the analysis, ALK inhibitors could be used in 379 (85.9%) of the total ALK-positive patients and 292 patients (66.2%) received ALK inhibitors in the first line in any strategy. The major reason for not starting ALK inhibitors upfront was financial constraints in 69% of the patients. The median progression-free survival on first-line therapy for the entire cohort was 14.1 months (95% confidence interval [CI]: 12.2–15.9), with a significant difference between patients receiving ALK inhibitor in first line in any strategy versus not in first line (17.2 mo [95% CI: 14.5–19.9] versus 5.9 mo [95% CI: 4.2–7.6], $p < 0.001$). The median overall survival was 30.7 months (95% CI: 27.3–34.2), with 37.6 months (95% CI: 28.1–47.1) for ALK inhibitor in the first line versus 20.5 months (95% CI: 15.8–25.1) for subsequent lines of therapy ($p < 0.001$).

Conclusions: Most of our patients with ALK-positive NSCLC were exposed to ALK inhibitors through various support mechanisms. Those patients who could receive ALK inhibitors in the first line had a significant survival advantage as compared with others.

*Corresponding author.

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Address for correspondence: Kumar Prabhash, MD, DM, ECMO, Department of Medical Oncology, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute, Ernst Borges Road, Parel, Mumbai 400012, India. E-mail: kumarprabhashtmh@gmail.com

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Introduction

There have been significant advances in the personalized treatment of NSCLC with ALK-directed therapy representing the success story in this field.[1] Access to treatment is a challenge to this effective treatment especially in developing countries such as India.[2] Though alectinib and lorlatinib were found to have improvement in outcome, the utilization of these drugs remains limited in low-middle income countries (LMICs) primarily due to financial constraints.[3] In resource-constrained settings, crizotinib and ceritinib, which are first- and second-generation ALK inhibitors, respectively, are provided to patients utilizing various available support programs for these drugs.[4] 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 LMICs and developed countries.[5] Though large phase 3 randomized trials are available for ALK inhibitors, the real-world data on the use of these drugs are limited especially from the LMICS. Such data are important to understand the benefits of ALK inhibitors when the cost of testing and treatment limits their widespread use. Thus, we conducted an audit of our lung cancer database to find out the treatment patterns of ALK-positive NSCLC highlighting the access to treatment and impact on outcomes of ALK-directed therapy.

Materials and Methods

Study Design and Testing Algorithm

This study is a retrospective audit of a prospectively collected database at the Department of Medical Oncology, Tata Memorial Hospital, Mumbai, India. The details of the patients were obtained from the prospective lung cancer audit database, wherein patients sign a written informed consent before their information is recorded as a part of the lung cancer audit. The lung cancer audit is an Institutional Ethics Committee–approved observational protocol and is registered with the Clinical Trials Registry India (registration number: CTRI/2013/01/003335). Other relevant clinical details were obtained from hospital electronic medical records. The study was conducted according to ethical guidelines established by the Declaration of Helsinki and other guidelines such as the Good Clinical Practice Guidelines and those established by the Indian Council of Medical Research.

Patients with ALK-positive advanced NSCLC planned for palliative therapy from June 2012 to March 2018 were included in this analysis. The ALK fusion was reported as positive by either immunohistochemistry (IHC) or break-apart fluorescence in situ hybridization (FISH). The IHC for ALK was performed with the monoclonal antibody D5F3 (Ventana Medical Systems, Tucson, AZ). The FISH analysis was performed with the "Abbot Molecular" platform, according to manufacturer's instructions. A total of 100 nuclei were scored to determine the final percentage of ALK positivity. The cells were recorded as ALK positive when their nuclei contain rearranged or "broken-apart" signals (individual green and orange signal), 2 or more signal diameters apart. A cutoff of 15% was used to denote samples as positive or negative for ALK. On the basis of the departmental policy, both IHC and FISH were used for patients diagnosed until 2016; afterward, the policy was changed to do IHC first and perform FISH only in equivocal cases with IHC. The analysis of details of the patients having discordant results with IHC and FISH has been published separately from our institute.[6] Because accessibility to next-generation sequencing was low during the study period, the analysis of variants of ALK fusion and of resistance pathways at progression was not considered for the study. During the study duration, no clinical trial for ALK-positive lung cancer was available at our institute.

Evaluation

Patients underwent a complete history and physical examination and routine blood testing (complete hemogram, renal and liver function test) before 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 or whole-body fluorodeoxyglucose positron emission tomography–computed tomography. Patients were started on therapy based on age, comorbidities, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and disease burden requiring emergent therapy initiation. Patients were started on either of the following treatments upfront:

1. Chemotherapy
2. Crizotinib 250 mg orally twice daily, or alectinib 600 mg twice daily, or ceritinib 450 mg once daily
3. Other treatments in view of poor ECOG PS (i.e., >2)
4. Best supportive care

As per the institutional protocol, patients who were symptomatic for brain metastasis at presentation received whole brain radiotherapy (WBRT) followed by systemic therapy. If patients were not symptomatic but

had multiple brain metastases especially those involving critical areas of the brain, they were also considered for WBRT. At the same time, if patients had even single brain metastasis but could not be started on ALK-directed therapy, they were also considered for WBRT.

Patients underwent routine blood investigations, including a complete hemogram and biochemistry before each cycle of chemotherapy and monthly or two months if on crizotinib. In addition, electrocardiogram was performed for monitoring 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 version 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. At progression, further therapy was considered based on standard recommendations. The patients were divided into those who received crizotinib upfront, received crizotinib later, or were never exposed to crizotinib. Potential reasons for not administering crizotinib upfront were retrieved. Patients receiving crizotinib at some later point of their treatment course were evaluated for reasons of this shift in therapy. The source of financing for patients on crizotinib was also reported.

Statistical Analysis

All statistical calculations were performed using SPSS version 20 (Armonk, NY). Descriptive statistics were performed for all the baseline characteristics. Median value with interquartile range was provided for continuous variables. Progression-free survival (PFS) was calculated in months from the date of start of crizotinib to the date of progression on crizotinib or death without progressive disease or change in treatment. Patients who had not progressed at the time of last follow-up were censored. Overall survival (OS) was calculated in months from the date of diagnosis of advanced-stage disease until death. Patients who had not died at the time of the last follow-up were censored. Kaplan-Meier method was used for the time-to-event analysis. Log-rank test was used for univariate analysis of PFS and OS, whereas Cox proportional hazard model was used for multivariate analysis.

Results

Demographics

A total of 441 ALK-positive patients were included in this analysis on the basis of the predefined inclusion criteria. The median age of the patients was 50 (range: 19–75) years, with 18.4% having the age of 60 years or more; 62.4% were males; 78% had baseline ECOG PS of 0 to 1 whereas 7.3% had PS 3 to 4 (Table 1). In addition, 63 patients (14.3%) were ever smokers, and comorbidities were present in 37.9% of the patients. Figure 1 illustrates the flow diagram of the study.

Table 1. Baseline Characteristics of the Patients

Characteristics	Number (%)
Age	Median: 50 y
	Range: 19-75 y
Gender	
Male	275 (62.4)
Female	166 (37.6)
Histology	
Adenocarcinoma	430 (97.5)
Adenosquamous	6 (1.4)
Squamous	3 (0.7)
Others	2 (0.4)
ECOG PS	
0-1	344 (78.1)
2	64 (14.6)
3-4	32 (7.3)
Smoking	
Ever smoker	63 (14.3)
Never smoker	378 (85.7)
Stage	
III	43 (9.8)
IV	398 (90.2)
Comorbidities	
None	274 (62.1)
Hypertension	80 (18.1)
Diabetes mellitus	65 (14.7)
COPD or emphysema	10 (2.2)
Prior tuberculosis	8 (1.8)
Others	10 (2.2)
Multiple comorbidities (>1)	16 (3.6)
Location of disease	
Intrathoracic only	230 (52.1)
Extrathoracic metastasis	93 (21.1)
Both intrathoracic and extrathoracic metastases	118 (26.8)
Site of metastasis	
Contralateral lung	143 (32.4)
Pleural effusion	210 (47.6)
Bone	132 (29.9)
Liver	76 (17.2)
Brain	66 (14.9)
Others	10 (2.2)

COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Tumor Characteristics

ALK was detected by IHC in 75.7%, FISH in 15.7%, and by both methods in 8.6% of the patients. Metastatic disease (stage IV) was identified in 90.2% of the patients, whereas the rest had unresectable stage IIIB;

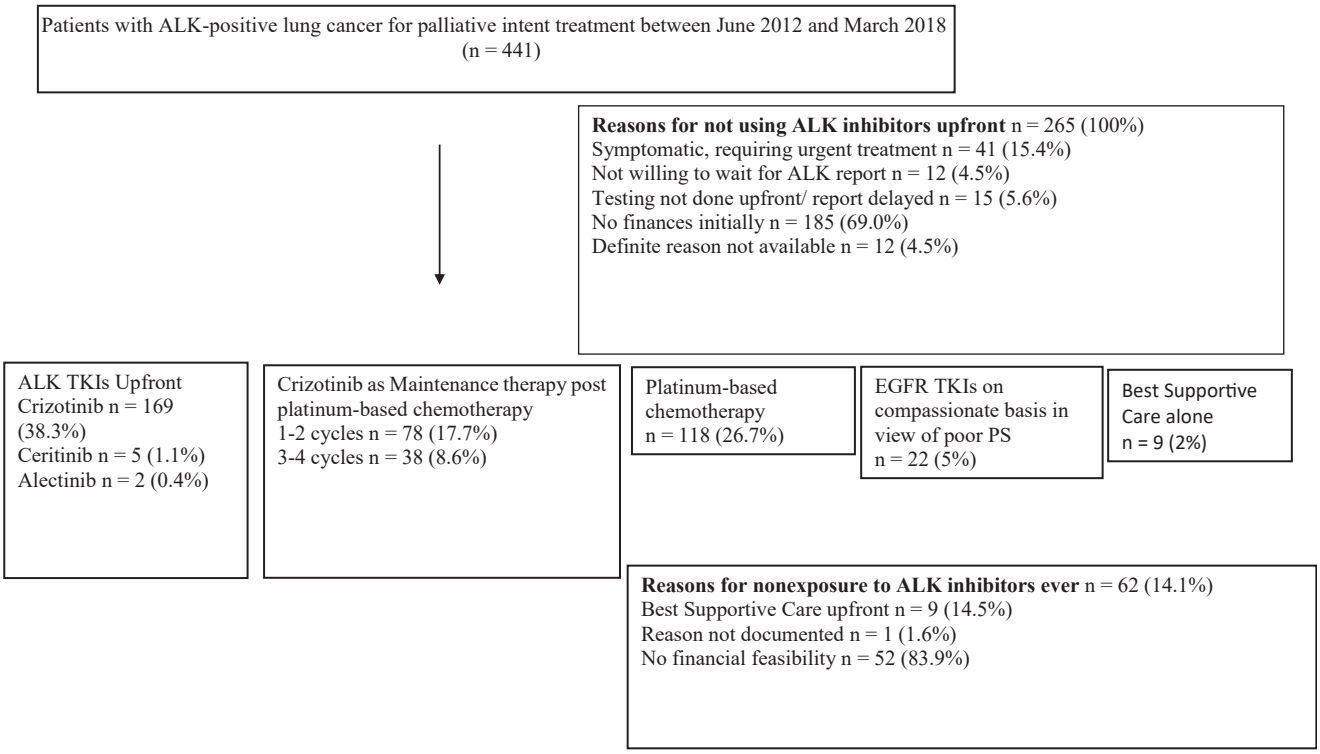

Figure 1. Flow diagram of the study. PS, performance status; TKI, tyrosine kinase inhibitor.

97.5% of the patients had adenocarcinoma subtype. The extrathoracic disease was present in 45.6% of the patients with bone metastasis in 29.9%, liver metastasis in 17.2%, and brain metastasis in 14.7% of the patients at baseline. Pleural effusion was noted in 47.6% of the patients. The median number of metastatic sites was 2 (range: 0–7).

Treatment in the First Line

Of 441 patients, 292 patients (66.2%) received ALK inhibitors in the first line in any strategy. Of these, crizotinib was received upfront by 169 patients (57.8%) as maintenance post 1 to 2 cycles of platinum-based chemotherapy in 78 patients (26.7%) and post 3 to 4 cycles in 38 patients (13.0%). A very small proportion of patients received ceritinib (n = 5) or alectinib (n = 2) in the first line. Although 118 (26.7%) received platinum-based doublet therapy, 22 (5%) were started on EGFR tyrosine kinase inhibitors (TKIs) on a compassionate basis in view of poor PS, and nine (2%) were offered supportive care alone in view of PS precluding any form of cancer-directed therapy.

Logistic Constraints With ALK Inhibitors

The ALK inhibitors could not be used upfront in 265 patients (60.1%). The reason for the same is depicted in a flow diagram (Fig. 1). The most important reason was financial constraints (69%) which led to use of other forms of treatment instead of ALK inhibitors in the upfront settings. It should be noted that of 169 patients (38.3%) who received crizotinib upfront, 127 (75.1%) received it with support from nongovernmental organizations (NGOs). When all the lines of therapies were included in the analysis, ALK inhibitors could be used in 379 (85.9%) of the total ALK-positive patients.

Outcomes of the Treatment

The median PFS on first-line therapy of the entire cohort was 14.1 months (95% confidence interval [CI]: 12.2–15.9); for patients in whom ALK inhibitor was used in any strategy in the first line, the median PFS was 17.2 months (95% CI: 14.5–19.9) whereas it was 5.9 months (95% CI: 4.2–7.6) in whom ALK inhibitor could not be used in the first line (hazard ratio = 0.41, 95% CI: 0.32–0.52, $p < 0.001$; Fig. 2).

The median OS of the entire cohort was 30.7 months (95% CI: 27.3–34.2; Supplementary Fig. 1); for patients in whom ALK inhibitor was used in any strategy in the first line, the median OS was 37.6 months (95% CI: 28.1–47.1) whereas it was 20.5 months (95% CI: 15.8–25.1) in whom ALK inhibitor could not be used in the first line (hazard ratio = 0.51, 95% CI: 0.38–0.68, $p < 0.001$; Fig. 3).

Of 169 patients who received crizotinib upfront, 116 (68.6%) had partial response, four (2.4%) had complete response, 39 (23.1%) had stable disease, whereas five

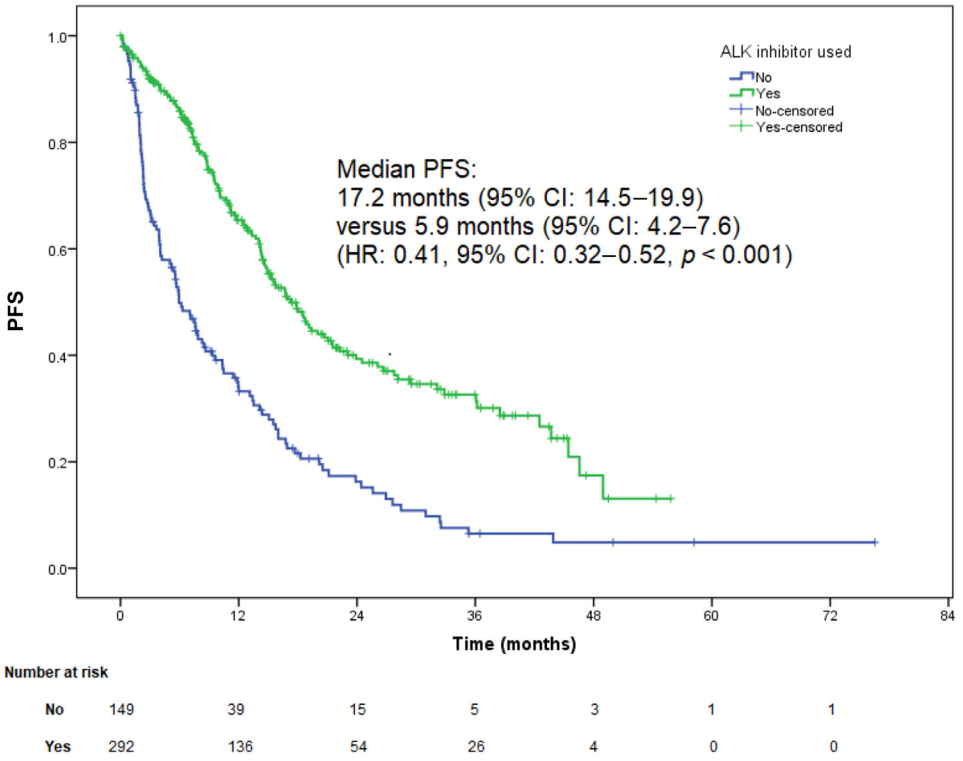

Figure 2. PFS for first-line therapy as per ALK inhibitor use. CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

(2.9%) had progressive disease as the best response. Response Evaluation Criteria in Solid Tumors scoring was not available in five patients (2.9%). On performing the univariate analysis for PFS in the first line (Table 2), ALK inhibitor used in the first line, PS, sex, and presence of extrathoracic disease were significantly related to PFS, and only PS maintained their significance in multivariate analysis. Similarly, univariate analysis for OS was found to be significant for PS, presence of extrathoracic disease, and use of ALK inhibitor in the first line; all these factors retained their significance in the multivariate analysis (Table 3).

Patients With Brain Metastasis at Baseline

Of 65 patients with brain metastasis at baseline, 15 (23.1%) had single brain metastasis. Nevertheless, because five (33.3%) of them could not receive ALK inhibitors at baseline, they were given WBRT. In addition, of the rest 10 patients, because five (50%) had symptoms of intracranial edema, they received WBRT. The median PFS of patients with baseline brain metastasis (n = 65) was 13.2 months (95% CI: 8.3–18.2) on the first-line treatment, which was statistically not different from the patients without brain metastasis at baseline (n = 376) with median PFS of 14.2 months (95% CI: 12.2–16.2) (p = 0.442). Of 65 patients, 44 (67.7%) received crizotinib, two (3.1%) ceritinib, one (1.5%) alectinib, 12 (18.5%) chemotherapy as first-line treatment, whereas six (9.2%) received best supportive care alone due to poor PS at presentation.

Toxicities of the Treatment

The adverse effects of crizotinib and ceritinib received in any line are depicted in Table 4. Anemia (58.6%), transaminitis (54.8%), and peripheral edema (35.6%) were the most common adverse effects of crizotinib, mostly of grade 1, or 2. Most significant grade 3, or 4 adverse effect was visual disturbances (6.8%). With ceritinib, anemia (39.5%) and transaminitis (31.9%) were the most common adverse effects.

Discussion

While applying the trial data to the patients in non-trial setup, there are certain challenges that can lead to different outcomes in the real-world scenario. The most important one is the availability of the drug to all the patients, especially in the resource-constrained settings. Other important factors that can lead to differences in the trial outcomes from the real world are the higher incidence of comorbidities, less stringent monitoring, higher baseline burden of disease, and poor PS.[7] Thus, the real-world data become important in guiding the physicians to tackle day-to-day patients. This study reports one of the largest real-world data of ALK-

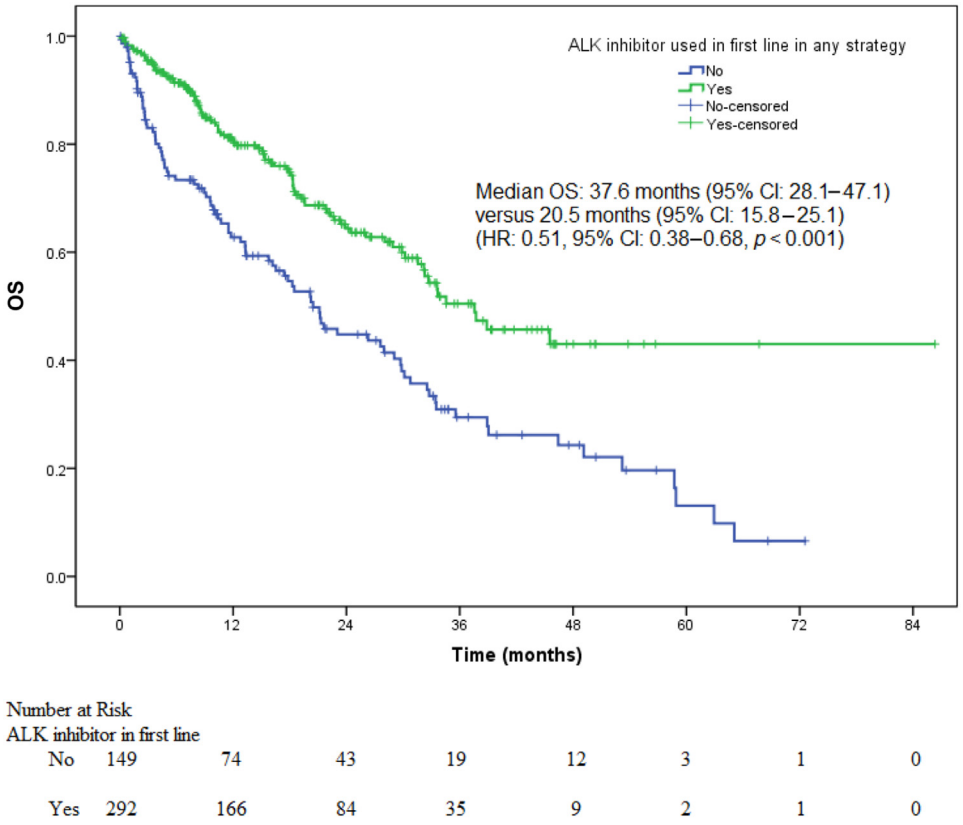

Figure 3. OS of the patients who received first-line therapy with ALK inhibitor versus those who could not. CI, confidence interval; HR, hazard ratio; OS, overall survival.

rearranged NSCLC treated with ALK inhibitors or chemotherapy.

An important difference in the demographic profile of our patients as compared with Western studies is the male preponderance (62.4%).[7,8] Although the real-world Western studies report equal distribution of males and females, previous experience from India also reports similar gender distribution as this study.[9] In addition, the percentage of smokers in this study was as low as 14.3% as compared with the usual 45% to 50% in Western literature.[7] Though the patients received various available ALK inhibitors, crizotinib was the most often used ALK TKI accounting for 365 (82.7%) of the mutated patients. This is similar to another study from India whereby crizotinib was used in 82.7% of the patients.[10] Another study from our center reports the long-term outcomes of crizotinib. The median PFS of crizotinib was 17.3 months (95% CI: 13.0–21.6) and 12.8 months (95% CI: 8.1–17.6) when used in the first line or subsequent lines, respectively.[11] One of the important aspects of patient care gets highlighted by finding that 75% of the patients received crizotinib with the help of NGOs. This is important as our study found significant survival benefits (both PFS and OS) of receiving ALK inhibitor in the first line. This is contrary to the usual belief that exposure to ALK TKI matters and not the sequence. This could be due to significant patient dropout rates with every subsequent line of therapy in patients with NSCLC.[12] Approximately 15% of the patients in our study could not receive any subsequent line of therapy after the first line due to worsening PS, whereas this was as high as 26.1% post second-line treatment. This is an important determinant of the success of therapies in the real-world scenario. Even in the landmark FLAURA trial for first-line therapy for EGFR mutated NSCLC, 20% of the patients in the osimertinib arm and 30% of the patients in the first-generation EGFR TKI could not receive any second-line anticancer treatment.[8]

In our study, ALK inhibitors could be used in approximately 37% of the patients in the first line, whereas these data touched 86% when all the lines of therapies were included in the analysis. This highlights the importance of NGOs and various support schemes for the availability of ALK inhibitors to needy patients so that they are not deprived of the benefit from the same. In fact, this is an improvement from our previous report in which 73.3% of the patients with ALK-positive NSCLC could receive ALK-directed therapy.[9]

Table 2. Univariate Analysis of Various Factors for Their Effect on PFS and OS

Characteristics	N	PFS HR (95% CI)	*p* Value	OS HR (95% CI)	*p* Value
Age (y)					
<60	360	Ref	0.641	Ref	0.112
≥60	81	1.08 (0.79-1.41)		1.38 (0.92-2.05)	
Sex					
Male	274	Ref	**0.009**	Ref	0.111
Female	168	1.18 (1.04-1.33)		1.12 (0.97-1.31)	
ECOG PS					
0-1	344	Ref	**0.023**	Ref	**0.046**
2-4	53	1.46 (1.05-2.00)		1.41 (1.01-1.97)	
Smoking					
Never smoker	378	Ref	0.289	Ref	0.175
Ever smoker	63	1.2 (0.85-1.68)		1.32 (0.88-1.96)	
Comorbidities					
None	266	Ref	**0.048**	Ref	**0.006**
Present	175	1.28 (1.00-1.64)		1.54 (1.13-2.10)	
Stage					
III	43	Ref	0.934	Ref	**0.002**
IV	98	0.98 (0.66-1.46)		2.82 (1.44-5.52)	
ALK inhibitor received in first line					
No	149	Ref	**<0.001**	Ref	**<0.001**
Yes	292	0.41 (0.32-0.52)		0.50 (0.37-0.67)	
Brain metastasis present at baseline					
No	376	Ref	0.441	Ref	0.512
Yes	65	1.14 (0.81-1.62)		1.15 (0.76-1.72)	
Extrathoracic disease					
No	240	Ref	**0.024**	Ref	**0.011**
Yes	201	1.32 (1.04-1.68)		1.46 (1.09-1.95)	

Statistically signficant values are indicated in bold.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PS, performance status; Ref, reference.

The present study confirms the efficacy and safety of ALK inhibitors in Indian patients. The median PFS of 17 months on upfront ALK inhibitors seems to be commensurate with the use of next-generation ALK inhibitors in a small proportion of the patients. The reason for this longer PFS could stem from various sources; the

Table 3. Multivariate Analysis of Factors Which Came Significant on Univariate Analysis for Their Effect on PFS and OS

Characteristics	N	PFS HR (95% CI)	*p* Value	OS HR (95% CI)	*p* Value
Gender					
Male	274	Ref	**0.024**	-	
Female	168	1.15 (1.02-1.31)			
ECOG PS					
0-1	344	Ref	0.316	Ref	**0.002**
2-4	53	1.16 (0.86-1.56)		1.68 (1.21-2.34)	
Comorbidities					
None	266	Ref	0.340	Ref	**0.006**
Present	175	1.13 (0.88-1.56)		1.56 (1.14-2.13)	
Stage		-			
III	43			Ref	**0.001**
IV	98			3.09 (1.54-6.18)	
ALK inhibitor received in first line					
No	149	Ref	**<0.001**	Ref	**<0.001**
Yes	292	0.42 (0.34-0.55)		0.52 (0.38-0.69)	
Extrathoracic disease					
No	240	Ref	**0.026**	Ref	**0.001**
Yes	201	1.32 (1.04-1.68)		1.11 (0.82-1.51)	

Statistically signficant values are indicated in bold.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PS, performance status; Ref, reference.

Table 4. Toxicities of Crizotinib and Ceritinib Received in Any Line

Adverse Effects	Crizotinib (n = 365)		Ceritinib (n = 91)	
	Grade 1/2 (Percentage)	Grade 3/4 (Percentage)	Grade 1/2 (Percentage)	Grade 3/4 (Percentage)
Anemia	206 (56.4)	8 (2.2)	34 (37.3)	2 (2.2)
Neutropenia	22 (6.0)	12 (3.2)	3 (3.3)	0
Thrombocytopenia	17 (4.6)	2 (0.5)	2 (2.2)	0
Transaminitis	188 (51.5)	12 (3.3)	23 (25.3)	6 (6.6)
Raised creatinine	44 (12.1)	0	8 (8.8)	0
Fatigue	106 (29.0)	7 (1.9)	17 (18.7)	1 (1.1)
Vomiting	102 (27.9)	7 (1.9)	18 (19.8)	1 (1.1)
QTc prolongation	74 (20.3)	11 (3.0)	4 (4.4)	0
Peripheral edema	128 (35.1)	2 (0.5)	5 (5.5)	0
Visual disturbances	60 (16.4)	25 (6.8)	0	0
Rash	38 (10.4)	4 (1.1)	1 (1.1)	0
Mucositis	19 (5.2)	1 (0.3)	2 (2.2)	0
Interstitial pneumonitis	2 (0.5)	1 (0.3)	0	0
Sinus bradycardia (symptomatic)	-	1 (0.3)	0	0

QTc, corrected QT interval.

most important one could be the frequency of scans done every 8 to 12 weeks in the real-world scenario as against strict 8 weeks in the randomized trials. In addition, brain imaging was not performed routinely and was performed only if the patient was symptomatic. This is also different from the randomized trials where brain imaging is usually routinely performed at 8 weeks along with systemic imaging.[3,8] Another feature that can lead to increased PFS can be the continuation of the same treatment despite radiological progression in the absence of clinical progression by the treating physician in real-world settings. This approach is supported by few small studies, especially when next-generation ALK TKI is not feasible in real-world settings.[13–15] One more point that can explain better PFS could be the ethnicity of the patients included in this study.[13,16] The PFS and OS benefit of the use of ALK inhibitors in the first-line treatment of ALK-rearranged lung cancers points toward the need of incorporating an ALK inhibitor early in the course of the disease, rather than reserving it for later lines of treatment. The safety profile of these drugs further adds to the benefits that can be ascertained from the oral treatment. Poor PS and presence of extrathoracic disease indicated poor prognosis and were significant in both univariate and multivariate analyses for both PFS and OS.

The present study has some important and obvious limitations, the most important being heterogeneous patients included in this study and the retrospective nature of this study, which can lead to potential underreporting of various subjective adverse effects such as fatigue. In addition, crizotinib is no longer the preferred first-line ALK inhibitor, but it needs to be emphasized that this is a real-world experience in resource-constrained settings. Thus, the importance of reporting real-world data in this scenario cannot be underestimated.

In conclusion, the treatment of ALK-positive NSCLC in Indian patients has significant logistic constraints. Nevertheless, with active extramural support, most patients could get exposed to crizotinib with clinically relevant efficacy, outcomes, and tolerability similar to published international data. Those patients who could receive ALK inhibitors in the first line had a significant survival advantage as compared with others.

CRediT Authorship Contribution Statement

Akhil Kapoor: Data curation, Formal analysis, Investigation, Methodology, Software, Roles/Writing—original draft, Writing—review and editing.

Vanita Noronha: Conceptualization, Investigation, Investigation, Supervision, Writing—review and editing.

Vijay Patil: Formal analysis, Investigation, Writing—review and editing.

Nandini Menon: Investigation, Writing—review and editing.

Amit Joshi: Data curation, Writing—review and editing.

Amit Kumar: Data curation, Writing—review and editing.

Ajay Kumar Singh: Data curation, Writing—review and editing.

Abhishek Mahajan: Investigation, Writing—review and editing.

Amit Janu: Investigation, Methodology, Writing—review and editing.

Rajiv Kumar: Methodology, Resources.

Trupti Pai: Investigation, Methodology, Writing—review and editing.

Anuradha Chougule: Investigation, Methodology, Writing—review and editing.

Omshree Shetty: Investigation, Methodology, Writing—review and editing.

Kumar Prabhash: Conceptualization, Project administration, Resources, Supervision, Writing—review and editing.

Data Availability Statement

The raw data on which calculations are based can be made available on reasonable request to the corresponding author.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2022.100443.

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