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Clinical Outcome of Crizotinib in ROS1-Positive Metastatic Non-small Cell Lung Cancer: A Single-Institution Experience From a Tertiary Care Centre in Northern India

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Abstract

Introduction

Crizotinib is a selective adenosine triphosphate (ATP)-competitive small-molecule ROS proto-oncogene 1 (ROS1) inhibitor with high clinical efficacy. In the current study, we attempted to add to the real-world experience of crizotinib, its efficacy, safety data and clinical characteristics of patients with ROS1-positive non-small cell lung cancer (NSCLC).

Methods

Thirty patients with ROS1-rearranged metastatic NSCLC fulfilling the inclusion and exclusion criteria were retrospectively analysed at Rajiv Gandhi Cancer Institute and Research Centre, New Delhi. Inclusion criteria included patients aged >18 years, Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS 1-3), metastatic, histologically confirmed NSCLC with measurable disease and ROS1 rearrangement. Crizotinib was administered orally at 250 mg twice daily until disease progression, unacceptable toxicity, study withdrawal or death. The primary efficacy endpoint was the overall response rate. The secondary endpoints included progression-free survival (PFS), overall survival (OS) and probability of survival at 12, 24, 36 and 60 months. Kaplan-Meier curves were generated to depict PFS (first-line/second-line setting) and OS. The study analysed the impact of various clinical and demographic covariates on OS and PFS using the Cox proportional hazards regression model.

Results

Thirty patients received ROS1 inhibitors as first-line (n = 23, 76.7%) or second-line treatment (n = 7, 23.3%). Around 70% (21/30) of patients had partial response, and 20% (06/30) had stable disease. Overall, median PFS was 20 months. Median PFS was 16 months and 34 months in the first-line and second-line treatments, respectively. Median OS was 47 months, with three-year and five-year survival probabilities of 75% and 45.3%, respectively.

Conclusions

Our study represents the largest single-institution patient cohort of ROS1-positive NSCLC patients treated with crizotinib from North India. Long-term OS and a favourable adverse-event profile support the continued use of crizotinib in the treatment of ROS1-rearranged NSCLC.

Categories: Oncology

Keywords: crizotinib, metastatic nscl, north india, real-world data, ros1 rearrangement

Introduction

Over the previous years, several oncogenic targets have been identified in non-small cell lung cancer (NSCLC), and targeting these mutations has led to considerable improvement in outcome. ROS1 is a known driver mutation in NSCLC. Although ROS1 rearrangement accounts for 1-2% of NSCLC patients, the impact of oral targeted therapy makes it essential to identify these patients. ROS1 proto-oncogene encodes tyrosine-kinase insulin-receptor family members with significant resemblance to anaplastic lymphoma kinase (ALK). Chromosomal changes activate ROS1, thereby leading to fusion of the ROS1 tyrosine kinase domain with partner proteins. This leads to increased cell transformation, proliferation, migration and survival via various oncogenic signalling pathways [1-4]. The use of immunotherapy or

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chemo-immunotherapy results in a poor outcome in the presence of a molecular driver mutation [5].

Crizotinib is a selective small-molecule multi-targeted tyrosine-kinase inhibitor of ALK, ROS, c-MET (mesenchymal-epithelial transition factor) and HGFR (hepatocyte growth factor receptor) with high clinical efficacy [4-8]. In view of high homology (77%) between the amino acid sequence of the kinase domain of ALK and ROS1, certain ALK inhibitors like crizotinib have efficacy in ROS1-driven tumors [7-9]. The PROFILE 1001 trial showed a significant improvement in response rate, progression-free survival (PFS) and overall survival (OS) in ROS1 fusion-positive patients with crizotinib [4]. This was followed by the Food and Drug Administration (FDA) approval of crizotinib in this subgroup. In view of the low overall incidence of ROS1-positive patients, real-world data with respect to ROS1 tyrosine kinase inhibitors (TKIs) from India is lacking. In the current study, we have attempted to complement to the real-world experience of crizotinib, its efficacy, safety data and clinical characteristics of patients with ROS1-positive NSCLC.

Materials And Methods

Between October 2017 and May 2024, all patients with metastatic NSCLC with ROS1 rearrangement registered at Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, were retrospectively analysed. Forty-three patients fulfilling the eligibility criteria were included in the current analysis. Of these 43 patients, 13 patients had not received ROS TKI due to logistics, accessibility issues and rapid clinical deterioration, or were lost to follow-up. Taking into consideration the last follow-up as 31st of October 2025, 30 patients were included for the final analysis. The median duration of follow-up was 42 months (33-84 months). Inclusion criteria included patients aged >18 years, Eastern Cooperative Oncology Group Performance Status (ECOG PS) 1-3 [10] (PS 1: restricted in strenuous physical activity, but ambulatory and able to do light or sedentary work/PS; 2: ambulatory and capable of self-care, but unable to work, up and about more than 50% of waking hours/PS; 3: capable of only limited self-care, confined to a bed or chair 50% or more of waking hours/PS; 4: completely disabled, cannot carry out any self-care, totally confined to a bed or chair/PS; 5: dead), metastatic, histologically confirmed NSCLC with measurable disease (Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1) [11] and positive for ROS1 rearrangement. Patients with solid central nervous system (CNS) metastases were eligible if they had asymptomatic brain metastases and did not receive increasing doses of steroids. ROS positivity was documented by either fluorescence in situ hybridisation (FISH), reverse transcriptase-polymerase chain reaction (RT-PCR), or next-generation sequencing (NGS). Patients were considered positive for ROS1 rearrangement by FISH if >15% of nuclei had evidence of gene rearrangement.

This study was approved by the Institutional Review Board of the Rajiv Gandhi Cancer Institute and Research Centre (RGCIRC/IRB-BHR/105/2024). Those patients with age <18 years, non-metastatic disease, absence of ROS1 rearrangement, symptomatic brain metastasis requiring increasing doses of steroids, non-measurable disease were excluded from the study. Patients' clinicopathological characteristics, treatment and follow-up records were retrieved and recorded. Baseline CNS imaging was done in all the patients using magnetic resonance imaging (MRI) scans. Crizotinib was administered orally at 250 mg twice daily in continuous 28-day cycles until RECIST-defined disease progression or clinical deterioration, unacceptable toxicity effects, study withdrawal or death. The primary efficacy endpoint was the overall response rate (ORR), defined as the proportion of patients who achieved the best response of partial or complete response (PR/CR). The secondary endpoints included PFS, OS and probability of survival at 12, 24, 36 and 60 months. Adverse events (AEs) were evaluated from the time of the first dose until 28 days following the last dose and were classified and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 [12].

Statistical analysis

Frequency distribution statistics were used for clinical variables. Time-to-event data were analysed using the Kaplan-Meier curves to estimate median time to event. Kaplan-Meier curves were generated to depict PFS (first-line/second-line setting) and OS. The study analysed the impact of various clinical and demographic covariates on OS and PFS using the Cox proportional hazards regression model. In addition, hazards ratio (HR) and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the relative risk of events and their association with OS and PFS. Univariate and multivariate analyses were undertaken to assess the impact of each variable on OS and PFS. A p-value of <0.05 was considered statistically significant. MedCalc Statistical Software version 23 (MedCalc Software Ltd, Ostend, Belgium) was used for the analysis.

Results

Clinicopathological characteristics

Between the 1st of October 2017 and May 2024, records of all metastatic NSCLC (n = 1,433) patients presenting to Rajiv Gandhi Cancer Institute and Research Centre, India, were retrospectively analysed (Figure 1).

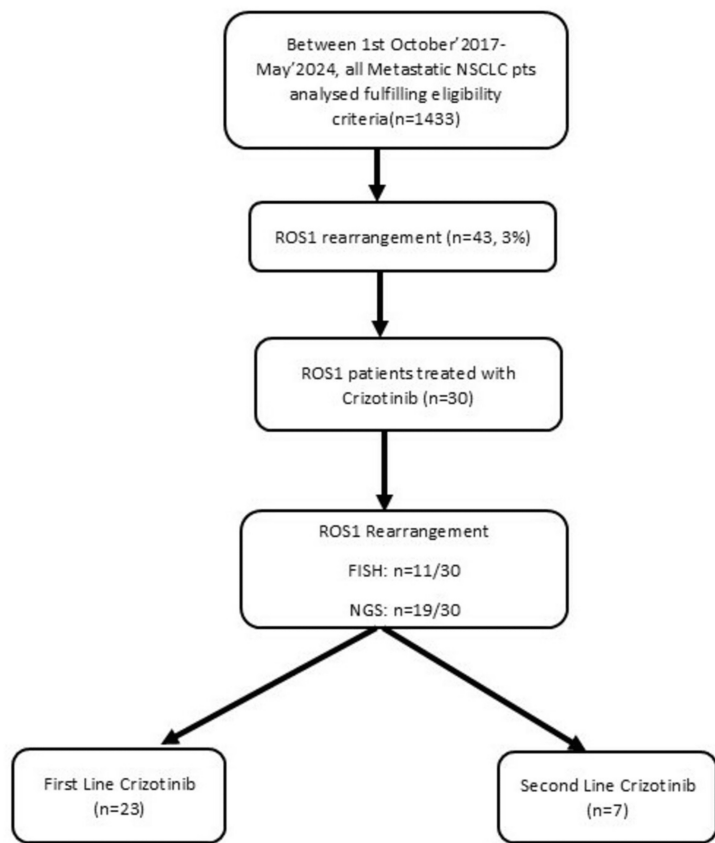


FIGURE 1: Schematic representation of ROS1 rearranged metastatic non-small cell lung cancer (NSCLC).

FISH: fluorescence in situ hybridisation, NGS: next-generation sequencing

A total of 43 patients diagnosed with ROS1-rearranged metastatic NSCLC were noted. Of these 43 patients, 30 patients received ROS1 inhibitors as first- or second-line treatment. Patient demographics and baseline disease characteristics are described in Table 1. Median age at presentation was 54 years (range, 32-85 years). There was a slight male preponderance (16/30, 53.3%). The majority of the patients were non-smokers (90%). Almost all the patients had adenocarcinoma histology (29/30, 96.7%), with one patient having squamous histology. ECOG PS 1-2 was seen in 93.33% of patients. The most common site of metastasis at baseline was extracranial (66.7%), with isolated brain metastasis seen in one (3.3%) patient. Both intra- and extracranial diseases at baseline was seen in seven (23.4%) patients. Baseline NGS was done for all 19/30 patients with CD74 as a fusion partner seen in nine (30.00%) patients and EZR in four (13.33%) patients. FISH positivity was seen in 11/30 patients.

Patient characteristic	Category	n = 30, (%)
Median age (years)	-	54 (range, 32-85)
Gender	Male	16 (53.3%)
	Female	14 (46.7%)
Histology	Adenocarcinoma	29 (96.7%)
	Squamous cell carcinoma	01 (3.3%)
Smoking status	Never smoker	27 (90%)
	Smoker	03 (10%)
	1	24 (80%)

ECOG PS	2	04 (13.33%)
	>2	02 (6.67%)
Stage at diagnosis	M1a	03 (10.0%)
	M1b	05 (16.7%)
	M1c	22 (73.3%)
M1 disease at baseline	Brain only	01 (3.33%)
	CSF +ve only	01 (3.33%)
	Extracranial only (excluding the liver)	17 (56.70%)
	Extracranial only (including the liver)	03 (10.00%)
	Intracranial + extracranial (excluding the liver)	03 (10.00%)
	Intracranial + extracranial (including the liver)	05 (16.70%)
Baseline brain metastasis	Yes	09 (30.00%)
	No	21 (70.00%)
Baseline liver metastasis	Yes	08 (26.67%)
	No	22 (73.33%)
Leptomeningeal disease	Detected	01 (3.33%)
	Absent	29 (96.67%)
PD-L1 status	>=50%	13 (43.33%)
	>1 to 49%	06 (20.00%)
	<=1%	11 (36.67%)
ROS1 variants (n = 30)	CD74-ROS1.C6R34.COSF1200	9 (30.00%)
	SDC4-ROS1.S2R32.COSF1265	3 (10.00%)
	EZR-ROS1.E10R34.COSF1267	4 (13.33%)
	SLC34A2-ROS1.S13R32.COSF1259	1 (3.33%)
	SLC34A2-ROS1.S13R34.COSF1261	2 (6.67%)
	FISH positive	11 (36.67%)
ROS1 TKI line of therapy	First-line setting	23 (76.67%)
	Second-line setting	07 (23.33%)

TABLE 1: Baseline clinical parameters of patients with ROS1-rearranged metastatic non-small cell lung cancer

ECOG PS: Eastern Cooperative Oncology Group (ECOG) Performance Status Calculator, CSF: cerebrospinal fluid, PD-L1: programmed death-ligand 1, ROS1: ROS proto-oncogene 1, TKI: tyrosine kinase inhibitor

Clinical efficacy of crizotinib

Of the 30 patients, 23 patients received crizotinib in the first-line setting. The best ORR was 73.33% (22/30). Almost 70% (21/30) of the patients had partial response, and 20% (6/30) had stable disease as the best response. Overall, the median PFS was 20 (95% CI, 13-34) months. In the first-line setting, the median PFS was 16 months (95% CI, 7-23) (Figure 2).

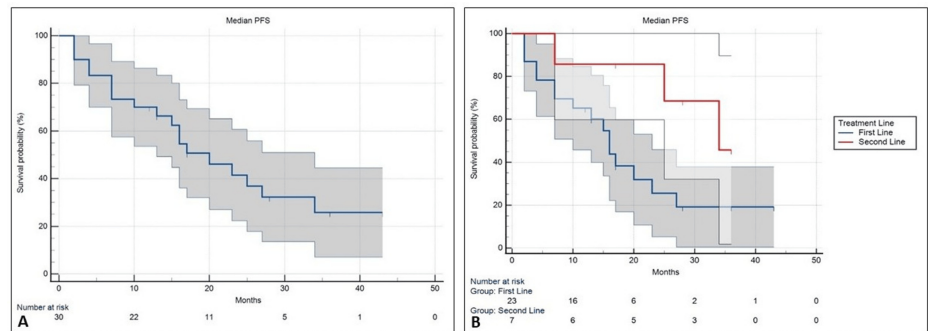


FIGURE 2: Kaplan–Meier curve estimating progression-free survival (PFS) among the 30 ROS1-positive NSCLC patients treated with crizotinib. (A) Overall population, (B) based on the line of treatment (first line vs. second line; log-rank $p = 0.08$).

NSCLC: non-small cell lung cancer

Patients without brain metastasis had an estimated median PFS of 25 months (95% CI, 13–34 months) vs. 15 months (95% CI, 2.0–23 months) in patients with baseline brain metastasis (HR 0.45, p -value = 0.15). Intracranial ORR of 23.33% (CR 1/30, PR 6/30) was noted. The median intracranial PFS was 34 months (95% CI, 17–39 months) (Figure 3A–3B).

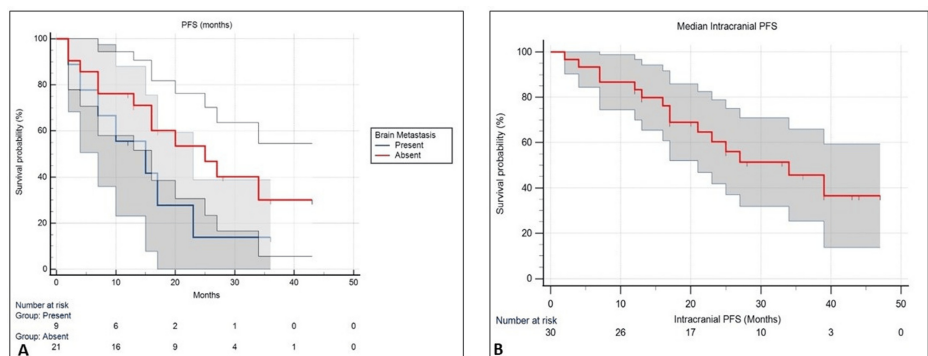


FIGURE 3: Kaplan–Meier curve showing median progression-free survival (PFS). (A) Stratified based on the presence/absence of brain metastasis; log-rank test, $p = 0.142$. (B) Intracranial PFS in 30 ROS1-positive NSCLC patients treated with crizotinib.

NSCLC: non-small cell lung cancer

Eight patients had baseline liver metastasis. Median PFS was longer in patients without liver metastasis (25 months (95% CI 13–34 months) vs. 7 months (95% CI, 2.0–23.0 months)); however, this difference was not significant (log-rank, p -value = 0.143) (Figure 4).

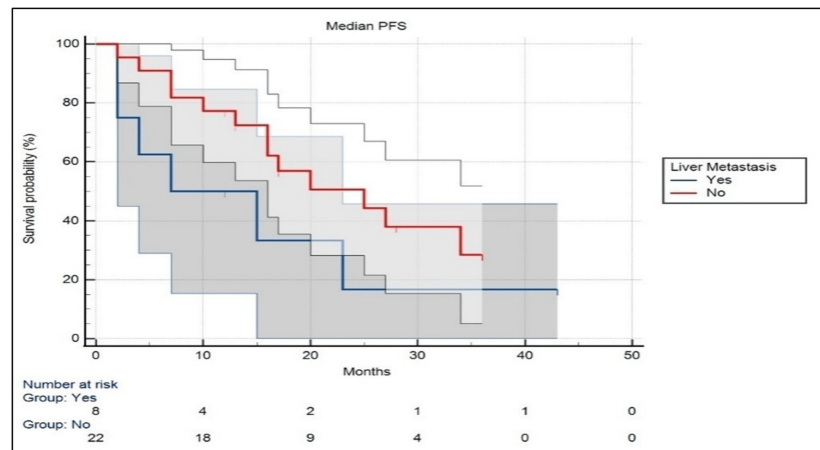


FIGURE 4: Kaplan–Meier curve showing median progression-free survival (PFS) stratified based on the presence/absence of liver metastasis in 30 ROS1 rearranged metastatic NSCLC patients (p-value = 0.143).

NSCLC: non-small cell lung cancer

Crizotinib in the second-line setting

Of the total 30 ROS1-positive patients, seven patients received crizotinib in the second-line setting. The median PFS of crizotinib in the second-line setting was 34 (95% CI 7.0–34.0) months (Figure 4). One of these seven patients had baseline brain metastasis, while none of them had baseline liver metastasis. Median PFS with crizotinib in those with baseline brain metastasis in the second-line setting was 6.8 months, while it was 13 months in those with no baseline brain metastasis (p-value 0.29). However, these numbers are derived from only one patient with baseline brain metastasis in the second-line subgroup and should be interpreted with extreme caution.

Overall survival

The median OS was 47 months (95% CI, 34–47 months), with projected three-year and five-year survival probabilities being 75% and 45.3%, respectively (Figure 5).

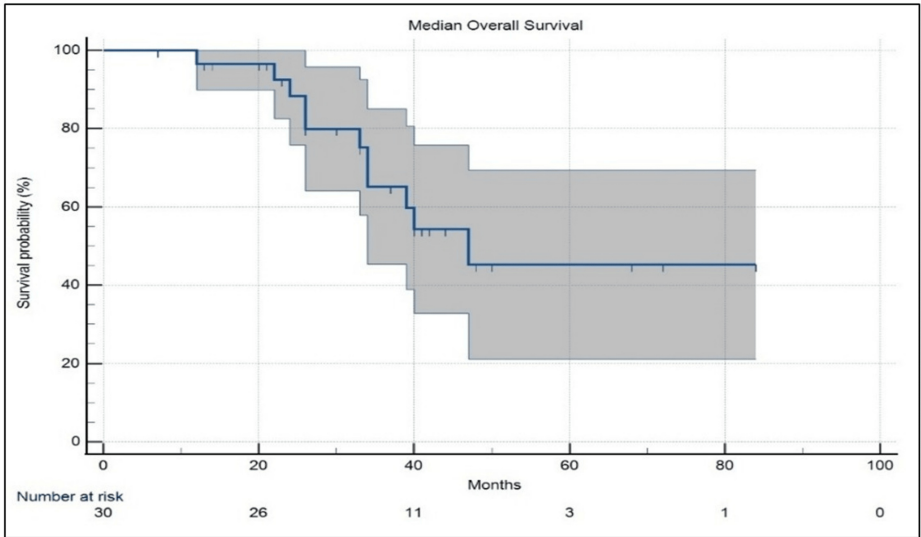


FIGURE 5: Kaplan–Meier curve estimating median overall survival (OS) among the 30 ROS1-positive NSCLC patients treated with crizotinib
NSCLC: non-small cell lung cancer

The median OS was 39 months (95% CI, 33-47 months) and not reached in the first- and second-line settings, respectively (Figure 6) ($p = 0.06$).

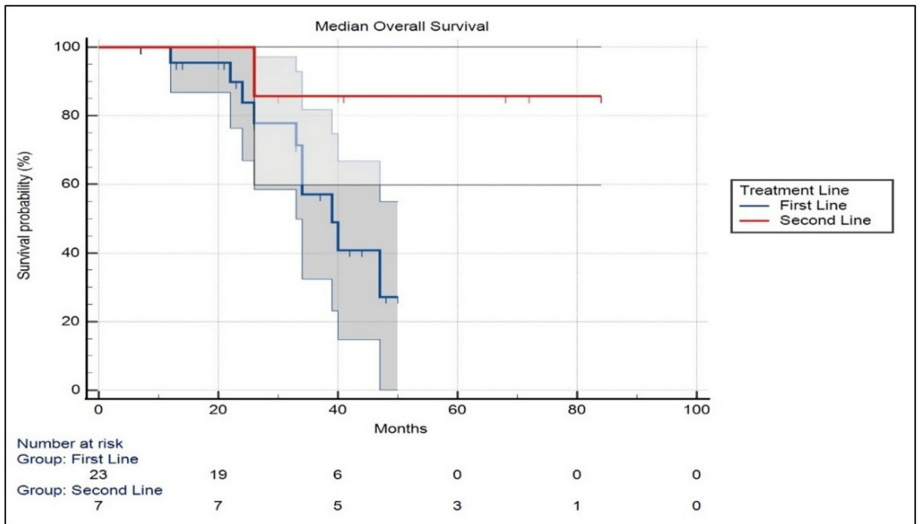


FIGURE 6: Kaplan–Meier curve estimating the median overall survival (OS) among the 30 ROS1-positive NSCLC patients treated with crizotinib stratified based on the line of treatment (log-rank, $p = 0.06$).
NSCLC: non-small cell lung cancer

In patients with brain metastasis, the median OS was 47 months (95% CI, 12-47 months), while it was not reached in patients without brain metastasis ($p > 0.05$). Patients without liver metastasis had a median OS of 40 months (95%, CI 33-40) vs. not reached in patients with Liver metastasis (Figure 7). However, this difference was not statistically significant.

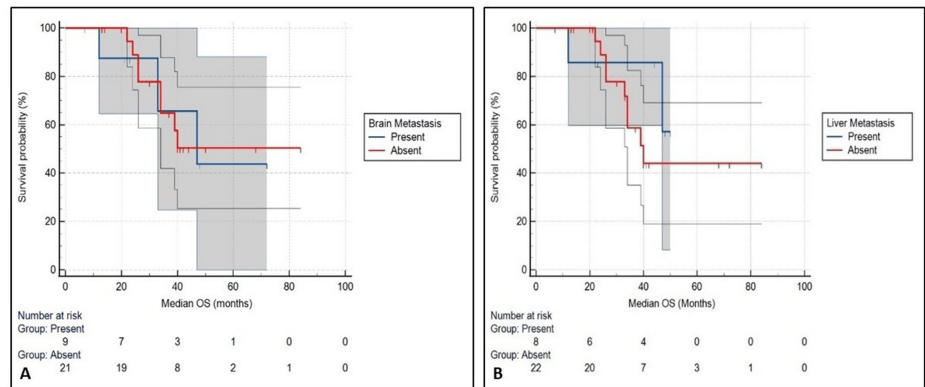


FIGURE 7: Kaplan–Meier curve estimating the median overall survival (OS) among the 30 ROS1-positive NSCLC patients treated with crizotinib stratified based on the presence of (A) brain metastasis and (B) liver metastasis.

Group differences were not significant (log-rank $p > 0.05$) for all comparisons.

NSCLC: non-small cell lung cancer

Factors affecting overall survival

On performing univariate regression, patients with ROS variant SLC34A2-ROS1.S13R32.COSF1259 had a significantly high risk of mortality with hazards ratio of 21.359 (95% CI, 1.354-336.881); however, this subgroup comprised only a single patient (Table 4), and the estimate should be interpreted as hypothesis-generating. The HRs for ECOG PS 1 and 2 ($\sim 2.5 \times 10^4$, with CI spanning over 170 orders of magnitude) similarly indicate that the Cox model did not converge for these covariates, most likely due to a near-empty reference stratum. As approximately nine univariate Cox analyses were performed without correction for multiple comparisons, these findings should be regarded as hypothesis-generating rather than confirmatory. None of the variables was independent significant risk factors of mortality on the multivariate analysis (p -value > 0.05) (Tables 2-3).

Variables	Beta coefficient	Standard error	P-value	Hazards ratio	95% CI for hazards ratio	
					Lower	Upper
Gender						
Female (reference)	-	-	-	1.000	-	-
Male	0.384	0.610	0.529	1.468	0.444	4.847
ECOG performance status						
0 (Reference)	-	-	-	1.000	-	-
1	10.129	196.728	0.959	2.50E+04	0.000	7.15E+171
2	10.041	196.731	0.959	2.30E+04	0.000	6.58E+171
3	-0.041	500.052	1.000	0.960	0.000	-
Leptomeningeal disease (LM)						
No	-	-	-	1.000	-	-
Yes	1.185	1.083	0.274	3.271	0.392	27.299
PD-L1 expression						
<=1% (Reference)	-	-	-	1.000	-	-
>1-49%	0.039	0.732	0.958	1.040	0.248	4.361
>=50%	-0.588	0.737	0.424	0.555	0.131	2.353
ROS variant						
CD74-ROS1.C6R34.COSF1200 (reference)	-	-	-	1.000	-	-
SDC4-ROS1.S2R32.COSF1265	-11.181	588.098	0.985	0.000	0.000	
EZR-ROS1.E10R34.COSF1267	0.278	1.226	0.821	1.320	0.119	14.590
SLC34A2-ROS1.S13R32.COSF1259	3.061	1.407	0.030	21.359	1.354	336.881
SLC34A2-ROS1.S13R34.COSF1261	1.622	1.319	0.219	5.063	0.382	67.162
FISH positive	0.733	0.824	0.374	2.080	0.414	10.450
Brain metastasis						
Absent	-	-	-	1.000	-	-
Present	0.004	0.687	0.995	1.004	0.261	3.860
Liver metastasis						
Absent	-	-	-	1.000	-	-
Present	-0.637	0.792	0.421	0.529	0.112	2.499
Treatment line						
First line (reference)	-	-	-	1.000	-	-
Second line	-1.694	1.053	0.108	0.184	0.023	1.448

TABLE 2: Univariate cox proportional hazard regression to assess significant risk factors of mortality (n = 30)

Variables	Beta coefficient	Standard error	P-value	Hazards ratio	95% CI for hazards ratio	
					Lower	Upper
ROS variant						
CD74-ROS1.C6R34.COSF1200 (reference)	-	-	-	1.000	-	-
SDC4-ROS1.S2R32.COSF1265	-9.924	19.508	0.611	0.000	0.000	1.972E+12
EZR-ROS1.E10R34.COSF1267	-4.280	9.851	0.664	0.014	0.000	3.36E+06
SLC34A2-ROS1.S13R32.COSF1259	-15.714	212.294	0.941	0.000	0.000	7.59E+173
SLC34A2-ROS1.S13R34.COSF1261	1.902	1.381	0.168	6.697	0.447	100.276
FISH positive	0.744	0.826	0.368	2.104	0.416	10.628

TABLE 3: Multivariate cox proportional hazard regression to assess significant risk factors for mortality (n = 30)

Kaplan-Meier survival analysis comparing OS between different variants is summarised in Table 4. A total of nine patients had CD74-ROS1.C6R34.COSF1200, three had SDC4-ROS1.S2R32.COSF1265, four had EZR-ROS1.E10R34.COSF1267, one had SLC34A2-ROS1.S13R32.COSF1259, and two had SLC34A2-ROS1.S13R34.COSF1261. OS at 12 months was 100% across all variants. At 24 months, OS was 100% in all except CD74-ROS1 (85.71%) and EZR-ROS1 (75.00%). By 60 months and at the end of the study, OS was highest in SDC4-ROS1 (100.00%), followed by EZR-ROS1 (75.00%), CD74-ROS1 (64.29%), SLC34A2-ROS1.S13R34 (50.00%), and FISH-positive patients (25.00%) and lowest in SLC34A2-ROS1.S13R32 (0%). No significant difference in OS was observed between variants (p-value = 0.122).

Variables	CD74-ROS1.C6R34.COSF1200	SDC4-ROS1.S2R32.COSF1265	EZR-ROS1.E10R34.COSF1267	SLC34A2-ROS1.S13R32.COSF1259	SLC34A2-ROS1.S13R34.COSF1261	FISH positive
Total N	9	3	4	1	2	11
N of events	2	0	1	1	1	6
Censored, n (%)	7 (77.78%)	3 (100.00%)	3 (75.00%)	0 (0.00%)	1 (50.00%)	5 (45.45%)
OS at the end of 12 months	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
OS at the end of 24 months	85.71%	100.00%	75.00%	100.00%	100.00%	100.00%
OS at the end of 60 months	64.29%	100.00%	75.00%	0.00%	50.00%	25.00%
OS at the end of the study	64.29%	100.00%	75.00%	0.00%	50.00%	25.00%

TABLE 4: Kaplan-Meier survival analysis curve to compare overall survival between reactive oxygen species (ROS) variants

P-values were calculated using the log-rank test. Overall survival distributions did not differ significantly between ROS1 fusion variants (p = 0.122). N denotes the total number of patients in each variant group; 'N of events' denotes the number of deaths observed in each variant group.
Censored: Patients who had not experienced the event (death) at the time of the last follow-up or database cut-off and whose survival time was therefore incomplete at analysis.

Factors affecting PFS

On performing univariate regression, none of the variables was significant risk factors for progression (p-value > 0.05) (Table 5).

Variables	Beta coefficient	Standard error	P value	Hazards ratio	95% CI for hazards ratio	
					Lower	Upper
Gender						
Female (reference)	-	-	-	1.000	-	-
Male	0.323	0.475	0.497	1.381	0.545	3.501
ECOG performance status						
0 (reference)	-	-	-	1.000	-	-
1	0.354	1.063	0.739	1.425	0.177	11.448
2	1.915	1.256	0.127	6.787	0.579	79.556
3	1.951	1.522	0.200	7.037	0.356	138.963
Leptomeningeal disease						
Absent (reference)	-	-	-	1.000	-	-
Present	1.091	1.062	0.304	2.977	0.371	23.868
PD-L1 expression						
<=1% (reference)	-	-	-	1.000	-	-
>1-49%	0.206	0.592	0.727	1.229	0.385	3.925
>=50%	-0.489	0.546	0.370	0.613	0.210	1.789
Variant						
CD74-ROS1.C6R34.COSF1200 (reference)	-	-	-	1.000	-	-
SDC4-ROS1.S2R32.COSF1265	0.844	0.844	0.317	2.326	0.445	12.167
EZR-ROS1.E10R34.COSF1267	-1.065	1.086	0.327	0.345	0.041	2.897
SLC34A2-ROS1.S13R32.COSF1259	1.456	1.138	0.201	4.290	0.461	39.907
SLC34A2-ROS1.S13R34.COSF1261	-0.080	1.097	0.942	0.923	0.107	7.930
FISH positive	-0.016	0.542	0.977	0.984	0.340	2.846
Brain metastasis						
Absent (reference)	-	-	-	1.000	-	-
Present	0.711	0.484	0.142	2.036	0.788	5.256
Liver metastasis						
Absent (reference)	-	-	-	1.000	-	-
Present	0.734	0.502	0.144	2.083	0.778	5.575
Treatment line						
First line (reference)	-	-	-	1.000	-	-
Second line	-1.117	0.637	0.080	0.327	0.094	1.141

TABLE 5: Univariate cox proportional hazard regression to assess significant risk factors for progression (n = 30)

Safety profile

All 30 patients experienced at least one treatment-related AE (TRAE). The majority of TRAEs were grade 1 or 2 in severity, with the most common being vomiting (12/30, 40%), edema (12/30, 40%), vision disorder (5/30,

16.66%), neutropenia (5/30, 16.66%), nausea (10/30, 33.33%), diarrhoea (8/30, 26.66%) and elevated transaminases (8/30, 26.66%). The most common Grade ≥ 3 TRAEs were neutropenia (3/30, 10%), hypophosphatemia (2/30, 6.66%), elevated transaminases (2/30, 6.66%), fatigue (2/30, 6.66%) and loss of appetite (2/30, 6.66%). There were no grade 4 or 5 TRAEs. No TRAEs were associated with permanent discontinuation of treatment.

Discussion

Initial results of EUCROSS and PROFILE 1001 confirmed crizotinib as a preferred management strategy in ROS1-rearranged NSCLC patients. The current study is a first real-world study offering a comprehensive summary of the clinical characteristics, safety and efficacy of crizotinib among 30 ROS1-fusion-positive lung cancer patients in the North Indian population. Crizotinib was associated with an extended median survival of 47 months (95% CI, 34–47 months) and an OS rate of 75% at 36 months (45.3% at 60 months). The adverse event profile in our cohort was consistent with previously reported experience with crizotinib and no new unexpected toxicities emerged [4–6].

The demographic and disease characteristics of our study cohort were broadly in keeping with previously reported series. Of the total 1,433 stage IV NSCLC patients screened, 43 patients (3%) were positive for ROS1 rearrangement, which was comparable to the published literature (1–2%) [1–3]. Of these, 30 patients were treated with crizotinib. The majority of our ROS population were non-smokers (90%) with an ECOG PS of 1–2. The female cohort comprised of 46.7% patient population. The patient characteristics were in concordance with previously published literature [4–8, 13]. Joshi et al. [7] retrospectively analysed data of 535 lung cancer patients, of whom 22 patients were ROS1 rearranged. Sixteen of these received crizotinib. This 4% positivity was apparently higher than our institutional and previously published data. This higher incidence of ROS1-positive NSCLC might be attributed to the initial clinical practice of recommending ROS1 FISH for the epidermal growth factor receptor (EGFR)/ALK-negative cohort or might be reflective of a higher actual incidence in India. Moreover, a larger number of non-smokers were noticed in our study, similar to other oncogene-addicted NSCLC reviews [7]. Joshi et al. [7] had a 40% female population in their study cohort, which was slightly less as compared to our study. This is in contrast to the PROFILE 1001 study, where a 57% female population was noted [4]. Zhang et al. [14] retrospectively reviewed ROS1 data in a Chinese population and reported a 2.59% ROS1 positivity, predominantly in non-smokers, females and a younger population (mean age, 55.68 + 11.3 years), which was in line with our study. Kim et al. [15] and the French ACSe study [16] analysed the real-world data of ROS1-positive patients and confirmed the above findings. Analysis by Kim et al. [15] identified ROS1-positive NSCLC predominantly in women (65%) and non-smokers (69.2%).

Use of chemotherapy or immunotherapy was associated with poor outcomes [5,17–20]. Shen et al. analysed clinical data of 77 ROS1-positive NSCLC patients, including 30 patients who received first-line crizotinib-based therapy. The remaining 47 patients received pemetrexed/platinum-based therapy. The study showed a significant clinical benefit in crizotinib arm with patients experiencing a median PFS of 18.4 months and an ORR of 86.7%, roughly doubling the benefits obtained in the control arm (mPFS: 8.6 months, ORR 44.7%, $p < 0.001$) and ORR (86.7% vs. 44.7%, $p < 0.001$) [19]. Masuda et al. [18] retrospectively analysed 24 ROS-positive patients, of whom 13 were treated with crizotinib. Patients treated with pemetrexed-based therapy and immunotherapy reported an inferior ORR of 45.1% (95% CI, 21.3–72%) and 14.3% (95% CI, 2.6–51.3%).

The overall efficacy of crizotinib in our real-world study closely aligns with previously published literature. Our analysis showed an ORR of 73.33% with a median PFS of 20 months (95% CI, 13–34 months). The seminal PROFILE 1001 study by Shaw et al. [4] reported an ORR of 72% (95% CI, 58–83%) among 53 largely pre-treated patients with a median PFS of 19.3 (95% CI, 15.2–39.1) months. A phase II European, prospective, single-arm study (EUCROSS) evaluated the safety and efficacy of crizotinib for patients with ROS1 fusion-positive advanced lung cancer and reported an ORR of 70% and a median PFS of 19.4 months, which was similar to our study. In a large phase II East Asian study, Wu et al. [13] reviewed data of 127 ROS1-positive patients and demonstrated a 72% ORR (95% CI, 63–79%) with a median PFS of 15.9 months (95% CI, 12.9–24.0 months). In a real-world Korean cohort, Kim et al. [15] reported data from 40 ROS1-rearranged adenocarcinoma patients treated with crizotinib (treatment-naïve: $n = 20$ /prior chemotherapy: $n = 20$). Consistent with earlier studies, Kim et al. [15] observed a high ORR of 70% (95% CI: 53.5–83.4). Furthermore, the median PFS was 24.1 months (95% CI: 15.0–not reached), with corresponding six-, 12- and 18-month PFS rates of 85.0%, 70.0% and 57.5%, respectively. In the real-world study by Panda et al. [8] from Tata Memorial Hospital (TMH), the upfront ROS TKI was used in 38 (55.8%) patients with a median PFS of 27.07 months (95% CI, 24.28 NR), which was better (first-line: median PFS of 16 months) than our study.

The principal outliers in the literature reinforce the importance of patient selection and timing rather than differences in intrinsic crizotinib activity. A French phase II study (ACSe study) [16] evaluated 37 ROS1-rearranged advanced NSCLC patients and reported an ORR of 69.4% (95% CI, 53–82%), which was comparable to our study, yet a markedly shorter median PFS of 5.5 months was noted. These findings were likely underestimated, as they were based on immature data with an undisclosed follow-up period. This variation in PFS between studies may be explained by a smaller patient cohort and differences in baseline patient characteristics (ACSe study: 25% of patients with ECOG PS 2; heavily pre-treated patient cohort included). Our cohort, despite having 21% of patients with ECOG PS 2, achieved substantially better

outcomes than the ACSe study, mainly because 76.7% of our patients received crizotinib in the first-line setting, whereas the ACSe cohort was almost exclusively second-line or later. Japanese real-world evidence by Nogami et al. [17] and Masuda et al. [18] showed a median PFS of 13 months (first-line, 95% CI: 4.4–32.0 months) and 10 months (95% CI, 5.1 to 27.0/ORR 80%), respectively, which was slightly inferior in comparison to the European and global clinical studies (19.2–22.8 months) [4–6], whereas real-world Chinese data have shown variations in clinical efficacy (median PFS, 11.0–23.0 months) [19,21–22]. This may be ascribed to the smaller Japanese patient cohort ($n = 13$), variable duration of crizotinib treatment and a large proportion of patients being censored in the analysis (first-line, 13/27 (48%)) [16]. In addition, inter-study comparisons warrant caution given the discrepancies in study methodologies, participant demographics and clinical setting [17–18]. A population-based Canadian cohort of Gibson and colleagues [20] reported an ORR of only 29% and median PFS of 10.6 months. Thus, most of the trials and real-world data indicate systemic anti-tumour activity of crizotinib in ROS1-rearranged disease of approximately 65–75%. By contrast, lower real-world response figures reflect a high baseline disease burden and inclusion of poor PS patients rather than primary drug resistance.

In our study, the median PFS was longer in patients receiving crizotinib in the second line (34 months) than in the first line (16 months). In the PROFILE 1001 study by Shaw et al. [4], nearly 46% of patients were pre-treated with a minimum of two or more prior chemotherapy regimens and a median PFS of 19.3 months was comparatively inferior to a median PFS of 34 months noted in our study cohort when crizotinib was used in the second-line setting. This difference in prior treatment exposure is one of several possible explanations for the numerical difference between the two cohorts' second-line PFS estimates; however, given the small size of our second-line subgroup ($n = 7$) and the retrospective, non-randomised design, no comparative efficacy conclusion can be drawn between the two studies or between treatment lines. Most of the phase II trials, EUCROSS (median PFS: 0–1 prior lines of therapy ($n = 16/30$): 17.8 months, >2 prior lines ($n = 14/30$): 20 months), METROS (median PFS: 22.8 months), East Asian study (median PFS 15.9 months (95% CI, 12.9–24.0 months)) and Kim et al. (mPFS2: NR (95% CI, 18.9–NR)) showed the PFS benefit of crizotinib in pre-treated patients with the majority of patients receiving at least one line of prior therapy [6,13,15,23]. Our higher second-line PFS results should be interpreted with caution, as a wider confidence interval for second-line PFS (95% CI: 7 to 34 months) reflects a smaller sample size (7/30 patients) and a high likelihood of selection bias. In the second-line setting, Nogami et al. [17] reported a median PFS of 14 months (95% CI: 4.6–22.2 months). However, these results were in contrast to our study (mPFS: 34 months) and the PROFILE 1001 study (mPFS: 19.3 months). Shen et al. [19] demonstrated that using crizotinib as a second- or later-line therapy does not impair survival if it cannot be administered as a first-line therapy. These second-line PFS findings should not be interpreted as evidence either for or against preferential use of crizotinib in the second-line setting and must not be read as demonstrating comparative efficacy between first- and second-line crizotinib. First-line crizotinib remains the standard of care for ROS1-rearranged NSCLC per current guidelines, and our data do not support deferring treatment to a later line.

In view of low central nervous system (CNS) penetration, the effect of crizotinib on CNS control is controversial. Better understanding of the intracranial impact of crizotinib is essential to guide further clinical decision-making. In line with our study (baseline brain metastasis, 30%), most of the published literature demonstrated 20–43% of patients with brain metastasis. Among patients with baseline brain metastases in our study, the median PFS and OS were 15 months (95% CI, two to 23 months) and 47 months (95% CI, 34 to 47 months), respectively. We observed an intracranial ORR of 23.3% with median intracranial PFS of 34 months. Among the nine patients with baseline brain metastasis, local CNS-directed therapy (stereotactic or whole-brain radiotherapy) was administered concurrently or sequentially with crizotinib in a subset of patients, which likely contributed to preserved OS despite inferior systemic PFS in this subgroup. Consistent with crizotinib's known limited blood-brain-barrier penetration, the predominant pattern of progression among these patients was intracranial, while extracranial disease control was sustained for a longer duration - a dissociation that explains why OS remained comparable between patients with and without baseline brain metastasis even though PFS was numerically shorter in the brain metastasis group.

Our findings were consistent with EUCROSS (median PFS 9.4 months, median OS 13 months) and Kim et al. (brain metastasis 32.5%, median PFS 13.1 months) in patients with baseline intracranial disease [6,15]. Stable disease was the optimal response achieved by four patients in the Italian METROS study and three patients in the EUCROSS trial [6,23]. Higher OS in patients with CNS metastasis may be due to the fact that ROS TKIs were continued in asymptomatic patients. Gibson et al. [20] retrospectively reviewed data of 21 ROS1-rearranged patients treated with crizotinib and reported 43% brain metastasis at the time of analysis. Survival outcomes, including OS (33.1 vs. 25.3 months) and PFS (2.6 vs. 13 months), were comparable regardless of brain metastasis status ($p > 0.05$). The overall response remained consistent with other studies, despite varying instances of CNS metastasis among patients [4–8,13–16]. A marginal decrease in the median PFS/OS was observed among the brain metastasis cohort, although the difference was not significant.

Convergence of our intracranial PFS (34 months) with that of the EUCROSS trial (32.2 months) suggests that although crizotinib has limited blood-brain-barrier penetration, it can deliver prolonged intracranial disease control, particularly when combined with local CNS-directed therapy. Higher intracranial ORR seen in our study adds to the evidence that crizotinib is not entirely inert in the brain. Nevertheless, consistent observation of shorter systemic PFS across various cohorts with baseline brain metastasis reinforces the need for superior CNS-penetrating agents like lorlatinib, entrectinib and repotrectinib. In addition, the

prevalence of brain metastasis is comparatively lower in ROS1-positive NSCLC than in ALK-positive patients (19.4% vs. 39.1%). Owing to limited data, conclusions regarding the efficacy of blood-brain-barrier-penetrating agents may show a distinct impact in ROS1-positive patients relative to ALK-positive patients and remain preliminary and should be viewed tentatively [6].

The median OS in our study cohort was 47 months, which is in concordance with results of major published trials including PROFILE 1001 (median OS: 51.4 months), East Asian study (median OS: 44.2 months), TMH Indian study (Panda et al.) (48.59 months), Kim et al. (not reached) and phase II European EUCROSS study (54.8 months). Notably, the three-year OS rate in our cohort (75%) was numerically higher than the 53% reported in PROFILE 1001 and the 53-55% range reported across major global studies. This difference should be interpreted cautiously given our modest sample size (n = 30), wider confidence intervals around survival estimates, the higher proportion of patients receiving crizotinib as first-line therapy (76.7%) compared to the more heavily pre-treated PROFILE 1001 population, and potential selection bias inherent to a single-institution retrospective design. Results from our study and other global studies reiterate the OS benefit of crizotinib even when used in the second-line setting. Gibson et al. [20] presented real-world data from Canada and observed a median OS (33.1 months) and median PFS (10.6 months), which was compatible with other North American real-world data [20,24], while falling mid-range of Asian and global data [4-6,15-19]. Clinical outcomes could be affected by patient characteristics (age/smokers/ECOG PS), variable follow-up time and therapies that were taken before or after crizotinib. This Canadian cohort had a significant 47% prior systemic-therapy rate [20]. Survival may be comparable if study patients had a longer follow-up duration. Patients having certain fusion variants such as CD74 had better OS compared to other patients harbouring non-CD74 fusion variants. The ROS variant SLC34A2-ROS1.S13R32.COSF1259 had a significantly high risk of mortality on univariate analysis (median OS: 24 months). However, these results, with fewer patients and a wide confidence interval, did not retain independent significance on the multivariate analysis in our study. Therefore, we should regard the apparent variant effect as hypothesis-generating only. No clear association was found between the specific ROS1 fusion partner and OS in the published literature [4,6,13]. Nevertheless, these data reinforce the established sustained clinical efficacy of crizotinib in treating ROS1-positive NSCLC.

Table 6 summarises the study comparison of patient characteristics, response rates and survival outcomes of ROS1-positive metastatic NSCLC treated with crizotinib.

	Present study	Profile 1001 [4]	Joshi et al. [7] (TMH)	EUCROSS [6]	METROS [23] (Landi et al.)	East Asian study (Wu et al.) [13]	Canadian study (Gibson et al. [20])	Panda et al. [8] (TMH)	Real world (USA) (Waterhouse et al. [24])	Real world (Korea) (Kim et al. [15])	Netherlands – real world (Berge et al. [25])	AcSe (Morosibilot et al. [16])
Baseline characteristics												
Sample size	n = 30	n = 53	n = 22 (treated with crizotinib; n = 16)	Phase II: n = 34 (response evaluable, n = 30)	Cohort A, n = 26	n = 127	n = 21	n = 70 (38 points treated with ROS TKI, nine points treated with crizotinib – first line)	n = 38	n = 40	n = 67 (34 points treated with crizotinib – first line)	n = 37
Median age (years)	54 years (range, 32-85)	55 years (range, 25-70)	54 years (range, 45-70)	60 years (range, 33-84)	68 years (range, 28-86)	51.5 years (range, 22.8-79.7)	51.6 years (IQR, 43.9-59.7)	52 years (range, 26-78)	68 years	60.5 years (range, 27-83)	62 years (range, 55-72)	62 years (range, 33-81)
Sex – male, n (%)	16 (53.3%)	23 (43%)	13 (60%)	13 (43%)	10 (38%)	54 (42.5%)	7 (33.3%)	39 (55.7%)	34.2%	14 (35%)	30 (44.8%)	11 (30%)
Sex – female, n (%)	14 (46.7%)	30 (57%)	9 (40%)	17 (57%)	16 (62%)	73 (57.5%)	14 (66.67%)	31 (44.3%)	65.8%	26 (65%)	37 (55.2%)	26 (70%)
ECOG PS 0, n (%)	0 (0%)	23 (43%)	-	12 (40%)	18 (69%)	34 (26.8%)	14 (PS 0–1 combined)	45 (64.3%) (PS 0–1 combined)	-	7 (17.5%)	14 (20.9%)	11 (31%)
ECOG PS 1, n (%)	24 (80%)	29 (55%)	-	17 (57%)	7 (27%)	93 (73.2%)	-	-	-	30 (75.0%)	24 (35.8%)	16 (44%)
ECOG PS 2, n (%)	4 (13.33%)	-	-	1 (3%)	1 (4%)	-	6 (PS 2–3 combined)	15 (21.4%)	-	3 (7.5%)	≥2: 9 (13.4%)	9 (25%)
ECOG PS >2, n (%)	2 (6.67%)	-	-	-	-	-	-	10 (14.3%)	-	-	-	-
ECOG PS unknown, n	-	-	-	-	-	-	1	-	-	-	-	1

Histology – adenocarcinoma, n (%)	29 (96.7%)	51 (96%)	21 (95%)	28 (93%)	26 (100%)	124 (97.6%)	21 (100%)	70 (100%)	18.4%	40 (100%)	-	33 (89%)
Histology – squamous cell carcinoma, n (%)	1 (3.3%)	1 (2%)	0 (0%)	2 (7%)	-	1 (0.8%)	-	-	-	-	-	-
Histology – other, n (%)	-	1 (2%)	1 (5%) (sarcomatoid adenocarcinoma)	-	-	2 (1.6%)	-	-	-	-	-	-
Detectable ROS1 fusion partner												
ROS1 partner testing – evaluable, n	-	n=25	-	-	-	-	n=18	-	-	-	-	-
ROS1 partner – CD74, n (%)	9 (30%)	11 (44%)	-	-	-	-	9 (50%)	-	-	-	-	-
ROS1 partner – EZR, n (%)	4 (13.3%)	4 (16%)	-	-	-	-	3 (16.7%)	-	-	-	-	-
ROS1 partner – SDC4, n (%)	3 (10%)	4 (16%)	-	-	-	-	1 (5.55%)	-	-	-	-	-
ROS1 partner – SLC34A2, n (%)	3 (10%)	3 (12%)	-	-	-	-	3 (16.7%)	-	-	-	-	-
ROS1 partner – LIMA1, n (%)	-	1 (4%)	-	-	-	-	-	-	-	-	-	-
ROS1 partner – MSN, n (%)	-	1 (4%)	-	-	-	-	-	-	-	-	-	-
ROS1 partner – TPM3, n (%)	-	1 (4%)	-	-	-	-	1 (5.55%)	-	-	-	-	-
ROS1 partner – others, n (%)	FISH positive 11 (36.67%)	-	-	-	-	-	1 (5.55%)	-	-	-	-	-
Line of treatment												
Line of treatment – first line, n (%)	23 (76.67%)	-	2 (12.5%)	6 (20%)	0 (0%)	24 (18.89%)	-	09/38 (13.24%)	-	-	34	-
Line of treatment – subsequent line, n (%)	7 (23.33%)	-	14 (87.5%)	24 (80%)	26 (100%)	103 (71.11%)	-	03/08 (37.50%)	-	-	-	-
Progression-free survival												
Median PFS – overall (months)	20 months (95% CI, 13-34)	19.3 months (95% CI, 15.2-39.1)	Not reached	19.4 months (95% CI, 10.1-32.2)	22.8 months (95% CI, 15.2-30.3)	15.9 months	10.6 months	27.7 months (95% CI, 24.28 months–NR)	-	24.1 months (95% CI, 15.0-NR)	8.6 months [6.7–12.4] (based on 28 cases)	5.5 months (95% CI, 4.2-9.1)
Median PFS – first line (months)	16 months (95% CI, 7-23)	-	-	-	-	-	-	-	-	-	-	-
Median PFS – second line / subsequent (months)	34 months (95% CI, 7.0-34.0)	-	-	-	-	-	-	-	-	-	-	-
PFS rate – six-month												

(%)	-	-	-	-	80.6%	-	-	-	-	-	-	-
PFS rate – 12-month (%)	-	-	-	-	71.9%	-	-	-	-	-	-	-
PFS rate – 24-month / two-year (%)	-	-	54%	-	-	-	-	-	-	-	-	-
Overall survival												
Median OS – overall (months)	47 months (95% CI, 34-47)	51.4 months (95% CI, 29.3-NR)	Not reached	54.8 months (95% CI, 20.3-NR)	Not reached	44.2 months (95% CI, 32-NR)	33.1 months	ROS TKI: 48.59 months (95% CI, 37.85 months–NR)	36.2 months (95% CI, 15.9-NR)	Not reached	24.3 months (95% CI, 12.1-NR)	17.2 months (95% CI, 6.8-32.8)
Median OS – first line (months)	39 months (95% CI, 33-47)	-	-	-	-	-	-	-	-	-	-	-
Median OS – second line / subsequent (months)	Not reached	-	-	-	-	-	-	-	-	-	-	-
Median OS – post-crizotinib subgroup, months (Gibson et al.)	-	-	-	-	-	-	16.2 months	-	-	-	-	-
OS rate – six months (%)	-	-	-	-	96.2%	-	-	-	-	95%	-	-
OS rate – 12 months (%)	-	79%	72%	-	79.2%	-	-	-	-	92.4%	-	-
OS rate – 18 months (%)	-	-	-	-	-	-	-	-	-	87.3%	-	-
OS rate – 24 months (%)	-	67%	54%	-	-	66.4%	-	-	-	-	53%	-
OS rate – 36 months (%)	75%	53%	-	-	-	54.1%	-	71.8%	-	-	-	-
OS rate – 48 months (%)	-	-	-	-	-	46.7%	-	-	-	-	-	-
OS rate – 60 months (%)	45.3%	-	-	-	-	-	-	46.6%	-	-	-	-
Response												
ORR (%)	73.33%	72%	93.5%	70% (95% CI, 50.6-85.3%)	75%	72% (Overall)	29%	-	-	70.0% (95% CI, 53.5-83.4)	-	69.4%
ORR – crizotinib subgroup, % (East Asian study)	-	-	-	-	-	100%	-	-	-	-	-	-
CR, n (%)	1/30	6 (11%)	2 (12.5%)	-	-	-	-	-	-	0	-	-
PR, n (%)	21/30	32 (60%)	13 (81%)	21	-	-	-	-	-	28	-	-
SD, n (%)	6/30	10 (19%)	-	6	-	-	-	-	-	-	-	-
DCR (%)	-	-	-	90%	88%	-	62%	-	-	100%	-	-
Intracranial response												
Intracranial CR, n (%)	1/30	-	-	-	-	-	-	-	-	-	-	-
Intracranial PR, n (%)	6/30	-	-	-	-	-	-	-	-	-	-	-

Intracranial ORR (%)	-	-	-	-	2/6 (33.33%)	-	-	-	-	69.23% (09/13)	-	-
Intracranial DCR (%)	-	-	-	-	6/6 (100%)	-	-	-	-	-	-	-
Median intracranial PFS (months)	34 (95% CI, 17-39)	-	-	32.2 months (95% CI, 23.7- NR)	-	-	-	-	-	-	-	-
Intracranial DCR – brain met present, % (Gibson et al.)	-	-	-	-	-	-	17%	-	-	-	-	-
Intracranial DCR – brain met absent, % (Gibson et al.)	-	-	-	-	-	-	80%	-	-	-	-	-
Brain metastasis												
Brain metastasis, n (%)	30% (n=9)	-	-	20% (n=6)	23% (n=6)	-	43%	-	-	32.5% (n=13)	n=6/28	n=8 (21%)
Brain metastasis – median OS, present (months)	47 months (95% CI, 12-47)	-	-	13 months (95% CI, 1.7- NR)	-	-	25.3 months	-	-	-	5.2 months (95% CI, 4.3- NR)	-
Brain metastasis – median OS, absent (months)	NR	-	-	NR (95% CI, 21.6 vs NR)	-	-	33.1 months	-	-	-	-	-
Brain metastasis – OS p-value	-	-	-	-	-	-	0.73	-	-	-	-	-
Brain metastasis – median PFS, present (months)	15 months (95% CI, 2-23)	-	-	9.4 months (95% CI, 6.9- NR)	-	-	2.6 months	-	-	13.1 months	4.3 months (95% CI, 1.7- NR)	-
Brain metastasis – median PFS, absent (months)	25 months (95% CI, 13-34)	-	-	23.7 months (95% CI, 10.5- NR)	-	-	13 months	-	-	35.8 months	9 months (95% CI, 6.9-20.7)	-
Brain metastasis – PFS p-value	-	-	-	-	-	-	0.13	-	-	0.09	-	-
Liver metastasis												
Liver metastasis, n (%)	8/30	-	-	-	3 (11%)	-	-	-	-	-	n=11 (16.4%)	-
Liver metastasis – median PFS, present (months)	7 months (95% CI, 2-23)	-	-	-	-	-	-	-	-	-	-	-
Liver metastasis – median PFS, absent (months)	25 months (95% CI, 13-34)	-	-	-	-	-	-	-	-	-	-	-
Liver metastasis – median OS (months)	-	-	-	-	-	-	-	-	-	-	9.9 months (95% CI, 4.9- NR)	-

TABLE 6: Study comparison of patient characteristics, response rate and survival outcome of ROS1-positive metastatic non-small cell lung cancer treated with crizotinib

IQR: interquartile range, ROS1: ROS proto-oncogene 1, FISH: fluorescence in situ hybridisation, PFS: progression-free survival, OS: overall survival, NR:

not reached, TKI: tyrosine kinase inhibitor, ORR, DCR: disease control rate, CR: complete response, PR: partial response, SD: stable disease, DCR: disease control rate

All patients experienced at least one safety event in the current study. The tolerability data mirrored well with the findings of the historical data of ALK-/ROS1-rearranged NSCLC. Our data align well with the safety data of crizotinib (Tables 7, 8). As predicted, AEs rose with extended duration of the study. Most reported AEs were Grade 1/2 and were manageable, with none of the patients having to discontinue the medication due to AEs. The uniform safety profile of crizotinib in Western/Asian populations relative to other studies reinforces the confidence of oncologists and patients while initiating treatment with crizotinib in ROS1-rearranged NSCLC [13].

Parameter	Present Study (N=30)	PROFILE 1001 [4] (N=53)	Joshi et al. (TMH) [7] (N=22, n=16 treated)	EUCROSS Trial [6] (N=34)	METROS – Landi et al. [23] (N=26, Cohort A)	East Asian Study (Wu et al.) [12] (N=127)	Gibson et al. (Canadian Study) [19] (N=21)	Kim et al. [14] – Korea (N=40)
Sample size, N	30	53	22 (16 treated with crizotinib)	34	26 (Cohort A)	127	21	40
Any adverse event, n (%)	30 (100%)	53 (100%)	–	33 (97%)	26 (100%)	124 (97.6%)	11 (52.38%)	36 (40%)
Vision disorder, n (%)	5 (16.66%)	46 (87%)	1 (6.2%)	23 (68%)	23%	61 (48%)	2 (9.52%)	5 (12.5%)
Nausea, n (%)	10 (33.33%)	27 (51%)	–	15 (44%)	46%	53 (41.7%)	6 (GI disorders)	9 (22.5%)
Edema, n (%)	12 (40%)	25 (47%)	–	18 (53%)	50%	34 (26.8%)	1 (4.76%)	5 (12.5%)
Diarrhoea, n (%)	8 (26.66%)	24 (45%)	0 (0%)	19 (56%)	–	53 (41.7%)	–	8 (20%)
Vomiting, n (%)	12 (40%)	20 (38%)	–	11 (32%)	–	43 (33.9%)	–	4 (10%)
Elevated transaminases, n (%)	8 (26.66%)	19 (36%)	3 (18.7%)	12 (35%)	27%	85 (66.9%)	3 (14.28%)	15 (37.5%)
Constipation, n (%)	12 (40%)	18 (34%)	–	5 (15%)	–	41 (32.3%)	–	6 (15%)
Bradycardia, n (%)	3 (10%)	11 (21%)	01 (6.2%)	16 (47%)	–	14 (11%)	–	–
Fatigue, n (%)	7 (23.33%)	11 (21%)	–	6 (18%)	58%	15 (11.8%)	–	4 (10%)
Dizziness, n (%)	5 (16.66%)	10 (19%)	–	5 (15%)	–	–	1 (4.76%)	–
Hypophosphatemia, n (%)	5 (16.66%)	09 (17%)	–	2 (6%)	–	–	–	–
Decreased appetite, n (%)	5 (16.66%)	08 (15%)	–	2 (6%)	–	22 (17.3%)	–	–
Neutropenia, n (%)	5 (16.66%)	08 (15%)	01 (6.2%)	11 (32%)	–	43 (33.9%)	–	–
Increased creatinine, n (%)	–	–	–	9 (26%)	–	25 (19.7%)	–	–
Dose reduction, n (%)	–	–	0 (0%)	–	8 (15%)	17.3%	2 (9.52%)	15 (37.5%)
Temporary discontinuation, n (%)	–	–	3 (18.7%)	–	13 (25%)	30.7%	3 (14.28%)	–
Permanent discontinuation due to TRAE, n (%)	0 (0%)	0 (0%)	0 (0%)	–	3 (6%)	2.4%	3 (14.28%)	03

TABLE 7: Any-grade adverse events, by study

NR, not reported; AE, adverse event; NSCLC, non-small cell lung cancer; TMH, Tata Memorial Hospital; TRAE, treatment-related adverse event; GI, gastrointestinal; EUCROSS, European Trial of Crizotinib in Patients With Advanced or Metastatic ROS1-Rearranged Lung Cancer; METROS, crizotinib in MET-deregulated or ROS1-rearranged pretreated non-small cell lung cancer; n, number of patients; %, percentage

Parameter	Present study (N = 30)	PROFILE 1001 [4] (N = 53)	EUCROSS Trial [6] (N = 34)	METROS – Landi et al. [23] (N = 26, Cohort A)	Gibson et al. (Canadian study) [19] (N = 21)	Kim et al. [14] – Korea (N = 40)	Panda et al. [8] (TMH) (N = 70)
Sample size, N	30	53	34	26 (Cohort A)	21	40	70
Any adverse event, n (%)	12 (40%)	19 (36%)	11 (32%); Grade 5: 3%	–	4 (19.04%)	13 (32.5%)	4 (5.97%)
Vision disorder, n (%)	0 (0%)	0 (0%)	–	–	–	3 (7.5%)	–
Nausea, n (%)	0 (0%)	1 (2%)	–	–	–	–	–
Edema, n (%)	0 (0%)	0 (0%)	–	1 (4%)	–	–	–
Diarrhoea, n (%)	0 (0%)	0 (0%)	–	–	–	–	–
Vomiting, n (%)	1 (3.33%)	2 (4%)	–	–	–	–	–
Elevated transaminases, n (%)	2 (6.66%)	2 (4%)	–	2 (8%)	–	–	1 (1.49%)
Constipation, n (%)	0 (0%)	0 (0%)	–	–	–	–	–
Bradycardia, n (%)	0 (0%)	0 (0%)	–	–	–	–	–
Fatigue, n (%)	2 (6.66%)	0 (0%)	–	2 (8%)	–	1 (2.5%)	–
Dizziness, n (%)	0 (0%)	0 (0%)	–	–	–	–	–
Hypophosphatemia, n (%)	2 (6.66%)	8 (15%)	–	–	–	–	–
Decreased appetite, n (%)	2 (6.66%)	1 (2%)	–	–	–	–	–
Neutropenia, n (%)	3 (10%)	5 (9%)	–	1 (4%)	–	–	–
Increased creatinine, n (%)	–	–	–	–	–	–	–
Dose reduction, n (%)	–	–	–	8 (15%)	2 (9.52%)	15 (37.5%)	–
Temporary discontinuation, n (%)	–	–	–	13 (25%)	3 (14.28%)	–	–
Permanent discontinuation due to TRAE, n (%)	0 (0%)	0 (0%)	–	3 (6%)	3 (14.28%)	03	–

TABLE 8: Grade ≥3 (Grade 3–4) adverse events, by study

NR, not reported; AE, adverse event; NSCLC, non-small cell lung cancer; TMH, Tata Memorial Hospital; TRAE, treatment-related adverse event; GI, gastrointestinal; EUCROSS, European Trial of Crizotinib in Patients With Advanced or Metastatic ROS1-Rearranged Lung Cancer; METROS, crizotinib in MET-deregulated or ROS1-rearranged pretreated non-small cell lung cancer; n, number of patients; %, percentage

In a Korean study of patients with advanced ROS1-rearranged NSCLC, ALK inhibitor ceritinib showed effectiveness, particularly in a cohort of 32 patients, of whom 30 had not been previously treated. Beyond crizotinib, various TKIs targeting ROS1 have been investigated in this patient population. In a manner consistent with Shaw et al. [4], the crizotinib-naïve cohort demonstrated an ORR of 67% and a median PFS of 19.3 months (95% CI: one to 37 months). Furthermore, a 14-month follow-up revealed a median OS of 24 months (95% CI: five to 43 months) and a one-year survival rate of 56% [26].

In patients with advanced ROS1-positive NSCLC not previously treated with TKI, entrectinib, a potent

ROS1/NTRK/ALK inhibitor, has shown significant clinical efficacy [27]. A pooled analysis of three trials (n = 53) demonstrated that entrectinib achieved an ORR of 77% and a median PFS of 19.0 months (95% CI, 12.2-36.6 months). However, the overall survival data within this combined analysis lacked sufficient follow-up. Alternative TKIs showing encouraging therapeutic impact in ROS1-positive NSCLC feature new agents including lorlatinib [28] and repotrectinib [29-30]. A phase 1/2 study of lorlatinib did not report overall survival [28]. Crizotinib treatment is linked to noteworthy survival results in ROS1-rearranged advanced NSCLC, reinforcing its standard of care status as a key treatment strategy amid emerging alternative newer TKI data.

Despite the notable benefit of crizotinib in ROS1-positive NSCLC, its poor brain penetration makes the CNS a primary site of progression. The findings are limited by a small sample size, which requires careful interpretation. Lorlatinib/repotrectinib represent advanced therapeutic options with high intracranial efficacy in lung cancer patients. Compared to crizotinib, lorlatinib yielded a substantial intracranial efficacy rate of 64% (7/11) in the TKI-naïve population and 50% in crizotinib pre-treated patients (12/24) [28].

Results of an integrated analysis of three phase 1/2 trials (ALKA-372-001 and STARTRK-1/2) of entrectinib in ROS1-positive NSCLC (n = 53) revealed a median OS that was NR (95% CI: 15.1-NR) with a 12-month survival rate of 85% [27]. Efficacy outcomes for crizotinib and entrectinib in ROS1-rearranged NSCLC were evaluated in a previous study using simulated treatment comparison based on four phase 1/2 trials [27, 29]. Although the ORR was nominally higher with crizotinib, this difference did not reach statistical significance (RR, 1.04, 95% CI: 0.85-1.28). Following covariate adjustment, crizotinib showed a non-significant 1% higher mortality risk at a 12-month landmark for OS (RR = 1.01; 95% CI: 0.90-1.12). According to the comparative studies, Entrectinib and crizotinib provided equivalent clinical benefits for patients with ROS1-positive advanced lung cancer. Although identifying definitive OS data trends across various ROS1 TKIs remains challenging due to limited mature data, our data indicate that crizotinib is a highly effective treatment option. This fact remains true despite the heterogeneous nature of the patient populations studied.

Similar PFS rates observed between ROS1 inhibitors with variable CNS activity complicate the issue as to whether CNS penetrant ROS inhibitors are actually warranted. Future investigations are necessary to evaluate the efficacy of CNS-active agents in ROS1-positive disease.

Limitations

The current study was a single-institution retrospective study analysing data of ROS1-metastatic NSCLC patients. Our findings regarding ROS1-rearranged NSCLC are limited by a modest cohort size, a direct consequence of the low prevalence of this driver mutation. Data on post-progression therapy, ROS TKI resistance, and co-mutations were not available for this study. In addition, there was a lack of a comparative arm in our study. While most prospective trials exclude patients with ECOG PS $\geq 2-3$, our real-world cohort included two patients (6.67%) with ECOG PS 3, reflecting routine clinical practice; however, this small subgroup precluded meaningful statistical inference regarding outcomes in frail patients, and the Cox model did not converge reliably for this covariate. Despite these limitations, it has certain strengths too. First, we utilised a population-based approach to ensure our findings represent the comprehensive ROS1-rearranged cohort in North India. Our study sheds light on the clinical utility, real-world efficacy and safety of crizotinib in patients with ROS1-rearranged NSCLC in the North Indian population.

Our analysis represents one of the few single-institution North Indian cohorts describing real-world outcomes of ROS1-positive advanced NSCLC patients treated with Crizotinib. Following up for nearly four years with a median survival of 47 months, these findings add to the limited real-world evidence on long-term OS with crizotinib in the First-line/Second-line setting for the overall population and for patients with brain metastasis, thereby adding value and strength to our Indian experience. Baseline NGS testing should be done for all metastatic NSCLC patients. An attempt of studying ROS TKI resistance mechanism and establishing a relationship of ROS rearrangement partner with OS/PFS should be made in future studies.

Conclusions

This study represents one of the largest single-institution, real-world experiences of crizotinib in ROS1-rearranged metastatic NSCLC reported from North India, with a median follow-up of 42 months. Crizotinib produced a best overall response rate of 73.33%, a median PFS of 20 months, and a median OS of 47 months, with three-year and five-year OS probabilities of 75% and 45.3%, respectively - findings that are concordant with pivotal trials (PROFILE 1001, EUCROSS) and other real-world cohorts. Clinical benefit extended to patients with baseline brain metastasis, with an intracranial objective response rate of 23.3% and a median intracranial PFS of 34 months, supporting a meaningful, though incomplete, degree of CNS disease control. The safety profile was consistent with previously reported data, with no permanent treatment discontinuations.

Taken together, these findings reinforce the continued role of crizotinib as an effective, well-tolerated treatment option for ROS1-positive NSCLC in a real-world Indian population, while highlighting the need for larger, prospective, multi-institutional studies, including baseline next-generation sequencing (NGS)

testing and systematic evaluation of the impact of the ROS1-rearrangement partner on outcomes, to further refine treatment sequencing and resistance management in this setting.

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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