ORIGINAL ARTICLE

Crizotinib in Patients With *ROS1*-Positive NSCLC With or Without Brain Metastases: Post Hoc Analysis of Phase II METROS Trial

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ABSTRACT

Introduction: Crizotinib, the first approved targeted therapy for *ALK*-positive advanced NSCLC, is also indicated for *ROS1*-rearranged NSCLC. This post hoc analysis of the phase II METROS trial explores long-term survival outcomes with crizotinib, focusing on the impact of baseline brain metastases (BM).

Methods: This post hoc analysis of the METROS study assessed survival outcomes in patients with *ROS1*-rearranged NSCLC, evaluating progression-free survival (PFS), overall survival (OS), and the incidence and severity of adverse events, both in the overall cohort and by baseline BM status.

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Results: Among 64 patients with *ROS1*-positive NSCLC with a median follow-up of 54.4 months, median PFS and OS were 13.8 months (95% CI: 7.4–20.2) and 40.5 months (95% CI: 27.9–53.1), respectively. Patients with BM (N = 17) had significantly shorter PFS (6.8 versus 17.4 mo) and OS (16.4 versus 42.8 mo) than those without BM. The safety profile of crizotinib remained consistent with previous reports, with most adverse events being grade 1 or 2 and no new safety concerns identified.

Conclusion: This analysis supports the efficacy of crizotinib in patients with advanced NSCLC and *ROS1* rearrangements, although its activity in patients with BM remains limited, highlighting the need for brain-penetrant tyrosine kinase inhibitors to improve outcomes in this patient group.

Keywords: Crizotinib; Non-small-cell lung cancer; Brain metastases; Post hoc analysis

Introduction

Targeted therapy has revolutionized the treatment of NSCLC thanks to the discovery of specific, actionable mutations or translocations, such as *EGFR* mutations, *EML4–ALK* translocations, and *ROS1* translocations.[1] Multiple oncogene-directed agents, such as ALK inhibitors (e.g., crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib) and EGFR tyrosine kinase inhibitors (TKIs) (e.g., erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib), have been approved for the treatment of ALK-positive or EGFR-positive NSCLC, as they demonstrated significant survival benefits and superior responses compared with standard chemotherapy.[2,3]

Crizotinib, a dual ALK and c-MET inhibitor, was the first approved targeted therapy for ALK-positive advanced NSCLC and is currently indicated as both first- and second-line treatment in this population.[4,5] Crizotinib is also approved for the treatment of patients with *ROS1* rearrangement, a condition that occurs in 1% to 2% of patients with NSCLC and is more common in younger and nonsmoking individuals.[6–8]

Several trials have reported the efficacy and long-term survival benefits of crizotinib in patients with *ROS1*-rearranged NSCLC.[9–11] The EUCROSS trial, a multicenter, single-arm, phase II trial, revealed that crizotinib (250 mg twice daily) was highly effective in patients with *ROS1*-rearranged NSCLC who had no brain metastases (BM) or stable BM at baseline. The objective response rate (ORR) was 70%, and the median progression-free survival (PFS) was 19.4 months after a median follow-up of 20.6 months[12]; long-term results further confirmed the survival benefit in this population, with the median overall survival (OS) not reached after 55.9 months of follow-up.[9] The PROFILE 1001 study also demonstrated a durable and positive response to crizotinib in *ROS1*-rearranged advanced NSCLC, with an ORR of 72%, a median duration of response (DOR) of 24.7 months, and a median OS of 51.4 months.[10,13]

The multicenter, phase II METROS study further explored the activity of crizotinib in pretreated patients with NSCLC harboring *ROS1* rearrangements or *MET* deregulation (amplification or exon 14 mutations).[14] The study confirmed the efficacy of crizotinib in patients with *ROS1*-rearranged NSCLC, with an ORR of 65%, a median PFS of 22.8 months, and a median OS that was not reached after 21 months. In the *MET*-deregulated cohort, crizotinib demonstrated modest activity, with only a fraction of patients achieving a response (ORR of 27%), and the impact on the clinical course of the disease was minimal (median PFS: 4.4 mo; median OS: 5.4 mo).[14]

Despite the remarkable advances achieved with crizotinib and other targeted therapies in lung cancer, tumor resistance is frequent, and many patients experience progression due to on-target or off-target mutations.[15] One of the most common sites of progression is the central nervous system (CNS), with BM occurring in 37% to 64% of patients with EGFR-positive or ALK-positive NSCLC[16] and in 20% to 40% of those with *ROS1*-positive NSCLC.[17] BM occur frequently at both diagnosis and after treatment, particularly in patients treated with crizotinib, due to its poor blood-brain barrier penetration.[18] Although several studies have investigated the efficacy of targeted agents for ALK-positive NSCLC, particularly in patients with CNS metastases,[19,20] limited data are currently available on the activity of crizotinib and other targeted therapies in controlling BM in patients with *ROS1*-rearranged NSCLC.

The aim of this post hoc analysis of the METROS study is to assess long-term survival outcomes in patients with *ROS1*-rearranged NSCLC treated with crizotinib after a follow-up of more than 4 years. Moreover, the study investigates survival outcomes in relation to BM status to further characterize crizotinib activity in this subgroup.

Methods

Study Design

This is a post hoc analysis of the METROS study. The study design and methodology of METROS were published by Landi et al.[14] Briefly, METROS was a prospective, two-arm, parallel, noncomparative phase II

study investigating the use of crizotinib in pretreated patients with NSCLC with *ROS1* translocation (cohort A) or *MET* amplification or *MET* exon 14 mutation (cohort B). Patients with locally advanced or metastatic NSCLC, previously treated with at least one prior line of chemotherapy and with at least one measurable tumor lesion, were considered eligible for the study and received crizotinib (250 mg twice daily) orally until disease progression, unacceptable toxicity, or patient withdrawal. The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. Each center received approval from the local ethics committee, and all patients provided written informed consent before participation and for the use of their data.

The study began in December 2014 and enrolled patients across all Italian hospitals until March 2017; for this final analysis, the data cutoff was February 2022.

Patient Selection

Patients eligible for the METROS study had a histologically confirmed diagnosis of locally advanced or metastatic NSCLC and archival tissue available for biomarker analysis. Other inclusion criteria were as follows: Eastern Cooperative Oncology Group performance status (ECOG PS) less than or equal to 2, at least one prior line of chemotherapy, at least one measurable tumor lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and adequate bone marrow and organ function. Patients with known *EGFR* or *KRAS* mutations, those who had previously received ROS1 or MET inhibitors, or those with symptomatic BM were excluded. In this final analysis, only patients from the METROS study who had *ROS1*-rearranged NSCLC and were assigned to either cohort A or the expansion cohort, according to the latest protocol amendment, were included, which allowed the inclusion of more patients and access to crizotinib treatment.

Notably, the characteristics of the initial 26 patients were described in Landi et al.,[14] whereas partial data on 22 of the 38 patients from the expansion cohort were included in a subsequent report by Chiari et al.[21] The remaining 16 patients from the expansion cohort have not been previously reported and are presented here for the first time. The overall characteristics of the full expansion cohort are presented in Supplementary Table 1. Baseline characteristics were comparable between the expansion cohort and the original cohort.

Study Assessments

All patients eligible for METROS underwent a complete disease staging, including a computed tomography (CT) scan of the chest and abdomen and blood chemistry tests, such as liver function tests, performed within 4 weeks before enrollment. Bone scintigraphy and brain CT were performed only if clinically indicated; radiographic evaluation was limited to areas deemed suspicious on bone scintigraphy. During study treatment administration, disease assessment was performed every 2 months, with a confirmatory reassessment in all patients having response or disease stability at least 4 weeks after evidence of initial response, according to RECIST criteria. In cases of disease progression and if the patient chose to withdraw from the trial, a complete staging was performed. After completion of the treatment protocol, patients were followed up every 12 weeks for survival assessment. Adverse events (AEs), laboratory tests, and vital signs were classified according to the Common Terminology Criteria for Adverse Events version 4.0.

Study Objectives and End Points

For this latest analysis of the METROS study, patients' survival was assessed in terms of PFS and OS, both in the entire population and based on the presence of baseline BM. The safety profile of crizotinib was also evaluated by measuring the occurrence and severity of AEs in the overall population and the subgroup of patients with BM.

Statistical Analysis

Patient and disease characteristics were analyzed using descriptive statistics and expressed as relative frequencies (percentages) for discrete variables or medians and interquartile ranges (IQRs) for continuous variables. The associations between the factors were evaluated with the chi-square test, whereas differences in the distribution of the quantitative variables were assessed with the Mann-Whitney test. PFS and OS were calculated from the date of therapy initiation to the date of the first evidence of disease progression or patient death in the absence of documented disease progression (for PFS) or death from any cause (for OS). Patients who did not experience an event were censored at the last follow-up date. Survival times were estimated using Kaplan-Meier analysis and expressed as medians with corresponding two-sided 95% confidence intervals (CIs). Differences between curves were evaluated using the log-rank test.

Results

Patient Characteristics

In total, 64 patients with *ROS1*-mutated NSCLC were evaluated for this final analysis of the METROS study: 26 from cohort A and 38 from the expansion cohort.

Table 1. Characteristics of the Overall Population

Characteristics	Patients (N = 64), n (%)
Median age (range), y	55.5 (29-86)
Sex	
Male	22 (34.5%)
Female	42 (65.5%)
ECOG PS	
0	37 (57.8%)
1	24 (37.5%)
2	3 (4.7%)
Smoking status	
Never smoker	32 (50.0%)
Past smoker	26 (40.6%)
Current smoker	6 (9.4%)
Histology	
Adenocarcinoma	63 (98.5%)
Other histology[a]	1 (1.5%)
Brain metastases at baseline	
Yes	17 (26.6%)
No	47 (73.4%)
Prior line of therapy	
0	6 (9.4%)
1	40 (62.5%)
2	13 (20.3%)
>2	5 (7.8%)
Metastatic site	
1	7 (10.9%)
2	19 (29.7%)
>2	38 (59.3%)

[a]Other histology includes NSCLC not otherwise specified and pleomorphic carcinoma.
ECOG PS, Eastern Cooperative Oncology Group performance status.

Patients had a median age of 55.5 (range: 29–86) years and were mainly females (65.5%), never or former smokers (90.6%), with an ECOG PS of 0 (57.8%). All patients except one had adenocarcinoma and more than two metastatic sites. The most common sites of metastases were lung (92.2%), lymph nodes (65.6%), liver (76.6%), bones (35.9%), and brain (26.6%) (Table 1). In total, 17 patients had BM at baseline (Table 2). The characteristics of patients with and without BM were well balanced in terms of median age (50 versus 58 y), sex (males/females: 12/5 and 30/17), performance status (0/1: 9/8 versus 28/19), and previous treatments (1/≥2: 13/4 versus 33/14).

Efficacy

After a median follow-up of 54.4 months, the median PFS and OS in the entire population were 13.8 months (95% CI: 7.4–20.2) and 40.5 months (95% CI: 27.9–53.1), respectively (Fig. 1*A* and *B*). Median PFS was 6.8 months (95% CI: 0.1–13.5) in patients with BM compared with 17.4 months in those without BM (95% CI: 7.9–26.9; hazard ratio [HR]: 1.94 [95% CI: 0.99–3.40]). Median OS was 16.4 months (95% CI: 15.5–17.3) in patients with BM versus 42.8 months (95% CI: 28.6–57.0) in patients without BM (HR: 1.63 [95% CI: 0.81–3.30]) (Fig. 2*A* and *B*). Among patients with BM at baseline, the brain was a site of progression in all cases. Among patients without BM, progression to the brain was reported in 16 patients (34.0%).

Safety

The safety profile of crizotinib was consistent with data from the literature, and no new safety alerts were reported in this analysis. The safety profile observed in this extended follow-up was in line with the previous report.[14] No new AEs were reported, and no neurologic AEs or seizures were observed. Among patients with BM at baseline, 13 experienced an AE of grade more than or equal to 3 (Table 3).

Discussion

In this update of the METROS study, a total of 64 patients with *ROS1*-rearranged NSCLC were analyzed, comprising 26 patients from cohort A and 38 from the expansion cohort. After a median follow-up of 54.4 months, median PFS and OS in the overall population were 13.8 months and 40.5 months, respectively, confirming the efficacy of crizotinib in patients with advanced NSCLC and *ROS1* rearrangement. This long-term follow-up analysis also confirmed the known safety profile of crizotinib, with most AEs being grade 1 or 2 and no new safety signals detected.

Regarding the impact of BM on crizotinib efficacy, patients with BM (N = 17) were found to have a lower median PFS compared with patients without BM (N = 47; 6.8 versus 17.4 mo). OS also followed this trend and was higher in patients without BM compared with those with BM at baseline, among whom OS was just more than 1 year (42.8 versus 16.4 mo). This finding suggests that crizotinib can cross the blood-brain barrier and exert its activity in the CNS in patients with NSCLC and *ROS1* rearrangement. However, its efficacy in this compartment remains limited.

In addition to crizotinib, other targeted therapies have been developed for patients with *ROS1*-rearranged NSCLC, which may have greater blood-brain barrier permeability and could more effectively halt tumor growth in the CNS.[22] Ceritinib is a second-generation ALK inhibitor with 20-fold higher inhibitory activity than crizotinib. This agent seems to be highly effective in patients with *ROS1*-rearranged NSCLC, offering advantages compared with previous multi-line chemotherapy; however, its activity is more pronounced in crizotinib-naive patients than in crizotinib-experienced patients.[23]

Table 2. Characteristics of Patients With/Without Brain Metastases

Characteristics	Patients With BM (N = 17)	Patients Without BM (N = 47)
Median age (range), y	50 (29-74)	58 (38-86)
Sex (male/female)	12/5	30/17
ECOG PS (0/1)	9/8	28/19
Prior therapies (1/≥2)	13/4	33/14
Prior brain RT	9	NA

BM, brain metastases; ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not applicable; RT, radiotherapy.

Entrectinib is a multi-kinase inhibitor that has demonstrated superior blood-brain barrier penetration in vitro compared with crizotinib while retaining its activity in the CNS.[24] Based on a comprehensive analysis of three separate studies, which revealed its clinical activity in the CNS and other sites, entrectinib is now approved for patients with *ROS1*-mutated NSCLC. The analysis reported a PFS of 19 months and a median duration of effectiveness superior to crizotinib (24.6 mo versus 19 mo). Moreover, the intracranial remission rate was 55% in 20 patients with CNS metastases, and the median intracranial duration of response was 12.9 months.[25,26]

Lorlatinib is a third-generation ALK and ROS1 TKI with good kinase selectivity, brain penetration, and strong anti-proliferative activity; it reaches high concentrations in the cerebrospinal fluid by reducing P-glycoprotein–mediated efflux.[27,28] A multicenter phase II study

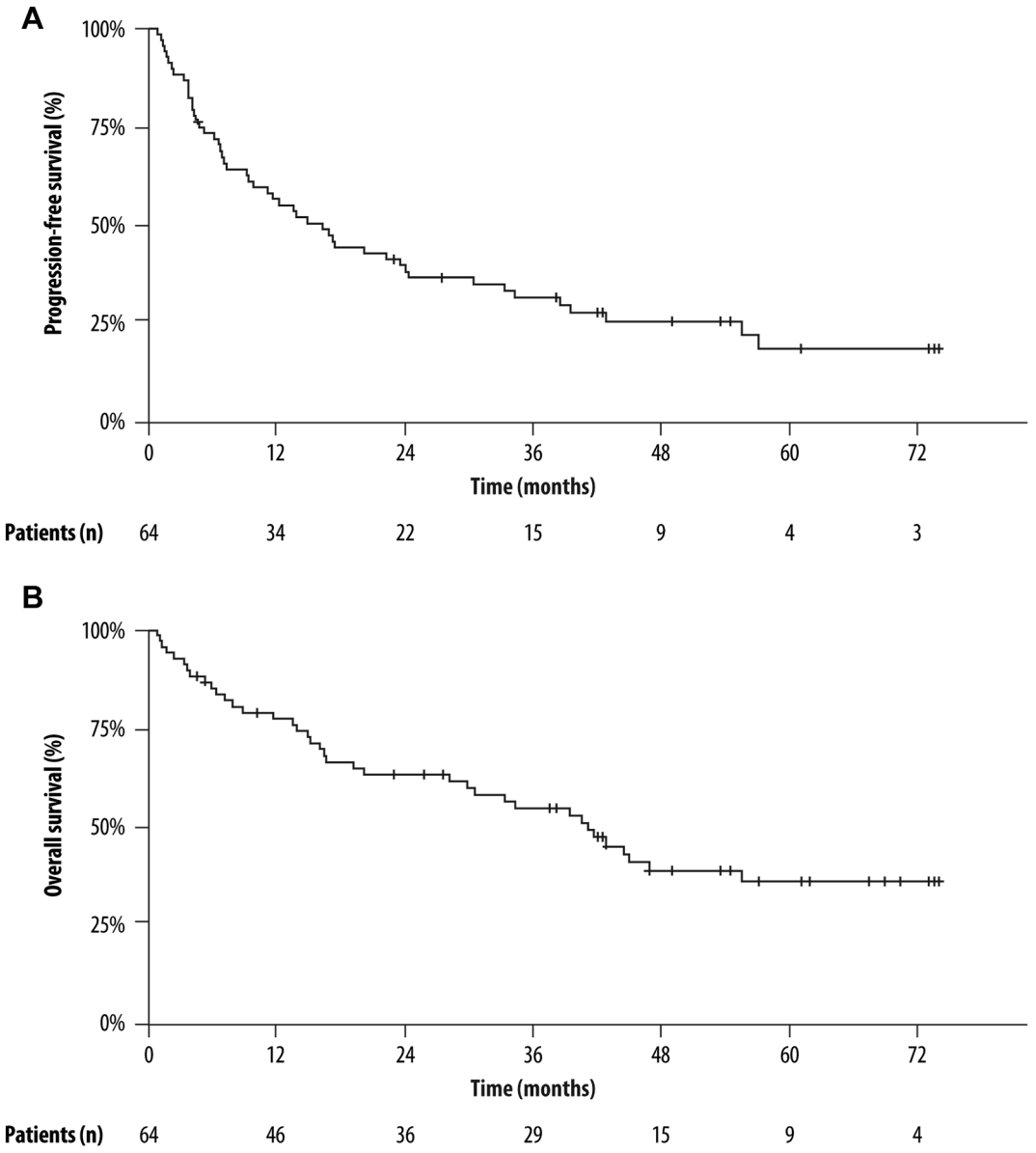

Figure 1. (*A*) Progression-free survival and (*B*) overall survival in patients with *ROS1*-mutated NSCLC receiving crizotinib.

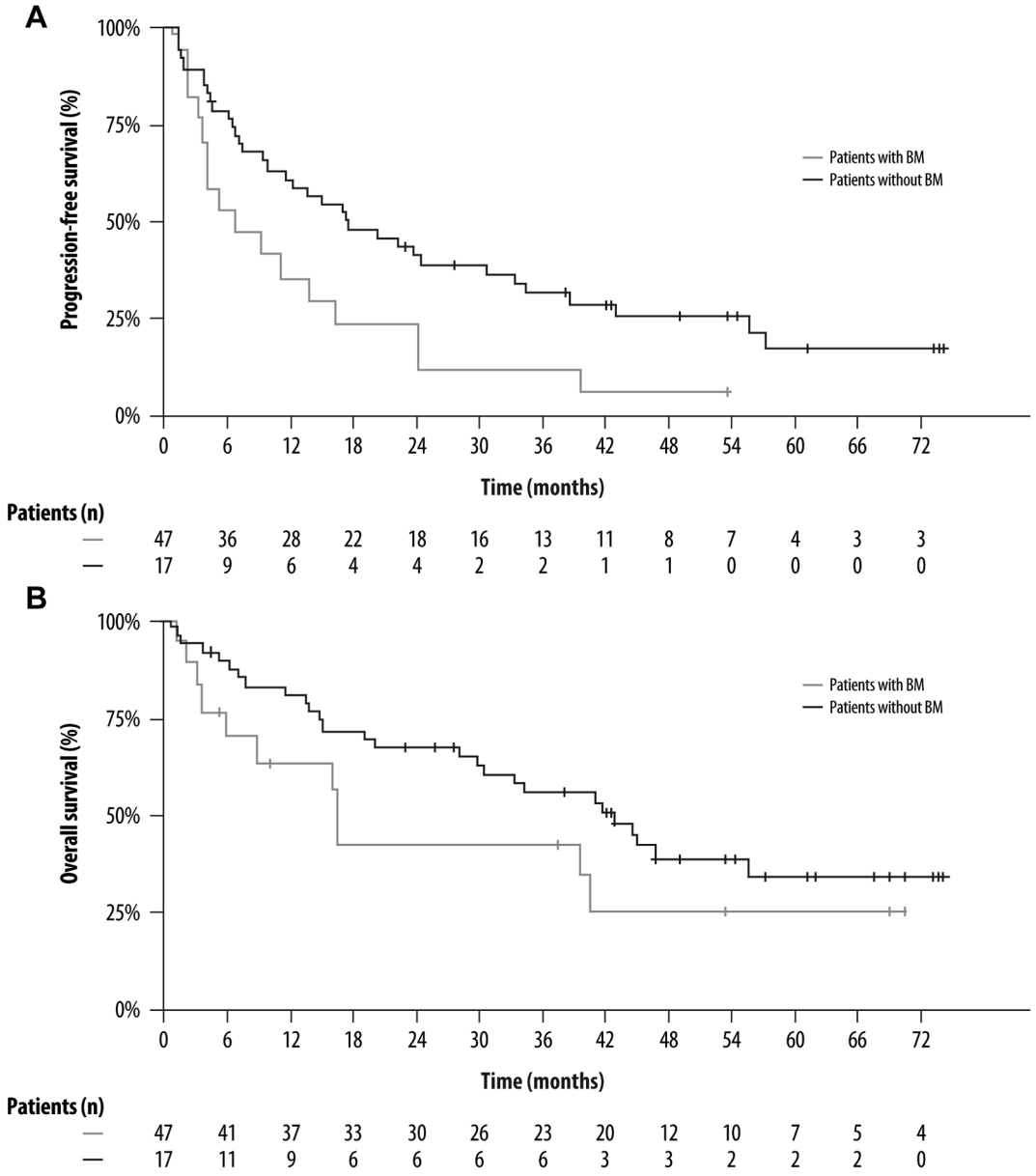

Figure 2. (*A*) Progression-free survival and (*B*) overall survival in patients with and without brain metastases receiving crizotinib. BM, brain metastases.

demonstrated the clinical antitumor activity of lorlatinib against both intracranial and extracranial lesions in patients with *ROS1*-positive NSCLC and greater efficacy after resistance to crizotinib.[29,30] These results were further confirmed by real-world evidence, revealing the efficacy of lorlatinib in *ROS1*-positive patients with or without intracranial metastases after resistance to first- and second-generation ROS1 inhibitors.[31,32]

Preliminary results from phase I/II studies or case reports on a limited number of patients are also available for several new molecules designed specifically to increase central permeability or to overcome *ROS1*-resistant mutations, such as brigatinib,[33–35] repotrectinib,[36] taletrectinib,[37–39] and zidesamtinib.[40]

Taletrectinib is a highly potent and selective ROS1 TKI with strong CNS penetration and high efficacy against the *ROS1* G2032R resistance mutation. A pooled analysis of two pivotal clinical trials, TRUST-I (NCT04395677)[41] and TRUST-II (NCT04919811),[42] investigated the effects of taletrectinib (600 mg) in patients with *ROS1*-positive NSCLC who were either TKI naive (N = 130) or had been previously treated with one ROS1 TKI (N = 87). The cumulative ORR was 92% in TKI-naive patients and 54% in those with prior TKI exposure, whereas intracranial response rates were 76% and 54% in the two populations, respectively. In TKI-naive patients, the median DOR and median PFS were not reached, whereas in TKI-pretreated patients,

Table 3. Adverse Events in Patients With BM

Adverse Events	Patients With BM (N = 17) Grades 3-4 (N)
Nausea	2
Neutropenia	5
Edema limbs	1
ALT/AST increase	4
Kidney infections	1
Pancreatitis	1
Lymphedema	2
Diarrhea	1
Fatigue	1
Syncope	1

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BM, brain metastases.

the median DOR was 24.9 months, and the median PFS was 9.6 months. Taletrectinib also exhibited a favorable safety profile, with low rates of treatment-related AEs, primarily elevated aspartate aminotransferase/alanine aminotransferase levels and diarrhea and mild neurologic AEs, such as dizziness.[39]

Zidesamtinib is a CNS-active, TRK-sparing, highly selective ROS1 TKI with activity against various *ROS1* fusions and resistance mutations, including *G2032R*. Preliminary results from the global ARROS-1 phase I trial (NCT05118789)[43] demonstrated promising efficacy and durability of zidesamtinib (25–150 mg) in 104 pretreated patients with *ROS1*-positive NSCLC, including those who had exhausted available therapies, harbored *ROS1* resistance mutations (e.g., *G2032R*), and/or had CNS metastases. The safety profile was favorable, with no dose-limiting toxicities or treatment discontinuations due to treatment-related AEs, which were primarily peripheral edema and transaminase elevations. The ORR was 65% in patients with known *ROS1 G2032R* mutations, 38% in those previously treated with repotrectinib, and 57% in patients with measurable intracranial metastases.[40] More extensive studies and real-world evidence are needed to explore the role of these second- and third-generation inhibitors in the treatment of *ROS1*-rearranged NSCLC, particularly in patients with BM. TKI resistance and BM development represent urgent challenges for patients with NSCLC and must be addressed by identifying the most brain-penetrant drugs and determining which patient subgroups are more likely to respond to specific agents.

This analysis has some limitations, including its post hoc nature and the limited sample size; however, it contributes to a better understanding of the role of crizotinib in patients with *ROS1*-rearranged NSCLC with or without BM, a condition for which limited data are currently available. These findings may serve as a foundation for further clinical studies and drug-specific comparisons on the effects of different targeted therapies in this population.

Conclusion

In conclusion, at a median follow-up of over 4 years, crizotinib has confirmed its strong activity in patients with *ROS1*-rearranged NSCLC. Patients with this mutation and BM at baseline have a higher risk of disease progression and death, highlighting the need for brain-penetrant drugs in the management of *ROS1*-rearranged NSCLC. Exploratory analyses are ongoing to correlate crizotinib sensitivity with additional biomarkers in patients' tissue or blood samples.

CRediT Authorship Contribution Statement

Lorenza Landi: Conceptualization, Study design, Research supervision, Data interpretation, Manuscript drafting.

Rita Chiari: Patient enrollment, Data acquisition, Critical revision of the manuscript for important intellectual content.

Marcello Tiseo: Patient enrollment, Data acquisition, Critical revision of the manuscript for important intellectual content.

Giulio Metro: Patient enrollment, Data acquisition, Critical revision of the manuscript for important intellectual content.

Filippo de Marinis: Patient enrollment, Data acquisition, Critical revision of the manuscript for important intellectual content.

Angelo Delmonte: Patient enrollment, Data acquisition, Critical revision of the manuscript for important intellectual content.

Silvia Novello: Patient enrollment, Data acquisition, Critical revision of the manuscript for important intellectual content.

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Francesco Grossi: Patient enrollment, Data acquisition, Critical revision of the manuscript for important intellectual content.

Andrea Torchia: Data analysis and interpretation.

Diana Giannarelli: Data analysis and interpretation.

Gloria Borra: Patient enrollment, Data acquisition, Critical revision of the manuscript for important intellectual content.

Francesca Mazzoni: Patient enrollment, Data acquisition, Critical revision of the manuscript for important intellectual content.

Sara Pilotto: Patient enrollment, Data acquisition, Critical revision of the manuscript for important intellectual content.

Federico Cappuzzo: Conceptualization, Study design, Research supervision, Data interpretation, Manuscript drafting.

All authors reviewed and approved the final version of the manuscript.

Disclosure

Dr. Landi received speakers' and consultants' fees from AstraZeneca, Pfizer, Bristol Myers Squibb, Novartis, Roche, Merck Sharp & Dohme, Amgen, Johnson & Johnson, AbbVie and Nuvalent. Dr. Tiseo received speakers' and consultants' fees from AstraZeneca, Pfizer, Eli Lilly, Bristol Myers Squibb, Novartis, Roche, Merck Sharp & Dohme, Boehringer Ingelheim, Takeda, Amgen, Merck, Sanofi, Johnson & Johnson, Pierre Fabre, BeiGene, and Daiichi Sankyo; received institutional research grants from AstraZeneca, Boehringer Ingelheim, and Roche; and received travel support from Amgen and Takeda. Dr. Morabito received speakers' and consultants' fees from AstraZeneca, Pfizer, Eli Lilly, Bristol Myers Squibb, Novartis, Roche, Merck Sharp & Dohme, Boehringer Ingelheim, Takeda, Regeneron, Johnson & Johnson, Pierre Fabre, and Amgen. Mazzoni received speakers' fee and served on the advisory board from AstraZeneca, Bristol Myers Squibb, Regeneron, Roche, Merck Sharp & Dohme, and Johnson & Johnson; received travel support from Roche and Merck Sharp & Dohme. Dr. Delmonte received speakers' and consultants' fees from AstraZeneca, Bristol Myers Squibb, Novartis, Takeda, Amgen, and Johnson & Johnson; institutional research grants from Merck Sharp & Dohme; and travel support from Pfizer, Takeda, Merck Sharp & Dohme, and Roche. Dr. Cortinovis received speakers' and consultants' fees from AstraZeneca, Pfizer, Bristol Myers Squibb, Novartis, Roche, Merck Sharp & Dohme, Boehringer Ingelheim, Takeda, Amgen, Regeneron, Johnson & Johnson, and BeiGene; travel support from Amgen and AstraZeneca. Dr. Bonanno received speaker fee/advisory board fees from AstraZeneca, Merck Sharp & Dohme, Bristol Myers Squibb, Roche, Pfizer, Novartis, Takeda, and Lilly; received research support from AstraZeneca; and is a coordinating PI and member of the steering committee for AstraZeneca. Dr. Pilotto received consulting fees from AstraZeneca, Merck Sharp & Dohme, Eli Lilly, Roche, Amgen, Pierre-Fabre, Daiichi Sankyo, Pfizer, Boehringer Ingelheim, and Regeneron; payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing, or educational events from AstraZeneca, Merck Sharp & Dohme, Eli Lilly, Roche, Amgen, Daiichi Sankyo, Boehringer Ingelheim, Johnson & Johnson, and Novartis; support for attending meetings and/or travel from Roche, Johnson & Johnson, and Amgen, outside the submitted manuscript. Dr. Cappuzzo received speakers' and consultants' fees from Amgen, AstraZeneca, Bayer, BeOne, Bristol Myers Squibb, Galecto, Illumina, Lilly, Mirati, Merck Sharp & Dohme, Novocure, OSE Immunotherapeutics, Pfizer, PharmaMar, Roche, Sanofi, Takeda, and ThermoFisher. The remaining authors declare no conflict of interest.

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Availability of Data and Material

All data generated or analyzed in this study are included in this article and/or its figures. Further enquiries can be directed to the corresponding author.

Ethics Approval

All procedures performed were in accordance with the 1964 Helsinki Declaration and its later amendments, Good Clinical Practice, and local applicable regulations. This study was approved by the local Ethics Committees of all the centers involved.

Consent to Participate

All subjects provided written informed consent before enrollment in the study.

Consent for Publication

All subjects provided written informed consent for the use of their data for publication.

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.2025.100909.

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