



Long-Term Efficacy and Safety of Entrectinib in ROS1 Fusion-Positive NSCLC

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ABSTRACT

Introduction: Entrectinib is an approved tyrosine kinase inhibitor (TKI) for *ROS1* fusion-positive NSCLC. An updated integrated analysis of entrectinib from the ALKA-372-001, STARTRK-1, and STARTRK-2 trials is presented, with substantially longer follow-up, more patients, and the first description of the median overall survival (OS). An exploratory analysis of entrectinib in *ROS1* fusion-positive NSCLC with the central nervous system (CNS)-only progression post-crizotinib is reported.

Methods: Adults with *ROS1* fusion-positive, locally advanced or metastatic NSCLC who received at least one dose of entrectinib and had 12 months or longer of follow-up were included in the analysis. Co-primary end points were confirmed objective response rate (ORR) and duration of response (DoR) by blinded independent central review. The data cutoff was on August 31, 2020.

Results: The efficacy-assessable population comprised 168 *ROS1* TKI-naïve patients. The median survival follow-up was 29.1 months (interquartile range, 21.8–35.9). The ORR was 68% (95% confidence interval [CI]: 60.2–74.8); the median DoR was 20.5 months. The median progression-free survival (PFS) was 15.7 months and the median OS was 47.8 months. In the 25 patients with measurable baseline CNS metastases,

the intracranial ORR was 80% (95% CI: 59.3–93.2), median intracranial DoR was 12.9 months, and median intracranial PFS was 8.8 months. Among 18 patients with CNS-only progression on previous crizotinib treatment, two achieved a partial response (11%) and four had stable disease (22%). In seven patients with measurable CNS disease from this cohort, the intracranial ORR was 14% (1 partial response).

Conclusions: Entrectinib is active and achieves prolonged survival in *ROS1* TKI-naïve patients with *ROS1* fusion-positive NSCLC. Modest activity is seen in patients with CNS-only progression post-crizotinib.

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Keywords: Entrectinib; Intracranial efficacy; NSCLC; *ROS1* fusions; Treatment post-crizotinib

Introduction

Gene rearrangements involving the tyrosine receptor kinase *ROS1* can result in constitutively active fusion

oncoproteins.^{1,2} *ROS1* fusions are found in a variety of tumor types, including 1% to 2% of NSCLC.^{1,3,4} Brain metastases are a common feature of *ROS1* fusion-positive NSCLC, detected in up to 40% of patients diagnosed with advanced disease.⁵⁻⁸

Crizotinib was the first tyrosine kinase inhibitor (TKI) to be approved by the U.S. Food and Drug Administration as a first-line treatment for *ROS1* fusion-positive NSCLC.⁹ However, crizotinib has limited ability to penetrate and remain in the central nervous system (CNS).¹⁰ In addition, the CNS is the first site of progression for approximately half of the patients with *ROS1* fusion-positive NSCLC receiving crizotinib.⁷ Thus, newer targeted therapies for the treatment of *ROS1* fusion-positive NSCLC must exhibit both overall and intracranial efficacy.

Entrectinib is a potent *ROS1* TKI that was specifically selected for its ability to cross the blood-brain barrier and remain within the CNS.¹¹⁻¹³ Results from an integrated analysis of three prospective, phase 1 or 2 clinical trials of entrectinib (ALKA-372-001: EudraCT 2012-000148-88; STARTRK-1: NCT02097810; STARTRK-2: NCT02568267) were previously published.^{14,15} In the efficacy-assessable population (N = 161; data cutoff May 2019), the objective response rate (ORR) was 67% (95% confidence interval [CI]: 59.3-74.3), with a median duration of response (DoR) of 15.7 months (95% CI: 13.9-28.6) and a median progression-free survival (PFS) of 15.7 months (95% CI: 11.0-21.1).¹⁵ Entrectinib also yielded durable intracranial responses in the subgroup of patients with baseline CNS metastases by blinded independent central review (BICR) (n = 46; intracranial ORR 52%; median intracranial DoR 12.9 mo). In patients without baseline CNS metastases (by the investigator; n = 105), only three had confirmed new CNS lesions while on treatment.¹⁵ Entrectinib was well tolerated across the studies with a manageable safety profile.¹⁵

Here, we report updated efficacy and safety findings from the integrated analysis of entrectinib in *ROS1* fusion-positive NSCLC, with almost a doubling of the survival follow-up duration (median survival follow-up: 29.1 versus 15.8 mo in the previous analysis¹⁵), the first estimation of median overall survival (OS), and additional patients. Furthermore, we provide the first published report of the activity of entrectinib in patients with intracranial-only progression post-crizotinib. Whereas the National Comprehensive Cancer Network (NCCN) guidelines recommend entrectinib as second-line therapy after progression on crizotinib, particularly for patients with CNS metastases,¹⁶ the activity of entrectinib in this population has not yet been reported. Finally, longitudinal changes in selected adverse effects such as the onset and improvement of neurologic and renal adverse effects are described.

Materials and Methods

Study Design and Patients

The full details of the three entrectinib studies included in our analysis (ALKA-372-001 and STARTRK-1 [phase 1]; STARTRK-2 [phase 2 global basket study]) have been published previously (study protocols are available online).^{14,17} Briefly, patients aged 18 years and older, with *ROS1* fusion-positive, locally advanced or metastatic measurable NSCLC at baseline (locally assessed by Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1¹⁸) and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2 were enrolled into one of the three studies. The enrollment cutoff for this analysis was July 31, 2019 and the clinical cutoff was August 31, 2020: patients in the efficacy analysis had 12 months or longer of follow-up from the first post-treatment initiation scan (≥ 13 months from enrollment). Patients who discontinued the study or died before 12 months' follow-up were also included.

In ALKA-372-001 and STARTRK-1, *ROS1* gene fusions were identified by local testing using fluorescence *in-situ* hybridization, quantitative polymerase chain reaction, or DNA- and RNA-based next-generation sequencing. In STARTRK-2, additional tumor tissue was collected by means of local testing (unless a biopsy was contraindicated) for independent next-generation sequencing. Patients with asymptomatic or pretreated and controlled CNS metastases were also eligible.

This analysis comprised data from two non-overlapping patient cohorts: a *ROS1* TKI-naïve cohort from the integrated analysis of entrectinib (N = 168; update to the previously published data sets),^{14,15} and a distinct data set of patients from STARTRK-2 who had previously received crizotinib, had CNS-only progression and did not discontinue crizotinib because of non-CNS disease progression or toxicity (N = 18; herein referred to as the post-crizotinib cohort). These are the first data to be reported for the post-crizotinib cohort. Patients with extracranial progression on previous crizotinib treatment were not enrolled in STARTRK-2, as these patients may potentially have mutations that also confer resistance against entrectinib.

All the studies included in this analysis were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. Written informed consent was obtained from all patients. Protocols for all studies were approved by relevant institutional review boards and ethics committees.

Treatment and Assessments

Patients received oral entrectinib 600 mg/d until documented radiographic disease progression (PD), unacceptable toxicity, or withdrawal of consent. Treatment

could continue at the investigator's discretion when there was evidence of clinical benefit despite radiographic PD. Computed tomography or magnetic resonance imaging scans were performed at screening, end-of-cycle 1 (4 weeks), and every 8 weeks thereafter and assessed by BICR using RECIST version 1.1. Patients with baseline CNS metastases (investigator-assessed) underwent brain scans at every tumor assessment. For patients without baseline CNS metastases, brain scans were only conducted when clinically indicated or when scans were routinely offered in clinical practice.

Safety was assessed by physical examination, laboratory tests, and adverse event (AE) monitoring. AEs were coded using the Medical Dictionary for Regulatory Activities (version 14.0 or higher for individual studies; version 21.0 for integrated safety analysis) and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). Dose reductions could occur in decrements of 200 mg, as needed, with no more than two reductions allowed.

Outcomes

The co-primary end points were confirmed ORR (i.e., proportion of confirmed complete and partial responders [CR and PR, respectively]) and DoR (measured from the date of first objective response to first documented radiographic PD or death by any cause), both assessed by BICR. Key secondary end points were PFS per BICR (i.e., time from the first dose to first documented radiographic PD or death from any cause), OS (i.e., time from the first dose to death from any cause), and safety.

Additional prespecified secondary end points included intracranial ORR (by RECIST version 1.1), intracranial DoR, and intracranial PFS, in patients with baseline BICR-assessed CNS metastases. Intracranial responses and progression were specifically assessed on CNS lesions. Per RECIST version 1.1, non-measurable CNS disease could only be categorized as CR, non-CR/non-PD, or PD. Time to CNS progression by BICR (deaths censored; only radiologically confirmed CNS progression counted as an event) was an exploratory end point, assessed in all patients and patients with or without investigator-assessed baseline CNS metastases.

Molecular Analysis of Resistance Mutations

Genomic analyses before and after entrectinib treatment were carried out using blood samples for circulating tumor DNA analyses to identify potential mechanisms of resistance in the post-crizotinib cohort. The analyses were carried out at Foundation Medicine (Cambridge, MA) using the FoundationOne Liquid CDx assay.¹⁹

Statistical Analyses

The efficacy-assessable population comprised all patients with *ROS1* fusion-positive NSCLC who had received at least 1 dose of entrectinib, had measurable disease at baseline, and had at least 12 months of follow-up from first posttreatment initiation tumor assessment (or scan). Patients in the post-crizotinib cohort had experienced CNS-only progression on crizotinib before enrolling in STARTRK-2. The safety-assessable population comprised all patients who had received at least 1 dose of entrectinib.

For response data, the number, percentage, and corresponding two-sided 95% Clopper-Pearson exact CIs were summarized. The Kaplan-Meier method was used to estimate time-to-event end points with corresponding 95% CIs. A competing risk analysis of CNS progression, with non-CNS progression and death as competing events, was carried out and cumulative incidence functions were estimated for each of these events.

Analysis of the post-crizotinib cohort was exploratory and used the same methods as the efficacy-assessable population. Patients were enrolled in this cohort under a two-stage sequential testing design. Up to 13 patients were to be enrolled sequentially in the first stage; this stage would be deemed successful on the fourth responder, and enrollment would continue to the second stage, otherwise, enrollment would be stopped.

All statistical analyses were performed using Statistical Analysis System software (v9.3 or higher; SAS Institute Inc., Cary, NC).

Results

Entrectinib in *ROS1* TKI-Naïve Patients

Baseline Demographics and Disease Characteristics.

The integrated efficacy-assessable population comprised 168 patients (Supplementary Fig. 1) and the median survival follow-up was 29.1 months (interquartile range [IQR]: 21.8–35.9). The baseline demographics and disease characteristics of the efficacy-assessable population are summarized in Supplementary Table 1. Overall, 63% (n = 105) of patients had received at least 1 previous line of treatment in the metastatic setting. Baseline CNS metastases (investigator-assessed) were present in 58 patients (35%) and confirmed by BICR in 48 patients. There were 27 patients (47%) with CNS metastases (by investigator) who received previous brain radiotherapy. Information on the type of radiotherapy received was available for 18 patients: 12 had whole-brain irradiation and six had stereotactic radiotherapy only. Thirteen different *ROS1* fusion partners were identified, the most frequent of which was CD74 (n = 72; 43%) (Supplementary Table 1).

Table 1. Overall Efficacy in Patients With ROS1 Fusion-Positive NSCLC Who Were ROS1 TKI-Naïve, With or Without CNS Metastases at Baseline, by Investigator

Efficacy Parameter	ROS1 TKI-Naïve Cohort		
	Efficacy-assessable Population (N = 168)	Baseline CNS Metastases ^a (n = 58)	No Baseline CNS Metastases ^a (n = 110)
Objective response, n (%; 95% CI)	114 (67.9, 60.2-74.8)	37 (63.8, 50.1-76.0)	77 (70.0, 60.5-78.4)
Best overall response, n (%)			
CR	22 (13.1)	5 (8.6)	17 (15.5)
PR	92 (54.8)	32 (55.2)	60 (54.5)
Stable disease	15 (8.9)	5 (8.6)	10 (9.1)
PD	14 (8.3)	8 (13.8)	6 (5.5)
Non-CR/non-PD	11 (6.5)	2 (3.4)	9 (8.2)
Missing or not assessable ^b	14 (8.3)	6 (10.3)	8 (7.3)
Duration of response			
Median, mo (95% CI)	20.5 (14.8-34.8)	14.9 (11.0-20.5)	34.8 (14.9-39.2)
Range, mo	2.2-55.2 ^c	2.2-42.3 ^c	2.8-55.2 ^c
Patients with event, n (%)	64 (56.1)	23 (62.2)	41 (53.2)
12-mo event-free probability, % (95% CI)	65 (56-74)	62 (45-78)	67 (56-77)
18-mo event-free probability, % (95% CI)	53 (44-63)	44 (27-62)	57 (45-68)
24-mo event-free probability, % (95% CI)	48 (38-58)	31 (14-49)	55 (43-66)
36-mo event-free probability, % (95% CI)	34 (22-46)	17 (0-34)	42 (27-57)
Progression-free survival			
Median, mo (95% CI)	15.7 (12.0-21.1)	11.8 (7.7-15.5)	21.1 (15.1-36.6)
Patients with event, n (%)	105 (62.5)	43 (74.1)	62 (56.4)
12-mo event-free probability, % (95% CI)	57 (49-64)	45 (32-59)	63 (53-72)
18-mo event-free probability, % (95% CI)	45 (37-53)	30 (18-43)	53 (43-63)
24-mo event-free probability, % (95% CI)	40 (32-48)	20 (8-32)	50 (40-60)
36-mo event-free probability, % (95% CI)	32 (24-40)	16 (4-28)	40 (29-50)
Overall survival			
Median, mo (95% CI)	47.8 (44.1-NE)	28.3 (18.2-NE)	NE (44.1-NE)
Patients with event, n (%)	54 (32.1)	26 (44.8)	28 (25.5)
12-mo event-free probability, % (95% CI)	81 (75-88)	75 (63-87)	85 (78-92)
18-mo event-free probability, % (95% CI)	74 (67-81)	64 (50-77)	79 (72-87)
24-mo event-free probability, % (95% CI)	71 (63-78)	59 (45-73)	76 (68-85)
36-mo event-free probability, % (95% CI)	61 (52-70)	43 (27-59)	71 (61-81)

Note: Objective response rate, duration of response, and progression-free survival by BICR (RECIST version 1.1).

^aCNS disease at baseline as judged by the investigator.

^bMissing or not assessable included patients with no postbaseline scans available, missing subsets of scans, or patients who discontinued before obtaining adequate scans to assess or confirm response.

^cCensored.

BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; NE, not estimable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.

Overall Efficacy With Entrectinib. In the efficacy-assessable population, the ORR was 68% (n/N = 114/168; 95% CI: 60.2–74.8), comprising 22 patients (13%) with a CR and 92 (55%) with a PR (Table 1). The ORR by fusion partner is detailed in Supplementary Table 2. The median time to response was 1.0 month (range: 0.7–26.6) (Supplementary Fig. 2). Most patients had a reduction in the size of their target lesions during treatment with entrectinib (Fig. 1A), including those with baseline CNS metastases. The ORR was also assessed in patients with and without investigator-assessed baseline CNS metastases and was 64% (95% CI: 50.1–76.0) and 70% (95% CI: 60.5–78.4) in these populations, respectively. Among all responders, the median DoR was 20.5 months (95% CI: 14.8–34.8), with 65% of patients (95%

CI: 56–74) having a DoR of at least 12 months (Table 1 and Supplementary Fig. 3). The median PFS was 15.7 months (95% CI: 12.0–21.1; 12-month PFS rate 57%) in the overall population (Fig. 1B), 11.8 months (95% CI: 7.7–15.5) in patients with investigator-assessed baseline CNS metastases and 21.1 months (95% CI: 15.1–36.6) in those without (Table 1). There were 54 patients (32%) who died during follow-up. The OS data are immature, with a median OS of 47.8 months (95% CI: 44.1–not estimable) and a 12-month OS rate of 81% (Table 1 and Fig. 1C).

Intracranial Efficacy With Entrectinib. Overall, 48 patients had baseline CNS metastases by BICR, of whom 25 had the measurable disease (Table 2). In patients

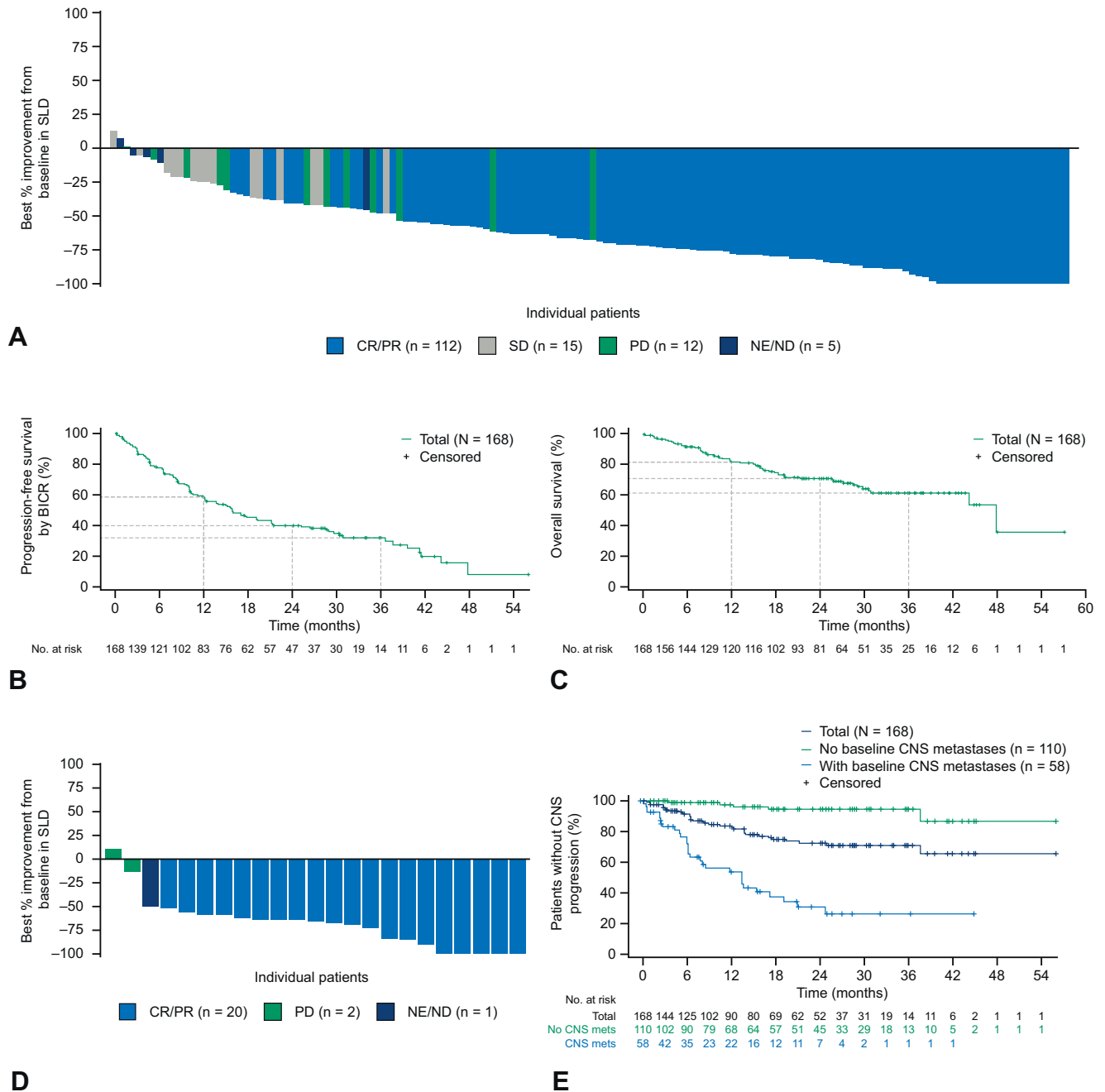


Figure 1. Efficacy in patients with *ROS1* fusion-positive NSCLC who were *ROS1* TKI-naïve (efficacy-assessable population). (A) Best overall response with entrectinib. (B) Time-to-event analysis for progression-free survival. (C) Time-to-event analysis for overall survival. (D) Best intracranial responses with entrectinib in patients with BICR-assessed measurable CNS metastases at baseline. (E) Time to CNS progression (deaths censored) in all patients, patients with baseline investigator-assessed CNS metastases, and patients without baseline investigator-assessed CNS metastases. Best response (panels A and D) was measured as the maximum percentage improvement in the SLD of identified target lesions compared with baseline. Patients with missing SLD change were excluded from the waterfall plots. Patients with new CNS lesions or unequivocal progression of nontarget lesions had an overall response classified as PD, even if the SLD of all lesions was reduced. As brain scans were not required per the protocol, CNS progression in patients without CNS metastases at baseline was detected through scans triggered by symptoms or performed routinely at the investigator’s discretion. BICR, blinded independent central review; CNS, central nervous system; CR, complete response; ND, not determined; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of longest diameters; TKI, tyrosine kinase inhibitor.

with measurable baseline CNS metastases, the intracranial ORR was 80% (n = 20; 95% CI: 59.3–93.2) (Table 2

and Fig. 1D), including three intracranial CRs. Intracranial responses were durable, with a median DoR of 12.9

Table 2. Intracranial Efficacy in Patients With ROS1 Fusion-Positive NSCLC Who Were ROS1 TKI-Naïve and Had CNS Metastases at Baseline by BICR

Efficacy Parameter	ROS1 TKI-Naïve Cohort; Patients With CNS Metastases at Baseline ^a	
	All Patients (Measurable and Non-measurable Disease) ^b (n = 48)	Measurable Disease (n = 25)
Objective response, n (%; 95% CI)	25 (52.1, 37.2-66.7)	20 (80.0, 59.3-93.2)
Best overall response, n (%)		
CR	8 (16.7)	3 (12.0)
PR	17 (35.4)	17 (68.0)
Stable disease	0	0
PD	5 (10.4)	2 (8.0)
Non-CR/non-PD	14 (29.2)	0
Missing or not assessable ^c	4 (8.3)	3 (12.0)
Duration of response		
Median, mo (95% CI)	12.9 (7.1-22.1)	12.9 (6.8-22.1)
Range, mo	1.8-27.6 ^d	1.8 ^d -25.4
Patients with event, n (%)	17 (68.0)	14 (70.0)
12-mo event-free probability, % (95% CI)	52 (32-73)	50 (27-73)
18-mo event-free probability, % (95% CI)	34 (15-54)	33 (10-55)
24-mo event-free probability, % (95% CI)	26 (5-46)	22 (0-44)
Progression-free survival		
Median, mo (95% CI)	8.4 (6.4-13.8)	8.8 (6.2-19.3)
Patients with event, n (%)	38 (79.2)	18 (72.0)
12-mo event-free probability, % (95% CI)	44 (29-59)	41 (21-62)
18-mo event-free probability, % (95% CI)	25 (12-38)	32 (12-51)
24-mo event-free probability, % (95% CI)	20 (7-32)	26 (7-45)

^aCNS disease at baseline as judged by BICR (RECIST v1.1).

^bAs per RECIST v1.1, non-measurable CNS disease could only be categorized as CR, non-CR/non-PD, or PD.

^cMissing or not assessable included patients with no postbaseline scans available, missing subsets of scans, or patients who discontinued before obtaining adequate scans to assess or confirm response.

^dCensored.

BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.

months in all patients with baseline CNS metastases and in the subset of patients with measurable disease (Table 2). The intracranial ORR in patients who had not received previous brain radiotherapy or had brain radiotherapy 6 months or longer before starting entrectinib was 48% (n = 13; 95% CI: 28.7–68.1; all patients with measurable and non-measurable baseline CNS disease, by BICR). In patients who had received previous brain radiotherapy shorter than 6 months before starting entrectinib, the intracranial ORR was 57% (n = 12; 95% CI: 34.0–78.2) (Supplementary Table 3).

In all patients with baseline CNS metastases (measurable and non-measurable), the median intracranial PFS, which counts both CNS progression and death as events, was 8.4 months (95% CI: 6.4–13.8); 12-month intracranial PFS rate was 44% (Table 2). In total, 38 (79%) patients had experienced an intracranial PFS event by data cutoff: 28 patients had PD and 10 patients died.

The time to CNS progression (deaths censored) was not estimable in the overall population and 13.6 months (95% CI: 6.7–19.3) in patients with investigator-assessed baseline CNS metastases (n = 58) (Fig. 1E).

Of the 110 patients without baseline CNS metastases, five reported new lesions (4.5%).

On the basis of a competing risks analysis, the risk of having CNS progression on entrectinib, without previous extracranial PD or death, at 12 months, was 39% in patients with investigator-assessed baseline CNS metastases, and 1.0% in those without (Supplementary Table 4). In this study, CNS PD did not necessarily equate to overall PD, depending on the target lesions.

Entrectinib in Patients With CNS-Only Progression After Crizotinib

Baseline Demographics and Disease Characteristics.

In total, 18 patients with CNS-only progression (by investigator) on crizotinib were included in the post-crizotinib cohort; recruitment to this cohort was stopped after the first stage of enrollment because of futility. Measurable CNS disease was not a requirement for inclusion in this cohort. Crizotinib could have been received at any previous line of treatment: 16 patients (89%) received crizotinib in the metastatic setting and two (11%) in the neoadjuvant or adjuvant setting. Fifteen patients (83%) received crizotinib

Table 3. Overall and Intracranial Efficacy in Patients With *ROS1* Fusion-Positive NSCLC and CNS-Only Progression^f on Previous Crizotinib Therapy

Efficacy Parameter	Post-crizotinib Cohort	
	Overall Efficacy End points ^a (N = 18)	Intracranial Efficacy End points ^b (n = 16)
Objective response, n (%; 95% CI)	2 (11.1, 1.4-34.7)	3 (18.8, 4.1-45.7)
Best overall response, n (%)		
CR	0	2 (12.5)
PR	2 (11.1)	1 (6.3)
Stable disease	4 (22.2)	2 (12.5)
PD	4 (22.2)	5 (31.3)
Non-CR/non-PD	6 (33.3)	5 (31.3)
Missing or not assessable ^c	2 (11.1)	1 (6.3)
Duration of response		
Range	7.4-29.3 ^d	7.4-23.9 ^d
Patients with event, n (%)	1 (50.0)	2 (66.7)
Progression-free survival		
Median, mo (95% CI)	4.7 (2.9-43.5)	4.5 (2.9-10.5)
Patients with event, n (%)	12 (66.7)	13 (81.3)
6-mo event-free probability, % (95% CI)	46 (22-71)	40 (15-65)
12-mo event-free probability, % (95% CI)	40 (16-64)	20 (0-40)
Overall survival		
Median, mo (95% CI)	43.5 (10.6-NE)	NA
Patients with event, n (%)	7 (38.9)	NA
6-mo event-free probability, % (95% CI)	76 (55-96)	NA
12-mo event-free probability, % (95% CI)	69 (46-92)	NA

^aPresence of CNS metastases, by investigator.

^bIntracranial efficacy end points were assessed in patients with CNS metastases by BICR (16 of 18 patients in the post-crizotinib cohort).

^cMissing or not assessable included patients with no postbaseline scans available, missing subsets of scans, or patients who discontinued before obtaining adequate scans to assess or confirm response.

^dCensored.

BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; NA, not applicable; NE, not estimable; PD, progressive disease; PR, partial response.

immediately before entrectinib, and three patients (17%) received it in other previous lines or settings.

The baseline characteristics of patients in the post-crizotinib cohort are summarized in [Supplementary Table 5](#). All patients had an ECOG PS of 0 (n = 10, 56%) or 1 (n = 8, 44%), and 50% (n = 9) of patients had received more than 2 previous lines of treatment in the metastatic setting. The median duration of previous crizotinib treatment was 12.4 months (range: 2.5–49.0 months). In total, 11 patients (61%) had a PR and four patients (22%) had stable disease as their best overall response to previous crizotinib treatment. Genomic analyses before entrectinib treatment (data from 15 patients) revealed a nonsense *ROS1* mutation of unknown significance in one patient. No additional mutations were identified post-entrectinib (data were obtained from 11 patients).

Overall Efficacy After CNS-Only Progression on Crizotinib. Two patients (11%) in the post-crizotinib cohort achieved a PR with entrectinib and there were no CRs ([Table 3](#) and [Fig. 2A](#)). The two patients with a PR had

a DoR of 7.4 and 29.3 months ([Supplementary Fig. 4](#)). There were 4 patients (22%) who had stable disease and all four experienced a decrease in tumor size with entrectinib treatment ([Fig. 2A](#)). The median PFS was 4.7 months (95% CI: 2.9–43.5) ([Table 3](#) and [Fig. 2B](#)). The OS data remain immature, with seven deaths (39%) reported during follow-up ([Table 3](#) and [Fig. 2C](#)). However, we do not expect these data to mature further as some patients have left the study and withdrawn consent. The 12-month OS rate was 69% (95% CI: 46–92).

Intracranial Efficacy. Intracranial efficacy end points were assessed in patients with baseline CNS metastases by BICR (n = 16) ([Table 3](#)). There were 3 patients (19%) who had an intracranial response (two CRs and one PR); the intracranial DoR ranged from 7.4 to 23.9 months. In the subgroup of seven patients with measurable baseline CNS disease, one (14%) had an intracranial response (a PR). The median intracranial PFS was 4.5 months (95% CI: 2.9–10.5; n = 16 patients with baseline CNS metastases by BICR) ([Table 3](#)), and the median time to CNS progression (death censored) was 4.5 months (95%

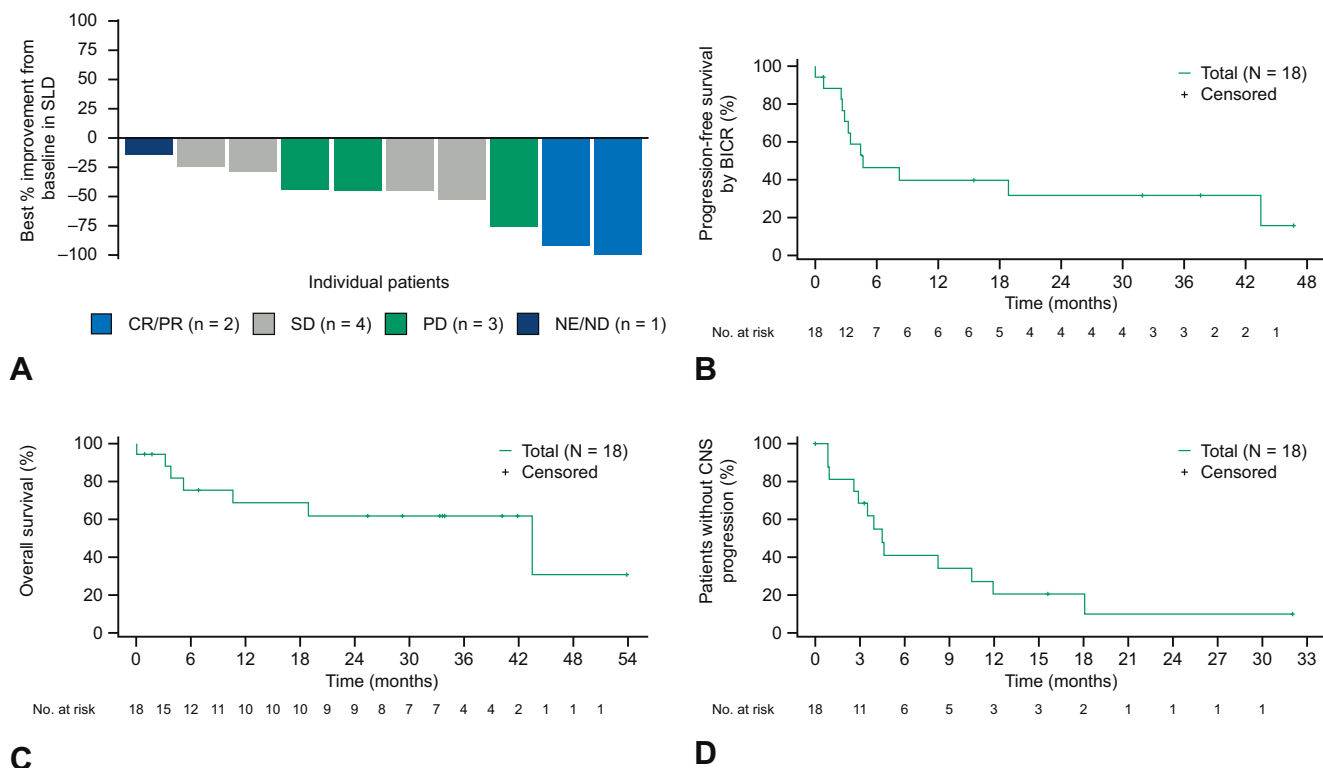


Figure 2. Efficacy in patients with ROS1 fusion-positive NSCLC and CNS-only progression on previous crizotinib therapy. (A) Best overall response with entrectinib. (B) Time-to-event analysis for progression-free survival. (C) Time-to-event analysis for overall survival. (D) Time to CNS progression in all patients (deaths censored). Best response (panel A) was measured as the maximum percentage improvement in the SLD of identified target lesions compared with baseline. Patients with missing SLD change were excluded from the waterfall plots. Patients with new CNS lesions or unequivocal progression of nontarget lesions had an overall response classified as PD, even if the SLD of all lesions was reduced. BICR, blinded independent central review; CNS, central nervous system; CR, complete response; ND, not determined; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of longest diameters.

CI: 2.9–11.9; n = 18 patients with CNS metastases by investigator) (Fig. 2D).

Safety

In total, 224 patients were included in the overall ROS1 fusion-positive NSCLC safety-assessable population. Most patients experienced at least 1 treatment-related AE (TRAE) (n = 211, 94%). The most frequent grade 1 to 2 TRAEs were dysgeusia (n = 90, 40%), dizziness (n = 82, 37%) and constipation (n = 71, 32%); the most frequent grade 3 TRAE was increased weight (n = 25, 11%) (Supplementary Table 6). Grade 4 TRAEs were rare and there were no TRAE-related deaths. Serious TRAEs occurred in 33 patients (15%) and the most frequent was pyrexia (n = 4, 2%) (Supplementary Table 7). The safety for the post-crizotinib cohort alone was in line with that of the overall ROS1 fusion-positive NSCLC population, with no new safety signals identified.

We also analyzed the time to onset and duration of selected AEs in the overall ROS1 fusion-positive NSCLC

safety-assessable population. The median time to onset of the first increased creatinine was 8.3 months (95% CI: 4.5–11.7). On the other hand, first neurologic toxicity was experienced early on in this population, with the median time to onset of 0.26 months (95% CI: 0.26–0.33). The most frequent neurologic TRAEs were dysgeusia (41%), dizziness (37%), and paresthesia (18%), and most were grade 1 to 2 (Supplementary Table 6). Two patients experienced one neurologic TRAE each that led to treatment discontinuation (limbic encephalitis and myoclonus).

The time from onset to the time of resolution for AEs of interest is detailed in Table 4. Liver dysfunction and hematological events were short-lived, resolving in less than 1 month on average, whereas eye disorders lasted for longer than 8 months. On average, neurologic toxicities lasted for 4.3 months.

There were 12 patients (5%) in the overall ROS1 fusion-positive NSCLC safety-assessable population who discontinued entrectinib because of TRAEs. The most common TRAEs leading to discontinuation were cardiac

Table 4. Time From Onset to Time of Resolution For Selected AEs of Potential Risk in the Overall *ROS1* Fusion-Positive NSCLC Safety Population

Median Time From Onset to Resolution of AEs, Months (95% CI)	Overall Safety-Assessable Population (N = 224)
QT interval prolongation	0.26 (0.2-1.0)
Clinical liver dysfunction	0.89 (0.5-1.0)
Hematological events	0.95 (0.8-1.9)
Increased creatinine	1.8 (0.9-3.8)
Pneumonitis events	2.8 (1.0-NE)
Neurologic toxicity	4.3 (2.3-7.3)
Eye disorders	8.3 (2.5-19.6)

Note: Includes patients who were *ROS1* TKI-naïve and patients who had had CNS-only progression on previous crizotinib therapy. AE, adverse event; CI, confidence interval; CNS, central nervous system; NE, not estimable; TKI, tyrosine kinase inhibitor.

disorders (n = 4; 2%). There were 82 patients (37%) who had a dose interruption and 75 patients (34%) who had a dose reduction because of TRAEs. The median dose intensity over the duration of the study was 91% (IQR: 66.7–99.5).

Discussion

We report updated efficacy and safety data from an integrated analysis of three entrectinib trials in patients with *ROS1* fusion-positive NSCLC, with an expanded population and longer follow-up compared with the previous analysis. With a median survival follow-up of 29.1 months, almost double the previous length of follow-up,¹⁵ responses were more durable than in the previous analysis (median DoR: 20.5 versus 15.7 mo, respectively). These more mature data reinforce those from the earlier data-cuts,^{14,15} and provide new observations. For example, more patients achieved a CR (13% versus 8.7%, respectively),¹⁵ suggesting that responses continued to deepen over time. Most importantly, we provide the first estimate of the median OS with entrectinib in patients with *ROS1* TKI-naïve *ROS1* fusion-positive NSCLC (47.8 mo, comparable to that with crizotinib [51.4 months]²⁰), although these data remain immature (~30% of patients had an event) and longer survival follow-up is needed. Our analysis also includes a cohort of patients who received entrectinib after CNS-only PD post-crizotinib. Whereas derived from a small number of patients, to date these results represent the most comprehensive data set from a clinical study in this subgroup of patients and should be taken into account when making treatment decisions.

The median PFS with entrectinib in our analysis (15.7 mo [95% CI 12.0–21.1]) was comparable to that reported for crizotinib (15.9 mo; N = 127)⁸ and ceritinib (19.3 mo; N = 30)²¹ and lower than that reported for lorlatinib (21.0 mo; N = 21),²² repotrectinib (24.6 mo; N = 11)²³ and taletrectinib (29.1 mo; N = 11).²⁴ However, it should be noted that the number of patients in this entrectinib study was much higher than in the studies of the other TKIs. Generally, cross-trial

comparisons should be viewed with caution because of the differences in study populations.

In total, 35% of the *ROS1* TKI-naïve patients had investigator-assessed baseline CNS metastases. In these patients who tend to have a poorer prognosis than those without CNS involvement,²⁵ the ORR was high (64%) and responses were durable (12-mo DoR rate: 62%). More importantly, the intracranial activity observed previously with entrectinib was maintained with the extended follow-up, with an intracranial ORR of 80% and a 12-month intracranial DoR rate of 50% in patients with measurable baseline CNS metastases (overall intracranial ORR: 52%; 12-mo DoR rate: 52%). This was also true for intracranial ORR in patients who had not received previous brain radiotherapy or had received previous brain radiotherapy at least 6 months before entrectinib treatment. As we highlighted previously,¹⁵ this suggests that the intracranial efficacy observed with entrectinib is unlikely confounded by the ongoing effects of brain radiotherapy. Of note, only five patients (4.5%) without baseline CNS metastases developed new brain lesions. Although brain scans were not mandated for these patients, these data suggest a role for entrectinib in delaying or preventing the development of brain metastases, even in patients without baseline CNS disease. More data would be needed to make any definitive conclusions.

The intracranial benefit seen with entrectinib is of clinical relevance, given that approximately 40% of patients with *ROS1* fusion-positive NSCLC will have CNS metastases at diagnosis.⁷ As noted previously, evidence of intracranial efficacy with other *ROS1* TKIs remains limited because of small sample sizes,¹⁵ with ORRs of 25% (2 out of 8 patients) for ceritinib,²¹ 64% (7 out of 11 patients) for lorlatinib²² and not reported for crizotinib, recognizing the caveats of cross-trial comparisons. No head-to-head trials have yet been conducted, although a randomized, open-label, phase 3 trial of entrectinib versus crizotinib in patients with *ROS1* fusion-positive NSCLC (NCT04603807)²⁶ has recently started recruiting.

For the first time, we also report data from a retrospective, exploratory analysis of entrectinib in patients with *ROS1* fusion-positive NSCLC who had CNS-only progression on crizotinib before entering the STARTRK-2 trial. We included this cohort of patients to determine the efficacy of entrectinib after the presumed pharmacologic failure of crizotinib in the CNS. Baseline characteristics for this post-crizotinib cohort were generally similar to those of the *ROS1* TKI-naïve population, with a few notable differences. Patients in the post-crizotinib cohort were overall more fit (none had ECOG PS 2, versus 10% of patients in the *ROS1* TKI-naïve population) albeit more heavily pretreated (17% versus 8% of patients had received at least 4 previous lines of systemic therapy in the metastatic setting, respectively).

Both the systemic and the intracranial efficacy of entrectinib were modest in the post-crizotinib cohort compared with the *ROS1* TKI-naïve cohort. This may reflect the development of cross-TKI resistance mechanisms in the CNS after previous crizotinib treatment, in addition to heavy pretreatment possibly increasing overall genomic complexity. Notably, lorlatinib also yielded a low ORR (35%) and short median PFS (8.5 months) in crizotinib-refractory patients with *ROS1* fusion-positive NSCLC.²² Unlike its activity in *ALK* fusion-positive lung cancers, lorlatinib is unable to target recalcitrant resistance mutations in *ROS1*, such as those involving the solvent front.² Acquired resistance to TKIs is still not fully understood. In an analysis of TKI-naïve patients from the STARTRK-2 study (data cutoff: May 2018), 26% (n = 5 out of 19) of patients had detectable acquired mutations in *ROS1* (*ROS1*^{G2032R}, *ROS1*^{F2004C/I}) at PD after treatment with entrectinib.²⁷ Although no known *ROS1*-acquired resistance mutations were identified in our study (analysis in the post-crizotinib cohort), other still unidentified mechanisms, such as epigenetic changes, may be involved. In addition, our molecular analysis was carried out on circulating tumor DNA, which may have limitations compared with the sequencing of tumor tissue.

Finally, the safety profile of entrectinib in this updated analysis was consistent with that of the previous two analyses.^{14,15} We observed an early onset of neurologic adverse effects that resolved in many patients within approximately 4 months. These were not unexpected given that entrectinib is a potent inhibitor of TRKA, TRKB, and TRKC, which maintain important neurologic roles in adults, including the regulation of balance, appetite (the most common grade 3 TRAE in this data set was weight gain) and pain thresholds.²⁸ A late onset of increased creatinine, which resolved within approximately 2 months, was also observed, consistent with the role of entrectinib as a MATE1 inhibitor in the kidney.²⁹

The inhibition of MATE1 can result in the false estimation of true kidney health if creatinine alone is used to calculate the glomerular filtration rate. As such, a patient's renal function may seem artificially impaired. Measuring the glomerular filtration rate by means of cystatin-C can provide a better estimate.²⁹

Limitations of this study include the relatively small sample size, the single-arm study design, and the lack of mandatory requirements for post-progression tissue collection.

Investigating the effect of entrectinib after CNS-only progression on crizotinib is relevant for clinical practice. The NCCN guidelines recommend crizotinib or entrectinib as preferred first-line TKIs, whereas lorlatinib is only recommended for use after progression on previous TKI treatment.¹⁶ After a recent update, the guidelines now also recommend entrectinib as second-line therapy after progression on crizotinib, particularly for patients with CNS metastases.¹⁶ Although there is some evidence of intracranial efficacy in the post-crizotinib cohort in this study, patients who receive entrectinib for CNS PD should be monitored carefully, preferably with an early scan, given the overall modest outcomes and low likelihood of response observed in this analysis.

In conclusion, entrectinib exhibited substantial systemic and intracranial efficacy in *ROS1* TKI-naïve patients with *ROS1* fusion-positive NSCLC. The overall efficacy and intracranial efficacy seen with entrectinib when patients have had CNS progression on previous crizotinib treatment was modest. On the basis of these data, physicians should carefully consider the most appropriate TKI treatment sequence for individual patients. To ensure maximal efficacy, entrectinib should be considered as a first-line treatment for patients with *ROS1* fusion-positive NSCLC.

CRediT Authorship Contribution Statement

Alexander Drilon: Investigation, Writing - original draft, Writing - review & editing.

Chao-Hua Chiu; Yun Fan, Byoung Chul Cho, Shun Lu, Myung-Ju Ahn, Matthew G. Krebs, Stephen V. Liu, Thomas John, Gregory A. Otterson, Daniel S. W. Tan, Tejas Patil, Rafal Dziadziuszko, Erminia Massarelli, Takashi Seto, Robert C. Doebele, Salvatore Siena: Investigation, Writing - review & editing.

Bethany Pitcher: Software, Formal analysis, Data curation, Writing - review & editing.

Nino Kurtsikidze: Writing - review & editing.

Sebastian Heinzmann: Data curation and interpretation; Writing - original draft; Writing - review & editing.

Role of the Sponsor

F. Hoffmann-La Roche Ltd was involved in the design of the study; the analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

Data Availability Statement

For eligible studies, qualified researchers may request access to individual patient-level clinical data through a data request platform. At the time of writing, this request platform is Vivli (<https://vivli.org/ourmember/roche/>). For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://go.roche.com/data_sharing. Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked because of a potential increase in the risk of patient re-identification.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at <https://doi.org/10.1016/j.jtocrr.2022.100332>.

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