

Lung Cancer

Real-World Data on Treatment Outcome of ALK-Positive Non-Small Cell Lung Cancer from an Indian Multicentric Cancer Registry

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South Asian J Cancer 2024;13(2):114–120.

Abstract



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Keywords

- ▶ real-world data
- ▶ anaplastic lymphoma kinase
- ▶ non-small cell lung cancer

The Anaplastic lymphoma kinase inhibitors (ALKi) represent the standard of care for metastatic non-small cell lung cancer (NSCLC) patients with EML4-ALK rearrangements. Various ALKi agents are available; however, not all eligible patients receive treatment with them due to various reasons. Given the limited real-world data available in our country, we aimed to assess treatment outcomes through a multicenter collaboration. This retrospective, multi-institutional study was conducted under the Network of Oncology Clinical Trials India and included a total of 67 ALK-positive metastatic lung cancer patients from 10 institutes across India, with a median follow-up of 23 months. In the first line setting, the objective response rate (ORR) with ALKi was 63.6% (crizotinib: 60.7%, ceritinib: 70%, alectinib: 66.6%, $p = 0.508$), while with chemotherapy, it was 26.1%. The median progression-free survival (mPFS) for the first line ALKi group was significantly higher than that for chemotherapy (19 vs. 9 months, $p = 0.00$, hazard ratio [HR] = 0.30, 95% confidence interval [CI]: 0.17–0.54). The mPFS for crizotinib, alectinib, and ceritinib was 17, 22, and 19 months, respectively ($p = 0.48$). Patients who received ALKi upfront or after 1 to 3 cycles of chemotherapy

DOI <https://doi.org/10.1055/s-0043-1776290> ISSN 2278-330X

How to cite this article: Moharana L, Panda SS, Devaraj S, et al. Real-World Data on Treatment Outcome of ALK-Positive Non-Small Cell Lung Cancer from an Indian Multicentric Cancer Registry. *South Asian J Cancer* 2024;13(2):114–120.

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or after 4 or more cycles of chemotherapy had mPFS of 16, 22, and 23 months, respectively ($p = 0.47$). ALKi showed superior mPFS compared to chemotherapy in the second line (14 vs. 5 months; $p = 0.002$) and the third line (20 vs. 4 months; $p = 0.009$). The median overall survival (OS) was significantly better in patients who received ALKi in any line of therapy (44 vs. 14 months, $p < 0.001$, HR = 0.10, 95% CI: 0.04–0.23). Brain progression was higher among those who did not receive ALKi (69.2 vs. 31.5%). In conclusion, the use of ALKi as first line treatment for ALK-positive metastatic NSCLC patients resulted in improved PFS. PFS and ORR did not significantly differ between patients who received ALKi upfront or after initiating chemotherapy. Notably, patients who received ALKi in second or later lines demonstrated significantly better outcomes compared to those receiving chemotherapy. The use of ALKi in any line of therapy was associated with significantly prolonged OS.

Introduction

Anaplastic lymphoma kinase (ALK) gene rearrangement is found in 1 to 7% of non-small cell lung cancer (NSCLC) patients.^{1–3} Its frequency is higher among nonsmokers, which may be as high as 17 to 20%.^{1,4} Crizotinib is the first potent inhibitor of ALK tyrosine kinases and the first targeted therapy approved for treating ALK-positive NSCLC.⁵ Second-generation and third-generation ALK inhibitors (ALKi) like ceritinib, alectinib, lorlatinib, and brigatinib are more efficacious and are better-tolerated agents.^{6,7} Despite being superior to conventional chemotherapy, resistance does develop to crizotinib, which can be treated with other agents.⁸

Till today, little real-world evidence is available from the developing countries like India with varied genetic and ethnic backgrounds and a relatively higher prevalence of the disease.

Because of the high cost, all the eligible ALK-mutated NSCLC patients do not get treated with ALKi. Also, due to delays in the availability of molecular testing reports, many patients in India receive chemotherapy before switching to ALKi maintenance, adding to the diversified approach. The present multicenter study was therefore conducted to evaluate the real-world experience related to the treatment patterns and clinical and survival outcomes of patients with ALK-positive NSCLC. Network of Oncology Clinical Trials India (NOCI) is a group of oncology centers supported by the Biotechnology Industry Research Assistance Council (BIRAC) to develop a registry of cancers and conduct collaborative clinical trials (www.noci-india.com). We collated data on patients with ALK-positive lung cancer from the six centers of NOCI. An additional four centers from the state of Odisha contributed their data. The combined data is presented in this article.

Methods

Collection of Data

Data of ALK rearrangement-positive NSCLC patients registered for treatment from 2014 to 2021 were collected retrospectively from the records maintained in each institu-

tion. ALK rearrangement was diagnosed by immunohistochemistry, fluorescent in situ hybridization, or next-generation sequencing.

Inclusion Criteria

Patients were eligible for enrolment if they had histologically confirmed locally advanced, recurrent, or metastatic NSCLC that was positive for an ALK rearrangement and received no previous systemic treatment for advanced disease, irrespective of the brain metastasis.

Key Exclusion Criteria

Patients with incomplete records and those who were lost to follow-up were excluded from the analysis.

The primary end point of the study was progression-free survival (PFS), whereas the secondary end point was overall survival (OS). Each institution entered the data into a pre-defined proforma common to all ten centers. The data elements captured were baseline characters, type of testing for ALK, treatment details, use of ALKi and line of use, the toxicity of ALKi, responses to treatment, and survival. The deidentified data were collated and analyzed.

Statistical Analysis

The baseline characters were described as proportions and presented in groups. Four groups were identified: those who received ALKi at the time of diagnosis of NSCLC, those who started chemotherapy and then switched to ALKi after three to four cycles (but before progression), those who received ALKi in later lines of treatment (after progression with chemotherapy), and those who never received ALKi. The Kaplan–Meier method estimated the median PFS and OS with 95% confidence intervals (CI). The log-rank test was used to compare treatment groups at a 5% significance level (two-sided). A stratified Cox proportional-hazards regression model was used to estimate the treatment effect, expressed as a hazard ratio (HR) with a 95% CI. The study was approved by the institutional ethics committee (vide IMS.SH/SOA/2021/097 letter dated 07.07.2021). All procedures performed in studies involving human participants

were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

Among the 67 patients who were diagnosed with ALK mutated lung cancer (males, $n=37$; median age: 52 [26–80] years, 16 (24%) patients were smokers, and 12 (18%) had brain metastasis at presentation. Forty-four (66%) patients received ALKi in the first line. Of those, 22 (33%) patients were started on ALKi upfront, while 22 (33%) started chemotherapy and switched to ALKi after a few cycles. Sixteen patients received one to three cycles, and six patients got more than or equal to four cycles of chemotherapy before switching to ALKi. The ALKis used were crizotinib ($n=28$), alectinib ($n=6$), and ceritinib ($n=10$). Twenty-three (34%) patients received only chemotherapy in the first line (→Table 1, →Fig. 1).

Response to Treatment

The objective response rate (ORR) (complete response [CR]+ partial response [PR]) at 6 months was superior for those who received ALKi in the front line compared to those who received chemotherapy alone (64% [28/44] vs. 26% [6/23], $p=0.02$). Six patients receiving upfront ALKi achieved CR, while no patient receiving front-line chemo-

therapy achieved CR. The responses were similar among those who started with ALKi and those who received ALKi after a few cycles of chemotherapy. ORR was similar among patients who received crizotinib, ceritinib, and alectinib (61% [17/28], 70% [7/10], and 67% [4/6], respectively, $p=0.508$) (→Table 2).

Survival Outcomes

The median follow-up duration was 23 months (1–99 months). Fifty-four (81%) patients received some ALKi in the first or subsequent lines, whereas 13 (19%) patients never received any ALKis. Median PFS among those who received ALKi in front-line treatment was superior to those who received chemotherapy alone (19 vs. 9 months; $p<0.001$, HR=0.30, [95% CI: 0.17–0.54]); →Fig. 2). Among the ALKi, median PFS achieved with crizotinib, ceritinib, and alectinib were similar (17, 19, and 22 months, respectively; $p=0.48$). PFS did not differ between those who received ALKi as front-line treatment or after a few cycles of chemotherapy (16 vs. 22 months; $p=0.24$; →Table 2). Patients who received more than or equal to 4 cycles of chemotherapy ALKi had a median PFS of 23 versus 22 months ($p=0.41$) for those who received one to three cycles of chemo before switching to ALKi. The rate of progression in central nervous system was lower among those who received ALKi (31 vs. 69%). In the second line, 21 patients received ALKi (crizotinib: 8, ceritinib: 8, alectinib: 3, lorlatinib: 2), and 28 received chemotherapy. Median PFS for ALKi or chemotherapy in the second line was

Table 1 Baseline characteristics of all patients with NSCLC who were ALK-positive

		Front-line treatment		
	All patients $n=67$	Chemotherapy alone ^c $n=23$ (34.3%)	Chemotherapy followed by ALKi ^b $n=22$ (32.8%)	ALKi upfront $n=22$ (32.8%)
Median age (range)	52 (26–80)	55	55	50
Sex				
Male	37 (55.2%)	10 (43.5%)	17 (77.3%)	10 (45.5%)
Female	30 (44.8%)	13 (56.5%)	5 (22.7%)	12 (54.5%)
ECOG PS				
0-1	51 (76.1%)	18 (78.3%)	15 (68.2%)	18 (81.8%)
≥2	16 (23.9%)	5 (21.7%)	7 (31.8%)	4 (18.9%)
Smoking status				
Never smoker	16 (23.9%)	3 (13.1%)	9 (40.9%)	4 (18.9%)
Nonsmoker	51 (76.1%)	20 (86.9%)	13 (59.1%)	18 (81.8%)
Stage at diagnosis				
IIIB /IIIC	4 (6.0%)	2 (8.7%)	0 (0%)	2 (9.1%)
IV	63 (94.0%)	21 (91.3%)	22 (100%)	20 (90.9%)
Brain metastasis ^a	12 (17.9%)	3 (13.1%)	3 (13.6%)	6 (27.2%)

Abbreviations: ALKi, anaplastic lymphoma kinase inhibitor; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, non-small cell lung cancer.

^aAt presentation.

^bALKi started after three to four cycles of chemotherapy or at any point before progression on first-line treatment.

^cOut of the 23 patients who received chemotherapy alone in front-line, 10 patients received ALKi as second-line treatment after progression, while 13 patients never received ALKi.

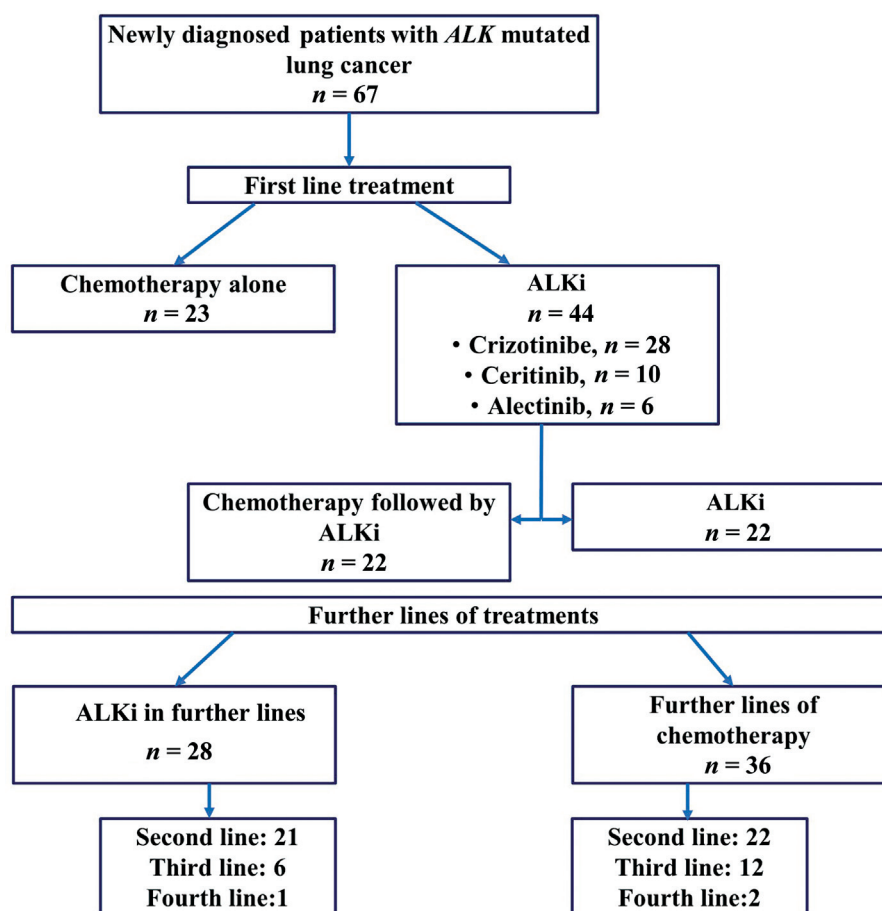


Fig. 1 Patient disposition chart. ALKi, anaplastic lymphoma kinase inhibitor.

Table 2 Outcomes in various treatment groups

	First-line chemo therapy	First-line ALKi		
Overall response rate at 6 months	26%	63.6%		
		ALKi upfront 64%	Chemotherapy→ALKi maintenance 64%	
		Crizotinib 61%	Ceritinib 70%	Alectinib 67%
Median PFS with first-line treatment	9 months	19 months ($p < 0.001$, HR = 0.30, 95% CI: 0.17–0.54)		
		ALKi upfront 16 months	Chemotherapy→ALKi maintenance 22.0 months	
		Crizotinib 17 months	Ceritinib 19 months	Alectinib 22 months
Median overall survival	23 months ^a	34 months, ($p = 0.19$)		

Abbreviations: ALKi, anaplastic lymphoma kinase inhibitor; CI, confidence interval; HR, hazard ratio.

^aSome ALKi in any lines versus no ALKi: 44 versus 14 months ($p < 0.001$, HR = 0.10, 95% CI 0.04–0.23).

14 and 5 months, respectively; $p = 0.002$. Among the ALKi, crizotinib, ceritinib, alectinib, and lorlatinib had median PFS of 8, 24, 4, and 4 months, respectively; $p = 0.77$. In third line, six patients received ALKi (crizotinib: 1, ceritinib: 2, Alectinib: 3), and 12 patients received chemotherapy. Median PFS

for ALKi and chemotherapy in third line were 20 and 4 months, respectively; $p = 0.009$. One patient received ALKi (crizotinib: 1), and two patients received chemotherapy in the fourth line. Median OS for those who received ALKi at any line of treatment was superior to those who never

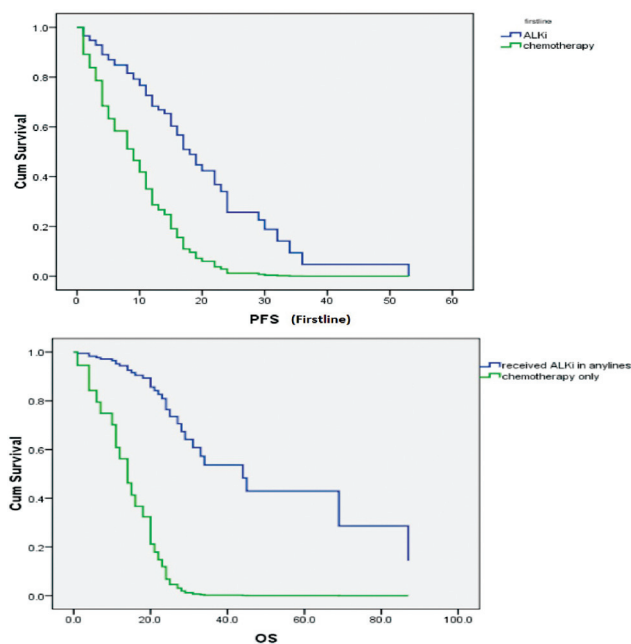


Fig. 2 Survival outcomes. ALKi, anaplastic lymphoma kinase inhibitor; OS, overall survival; PFS, progression-free survival;

received ALKi (44 vs. 14 months, respectively, $p=0.00$, HR= 0.10, [95% CI: 0.04–0.23]) ; ► **Table 2**, ► **Fig. 2**). Median OS for patients with or without brain metastasis at presentation was 20 versus 34 months, respectively; $p=0.01$.

Toxicity

The commonest toxicities associated with crizotinib (across all lines) were gastrointestinal (nausea and diarrhea) and were seen in 22/38 (58%) patients. Transaminitis was seen in 12/38 (31.5%) patients, and two patients (5%) discontinued crizotinib because of hepatotoxicity. Eight (out of 20) (40%) patients had gastrointestinal toxicities with ceritinib, 7/20 (35%) had transaminitis, and 2/20 (10%) had sinus bradycardia and QTc prolongation. One patient developed severe pneumonitis and discontinued ceritinib because of the same. With alectinib, 3/12 (25%) had gastrointestinal toxicity, and 3/12 (25%) developed transaminitis. But none had discontinued alectinib or lorlatinib because of toxicities.

Discussion

Our study is one of the few to report on the outcomes of ALK-positive lung cancers, a rare entity constituting less than 5% of all patients with NSCLC.^{9–13} The true incidence in India is unknown due to selective testing in most centers. Despite their proven survival benefit, not all eligible ALK-mutated NSCLC patients receive ALKi. Due to delays in the availability of molecular testing reports and the time required to arrange to fund, many patients in India receive chemotherapy before switching to ALKi maintenance. Despite these issues, our study clearly shows a significant survival advantage for patients who received ALKi therapy at some point in their treatment course. Nearly 60% of the patients in this series are

Table 3 Comparison of treatment outcomes for various ALK-positive metastatic lung cancer series

	Our study	Shaw et al ²³	Noronha et al ²⁸	Patel et al ²⁷
Type of study	Real-world multicenter	Clinical trial	Real-world single center	Real-world multicenter
Number of patients				
ALKi used	Crizotinib, ceritinib, alectinib, lorlatinib	Crizotinib	Crizotinib	Crizotinib, ceritinib
ORR to ALKi	63.6%	74%	53.6%	66%
ORR to chemotherapy	26.1%	45%	X	X
First-line PFS with ALKi	19 months	10.9 months	12 months	11.3 months
PFS with chemo followed by ALKi	22 months (1–3 cycles chemo) 23 months (≥ 4 cycles)	X	10 months	X
First-line PFS with chemo	9 months	7 months	X	X
OS with ALKi in any line	44 months (ALKi in any lines)	20.3 months (crizotinib followed by crossover to chemo)	Not reached	24.7 months (21.2 months for upfront ALKi, 26 months for switch maintenance with ALKi)
OS with chemo followed by ALKi in later lines	87 months	NR	39.8 months	38 months
OS with chemo	14 months	22.3 months (chemo followed by cross over to crizotinib)	X	X

Abbreviations: ALKi, anaplastic lymphoma kinase inhibitor; NR, not reached; ORR, objective response rate; PFS, progression-free survival; OS, overall survival.

from a government hospital where patients hailed from low economic backgrounds. Almost 80% of patients could access ALKi at some point in their treatment. The availability of support schemes has increased access to these agents. Tumors with ALK fusion oncogenes or their variants are relatively young, nonsmokers, and have adenocarcinoma histology.^{12,14–17} A similar patient profile was seen in our study (–Tables 1 and 3). In our study, five (7.4%) patients had signet ring cell histology, which may have a higher prevalence among ALK-positive lung cancers.^{18,19} Nearly one in five had brain metastasis at presentation. Response rate with first line ALKi was 63.6% (crizotinib: 60.7% [17/28], ceritinib: 70% [7/10], alectinib: 66.6% [4/6], $p=0.508$) and that with chemotherapy was 26.1%. These figures for ALKi are comparable to those of studies like PROFILE 1014 and ASCEND-4.^{20–26} But for patients treated with chemotherapy in first-line, response rates in our study are much less numerically compared to the response rates of chemotherapy-treated patients of the PROFILE 1014 trial (26.1 vs. 45%; –Table 3). This difference may be attributed to the poorer performance status of the patients in the real world compared to those typically enrolled in clinical trials. The ORR for patients who were started on ALKi upfront was similar to those patients who were switched to ALKi after a few chemotherapy cycles; (63.6% [14/22] for both groups). But 18.2% (4/22) in the former group achieved CR, whereas only 9.1% (2/22) achieved CR in the latter group. Though guidelines recommend starting upfront ALKi, this may not be practicable in real-world settings. Delays are inevitable while waiting for molecular testing results, ranging from 1 to 3 weeks in our centers. Even after knowing that a patient is ALK mutated, time is required for them to arrange finances to procure the drugs. However, there was no difference in PFS between patients receiving ALKi upfront or those received after a few chemotherapy cycles. In the second and subsequent lines of treatment, the PFS was superior with ALKi compared to chemotherapy. The median OS for patients who received ALKi in any line of therapy was significantly longer than for patients who never received ALKi (44 vs. 14 months). This is similar to data from a multicenter study from India, which showed that a similar OS is achieved irrespective of the line of ALKi used.²⁷ The study also highlights the strength of cooperative research networks like NOCI, which helps in faster data acquisition and analysis in rarer cancer subsets similar to our study. Limitations of the study include its retrospective nature, thus affecting the quality of the real-world data. Also, under-reporting of adverse events cannot be ruled out in low and middle-income countries like ours and results are to be interpreted cautiously.

Conclusion

The use of ALKi in first line in ALK-positive metastatic NSCLC patients significantly improved PFS compared to chemotherapy. The use of ALKi in subsequent lines resulted in significantly prolonged OS in contrast to patients who never received ALKi. Efforts must be undertaken to incorporate

ALKi in the treatment of metastatic lung cancer patients with ALK-EML4 rearrangement.

Note

Clinical Trials Registry-India (CTRI) Number: CTRI/2022/01/039233.

Funding

The salary for the data entry operators and the biostatistician involved in collecting and analyzing this data was supported by a Biotechnology Industry Research Assistance Council, India (BIRAC) grant through the National Biopharma Mission.

Conflict of Interest

None declared.

Acknowledgements

The authors are thankful to Biotechnology Industry Research Assistance Council (BIRAC) through the National Biopharma Mission to provide funding for the research.

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