



Published in final edited form as:

N Engl J Med. 2024 January 11; 390(2): 118–131. doi:10.1056/NEJMoa2302299.

Repotrectinib in *ROS1* Fusion-Positive Non-Small Cell Lung Cancer

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Disclosure forms provided by the authors are available with the full text of this article at [NEJM.org](https://www.nejm.org).

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Abstract

BACKGROUND—Currently approved ROS1 tyrosine kinase inhibitors (TKIs) for patients with *ROS1* fusion-positive (*ROS1*+) non-small cell lung cancer (NSCLC) have antitumor activity but tumors develop resistance and these agents have suboptimal intracranial activity. Repotrectinib is a next-generation ROS1 TKI with preclinical activity against *ROS1*+ cancers, including those with resistance mutations like *ROS1* G2032R.

METHODS—TRIDENT-1 is a registrational, first-in-human phase 1/2 study assessing the efficacy and safety of repotrectinib in advanced solid tumors, including *ROS1* NSCLC. The primary efficacy endpoint for phase 2 was the confirmed objective response rate (RECIST v1.1, blinded independent central review) and antitumor activity analysis combined phase 1 and 2 results. Response duration, progression-free survival, and safety were secondary endpoints.

RESULTS—A dose of 160 mg daily for 14 days, then 160 mg twice daily was selected after phase 1. In the TKI-naïve *ROS1* NSCLC cohort (n=71), the response rate was 79% (95% CI, 68–88); median response duration was 34.1 months (95% CI, 25.6-not estimable [NE]); median PFS was 35.7 months (27.4-NE). In the one TKI-pretreated and chemotherapy-naïve cohort (n=56), the response rate was 38% (95% CI, 25–52); median response duration was 14.8 months (7.6-NE); median progression-free survival was 9.0 months (6.8–19.6). In *ROS1* G2032R-mutant NSCLC (n=17), the response rate was 59% (95% CI, 33–82). In patients with solid tumors treated at the phase 2 dose (n=426), the most common treatment-related adverse events were dizziness (58%), dysgeusia (50%), and paresthesia (30%); 3% of patients discontinued repotrectinib due to treatment-related adverse events.

CONCLUSIONS—Repotrectinib demonstrated durable clinical activity in TKI-naïve and TKI-pretreated *ROS1*+ NSCLC. Adverse events were mainly low grade and compatible with long-term administration.

(Funding: Turning Point Therapeutics, a wholly owned subsidiary of Bristol Myers Squibb Company; TRIDENT-1 [ClinicalTrials.gov: NCT03093116](https://clinicaltrials.gov/ct2/show/study/NCT03093116)).

INTRODUCTION

ROS1 fusions are oncogenic drivers that occur in $\leq 2\%$ of non-small cell lung cancer (NSCLC).¹ Currently approved *ROS1* tyrosine kinase inhibitors (TKIs), crizotinib and entrectinib, present two major challenges.²

First, acquired resistance mutations develop in $\geq 50\%$ of patients and limit the durability of response.^{3,4} Neither drug is active against recalcitrant *ROS1* mutations such as the solvent-front mutation G2032R,² commonly acquired on treatment with several *ROS1* TKIs,^{3,4} including lorlatinib,⁵ a potential therapeutic option after crizotinib or entrectinib.

Second, intracranial activity can be suboptimal and brain metastases are common with *ROS1* fusion-positive (*ROS1*+) NSCLC.² Crizotinib achieves low cerebrospinal fluid concentrations⁶ and about half of crizotinib-treated patients have disease progression in the central nervous system (CNS) first.⁷ Whereas entrectinib provides improved CNS coverage relative to crizotinib, only 11% of patients with CNS-only progression on crizotinib respond to entrectinib.⁸

A TKI is needed that addresses both challenges. Repotrectinib is a next-generation *ROS1* and TRK TKI.⁹ Due to its compact macrocyclic structure, repotrectinib has a small tyrosine kinase binding interface, circumventing steric hindrance from *ROS1* resistance mutations; this enables potent inhibition of both wild-type and G2032R-mutant *ROS1* fusions compared to other *ROS1* TKIs.^{9,10} Additionally, repotrectinib was designed for enhanced intracranial activity; compared with entrectinib, repotrectinib achieved increased brain tumor shrinkage and prolonged survival in a patient-derived *ROS1*+ intracranial model.¹¹

TRIDENT-1 is a global, registrational, first-in-human, phase 1/2 study evaluating repotrectinib in patients with advanced, fusion-positive cancers. We report the efficacy of repotrectinib in patients with *ROS1*+ NSCLC (phase 1/2) and safety in patients treated at the recommended phase 2 dose.

METHODS

STUDY DESIGN AND TREATMENT

The phase 1 study, conducted at 8 sites across 3 countries, enrolled patients with locally advanced or metastatic solid tumors harboring *ROS1*, *NTRK1–3*, or *ALK* gene fusions and evaluated multiple dose levels and schedules of repotrectinib to establish the phase 2 dose.

The phase 2 study, conducted at 152 sites across 19 countries, enrolled six cohorts defined by molecular characteristics and treatment history: four cohorts with *ROS1*+ NSCLC, the focus of the current report, and two cohorts with *NTRK* fusion-positive solid tumors which are included in the safety population. The TRIDENT-1 ([NCT03093116](#)) study design is shown in Fig. S1.

In phase 2, patients received repotrectinib until disease progression, unacceptable toxicity, or consent withdrawal. Phase 1 dose escalation methods and phase 2 dose escalation criteria are described in the Supplementary Appendix.

PATIENTS

Patients were aged ≥ 18 years (≥ 12 years permitted for phase 2) with tumors harboring a *ROS1* fusion as identified by tissue-based local testing and confirmed by a central diagnostic laboratory (Supplementary Appendix). Patients who had ≥ 1 measurable target lesion per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 prospectively confirmed by blinded independent central review (BICR) from phase 1 and phase 2 were included in the efficacy analysis. Patients with measurable disease only in the CNS per RECIST v1.1 could enroll; asymptomatic CNS metastases (treated or untreated) were allowed. *ROS1* resistance mutations were identified by either local tissue- or central plasma-based next-generation sequencing. See Supplementary Appendix for detailed eligibility criteria and biomarker assay methods.

In phase 2, patients with *ROS1*+ NSCLC were divided into four cohorts: patients who received no prior *ROS1* TKI, patients who received one prior *ROS1* TKI but were chemotherapy-naïve, patients who received one prior *ROS1* TKI and platinum-based chemotherapy, and patients who received two prior *ROS1* TKIs but were chemotherapy-naïve. For efficacy analyses, patients were pooled from phase 1 (received repotrectinib at any dose) and phase 2 portions based on predefined criteria to provide a robust sample size for this rare population. The primary efficacy population included patients from the TKI-naïve cohort and the one TKI-pretreated and chemotherapy-naïve cohort. The remaining two *ROS1*+ cohorts (that were not part of the primary efficacy population) were patients from the one *ROS1* TKI and platinum-based chemotherapy-pretreated cohort and the two *ROS1* TKI-pretreated and chemotherapy-naïve cohort.

The efficacy analysis population included patients with *ROS1*+ NSCLC who started repotrectinib at any dose by October 15, 2021, allowing a minimum of ~ 14 months follow-up (12-month duration of response [DOR] follow-up) as of the December 19, 2022, data cut-off. The safety analysis population included all patients treated at the phase 2 dose regardless of tumor or fusion type.

ENDPOINTS

Primary endpoints were dose limiting toxicities, maximum tolerated dose, and/or recommended phase 2 dose for repotrectinib (phase 1) and confirmed objective response rate, as assessed by BICR using RECIST v1.1 (phase 2). Secondary endpoints included response duration, clinical benefit rate, progression-free survival, overall survival, intracranial response rate assessed by BICR per modified RECIST v1.1 in patients with

measurable baseline brain metastases, safety per Common Terminology Criteria for Adverse Events version 4.03, and patient-reported outcomes assessed by European Organisation for Research and Treatment Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) questionnaire. The EORTC QLQ-C30 is used to evaluate health-related quality of life, functioning, disease symptoms, and treatment-related side effects in patients with cancer. The EORTC QLQ-C30 contains 30 questions that incorporate nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a Global Health Status/Quality of Life scale. Several single-item symptom measures are also included (dyspnea, insomnia, appetite, constipation, diarrhea, and financial impact).¹² A 10-point change from baseline in an item or domain is considered a clinically meaningful within-patient change.^{13,14} Exploratory endpoints included confirmed response rate in patient subgroups and repotrectinib resistance alterations. Tumor assessments occurred at prespecified intervals until disease progression; in phase 2, brain imaging was performed at all tumor assessments regardless of baseline brain metastasis status. See Supplementary Appendix for additional details.

STATISTICAL ANALYSIS

Confirmed response rate and intracranial response rate were reported as a proportion of patients, with confidence intervals (Cis) using the two-sided 95% Clopper-Pearson method. Time-to-event endpoints were estimated by Kaplan-Meier method with 95% Cis using Greenwood variance estimate. Sample size calculations, prespecified subgroup analyses, and definitions for time-to-event outcomes are described in the Supplementary Appendix.

STUDY OVERSIGHT

Turning Point Therapeutics, a wholly owned subsidiary of Bristol Myers Squibb Company, sponsored and designed the study with input from the investigators. As part of the site agreement, investigators agreed to keep all aspects and outcomes of the trial confidential. The study was conducted in accordance with the US Food and Drug Administration regulations and the International Council for Harmonisation E6 Guideline for Good Clinical Practice. The protocol was reviewed by appropriate health authorities and institutional committees. All patients provided written informed consent. The clinical safety committee (phase 1), data monitoring committee (phase 2), and Turning Point Therapeutics provided study oversight. All authors participated in data interpretation, reviewed, and approved the manuscript before submission. The first draft of the manuscript was written by the first and last authors, with medical writing support funded by the sponsor.

RESULTS

From February 27, 2017 through December 19, 2022, 520 patients enrolled and 519 received one or more doses of repotrectinib (Fig. S2); 103 were treated in phase 1 and 416 were treated in phase 2. Phase 1 dosing and schedules (Table S1), and dose escalation data are reported in the Supplementary Appendix. Four dose-limiting toxicities were observed in two patients who received 160 mg twice daily (grade 3 dizziness, dyspnea, and hypoxia) and one patient who received 240 mg once daily (grade 3 dizziness). The maximum tolerated dose was not reached. A dose of 160 mg once daily for 14 days, then 160 mg twice daily was

selected for phase 2. Rationales for dose selection and initial daily dosing are detailed in the Supplementary Appendix.

ACTIVITY IN *ROS1*+ NSCLC

Of 352 patients with *ROS1*+ NSCLC who received repotrectinib, 150 (43%) remained on treatment at the data cut-off; the most common reason for discontinuation was disease progression (106 of 352 patients [30%]; Fig. S2). Across the *ROS1*+ NSCLC cohorts, 171 patients received ≥ 1 dose of repotrectinib and had ≥ 14 months of follow-up. Treatment exposure, including the proportion of patients treated at the phase 2 dose, is summarized in Table S2.

The primary efficacy population included 71 patients in the TKI-naïve cohort and 56 patients in the one TKI-pretreated and chemotherapy-naïve cohort (Table 1). In both cohorts, the median age was 57 years. The majority were female (61%, TKI-naïve; 68%, one TKI-treated and chemotherapy-naïve) never smokers (63%; 64%) with stage IV (94; 98) adenocarcinomas (97%; 95%); 24% and 46% had baseline brain metastasis per BICR. Patients in the one TKI-pretreated and chemotherapy-naïve cohort had mainly received prior crizotinib (82%) or entrectinib (16%). Baseline characteristics for the additional cohorts are summarized in Table S3.

In the TKI-naïve cohort, 56 of 71 patients had a confirmed response (79%, 95% CI, 68–88); seven patients (10%) had a complete response and 49 (69%) had a partial response [Table 2, Fig. 1A]. The median time to response was 1.8 months (range, 0.9–5.6). With 24.0 months median follow-up (range, 14.2–66.6), the median response duration was 34.1 months (95% CI, 25.6 to not estimable [NE]; Fig. S3A). The estimated 18-month response duration was 79% (95% CI, 68–90). The median progression-free survival was 35.7 months (95% CI, 27.4-NE; Fig. 1B). The estimated 18-month progression-free survival was 70% (95% CI, 59–81). The estimated 18-month overall survival was 88% (95% CI, 80–96; Fig. S4A). Duration of treatment is shown in Fig. S5A. Among 51 patients without any prior chemotherapy in this cohort, the response rate was 82% (95% CI, 69–92) (Table S4). In patients treated at the phase 2 dose ($n=63$), the response rate was 78% (95% CI, 66–87) and the estimated 18-month progression-free survival was 70% (95% CI, 58–82; Table S5, Fig. S6A, B).

In the one TKI-pretreated and chemotherapy-naïve cohort, the response rate was 38% (95% CI, 25–52), with 21 of 56 patients with confirmed responses (CR, $n=3$ [5%]; PR, $n=18$ [32%]; Table 2, Fig. 1C). The median time to response was 1.8 months (range, 1.6–3.6). With 21.5 months median follow-up (range, 14.2–58.6), the median response duration was 14.8 months (95% CI, 7.6-NE; Fig. S3B). The estimated 12-month response duration was 56% (95% CI, 34–77). The median progression-free survival was 9.0 months (95% CI, 6.8–19.6; Fig. 1D). The estimated 12-month progression-free survival was 41% (95% CI, 27–56). The median overall survival was 25.1 months (95% CI, 17.8-NE; Fig. S4B). The estimated 12-month overall survival was 69% (95% CI, 56–82). Duration of treatment is shown in Fig. S5B. Responses were seen in 18 of 46 (39%) patients who received prior crizotinib and 2 of 9 (22%) who received prior entrectinib (Table S6). In patients treated at the phase 2 dose ($n=53$), the response rate was 38% (95% CI, 25–52), median response

duration was 14.8 months (95% CI, 7.5–NE); median progression-free survival was 9.0 months (95% CI, 6.8–19.6), and the estimated 12-month progression-free survival was 42% (95% CI, 28–57; Table S5, Fig. S6C, D). Response rates in key patient subgroups (age, race, region, and ECOG performance status) are in Table S7.

The response rate was 42% in the one TKI and chemotherapy-pretreated cohort (n=26), with a median response duration of 7.4 months (95% CI, 4.4–NE; Fig. S7A, B); the response rate was 28% in the two TKI-pretreated and chemotherapy-naïve cohort (n=18), with a median response duration of 7.4 months (95% CI, 3.5–NE; Fig. S7C, D). Subsequent therapies for all cohorts are summarized in Table S2. Of 17 patients across all TKI-pretreated cohorts with baseline *ROS1* G2032R mutation, ten had a confirmed response (59%; 95% CI, 33–82; Table S8, Fig. S8).

INTRACRANIAL ACTIVITY IN *ROS1*+ NSCLC

Across cohorts, systemic (intracranial and extracranial) repotrectinib activity was observed in patients with and without baseline brain metastasis (Table S9). Of patients with measurable baseline brain metastasis (phase 2 only), intracranial responses were observed in eight of 9 patients (89%; 95% CI, 52–100) in the TKI-naïve cohort and five of 13 patients (38%; 95% CI, 14–68) in the one TKI-pretreated and chemotherapy-naïve cohort; estimated 12-month intracranial response duration was 83% (95% CI, 54–100) and 60% (95% CI, 17–100), respectively (Table 2, Fig. S9, Fig 2A, B). Among those without baseline brain metastasis, the estimated 12-month intracranial progression-free survival was 91% (95% CI, 83–100) in the TKI-naïve cohort (n=54) and 82% (95% CI, 65–98) in the one TKI-pretreated and chemotherapy-naïve cohort (n=30; Fig. 2C, D).

REPOTRECTINIB RESISTANCE

An exploratory analysis of paired baseline and post-progression circulating tumor DNA samples was performed. In TKI-naïve patients (n=14) who progressed on repotrectinib, no emergent *ROS1* resistance mutations were observed. In TKI-pretreated patients (n=43) who progressed on repotrectinib, five emergent *ROS1* G2032R and one emergent *ROS1* L2086F mutations were identified in six patients; two of these also had a baseline *ROS1* mutation (one F2004I, one L2026M; Table S10).

SAFETY

Among 426 patients who were treated at the phase 2 dose (Table S11), the most common treatment-related adverse events of any grade (preferred terms) were dizziness (58%), dysgeusia (50%), and paresthesia (30%) [Table 3]. Grade ≥ 3 adverse events occurred in 122 patients (29%). The most common grade ≥ 3 adverse events were anemia (4%) and increased blood creatine phosphokinase (4%). Most adverse events were grade 1–2 (67%) and nervous system disorders were most common (86% any grade, 5% grade ≥ 3); grade ≥ 3 dizziness occurred in 11 patients (3%), and no patient discontinued repotrectinib due to dizziness. Pneumonitis was uncommon (11 patients, 3% any grade; 1% grade ≥ 3). Median (range) times to onset of most common adverse events of special interest (composite terms) were 7 days (1–526) for dizziness, 8 days (1–589) for dysgeusia, and 14 days (1–827) for paresthesia (Table S12). Any grade and grade ≥ 3 treatment-emergent adverse events are

reported in Tables 3 and S13. Overall incidence of adverse events by key subgroups (age, race, region, and ECOG performance status) were consistent with the overall population (Table S14).

Adverse events led to dose reduction in 163 patients (38%), dose interruption in 213 patients (50%), and treatment discontinuation in 31 patients (7%). The most common adverse event (preferred term) leading to dose reduction (11%) or dose interruption (8%) was dizziness. The most common adverse event leading to treatment discontinuation was pneumonitis (1%). Fatal adverse events were reported in 19 patients (4%); none were treatment-related (Table 3). Electrocardiograms from 398 patients showed no clinically significant effects on cardiac repolarization (QTcF), heart rate, PR interval, or QRS duration.

PATIENT-REPORTED OUTCOMES

Among 156 patients (ROS1 TKI-naïve, n=63; pooled from the three ROS1 TKI-pretreated cohorts, n=93) with baseline and post-baseline EORTC-QLQC30 assessments, completion rates were high (>86%) through cycle 12 and ranged from 64% to 100% between cycles 13 and 22. In the TKI-naïve cohort, the mean baseline global health status score was 61.38, with 65% and 60% of patients demonstrating stable (<10 point change in either direction from baseline) or improved (≥ 10 point increase from baseline) scores at cycles 12 and 22, respectively. In the pooled TKI-pretreated cohorts, baseline global health status score was 58.15, with 71% and 70% showing stable or improved score at cycles 12 and 22. The breakdown of stable, improved, or worsening global health status scores is included in the Supplementary Appendix. The mean changes from baseline scores of global health status score at each cycle are shown in Fig. S10.

DISCUSSION

In this phase 1–2 study, repotrectinib demonstrated activity in patients with *ROS1*+ NSCLC. In TKI-naïve patients, the response rate was 79% and response rates remained high regardless of prior chemotherapy treatment. Many responses were deep and occurred quickly, with a median time to response (1.8 months) coinciding with the first scan. Activity appeared durable, with a median response duration of 34.1 months and a median progression-free survival of 35.7 months. Of note, the median response duration and median progression-free survival of entrectinib are 20.5 months and 15.7 months, respectively⁸; the values for crizotinib are 24.7 months and 19.3 months, respectively.¹⁵

Repotrectinib was likewise active in TKI-pretreated patients with *ROS1*+ NSCLC, a population in which approved TKIs have limited activity²; responses were observed regardless of what prior TKI was received (crizotinib or entrectinib). The response rate of 59% in *ROS1* G2032R-mutant NSCLC confirms repotrectinib's preclinical activity against *ROS1* solvent-front mutations.^{9,10} Other ROS1 TKIs such as crizotinib, entrectinib, and lorlatinib have not demonstrated substantial activity against this mutation.^{2–5} Additional research will be needed to inform appropriate sequencing of targeted therapies.

Furthermore, in TKI-naïve patients who progressed on repotrectinib, no emergent *ROS1* resistance mutations were observed. While emergent *ROS1* mutations were identified in

six of 43 TKI-pretreated patients who progressed on repotrectinib, these data should be interpreted with caution due to sensitivity limitations of detection assays. Additional research is needed to understand potential bypass mechanisms.

Repotrectinib was active against intracranial disease, consistent with its preclinical data.^{9,11} Intracranial response rates were generally comparable with systemic disease response rates in each cohort. In patients with measurable baseline brain metastasis, the 12-month intracranial response duration was 83% in TKI-naïve patients and 60% in chemotherapy-naïve patients pretreated with one TKI. In patients without baseline brain metastasis, few developed brain metastasis (12-month intracranial progression-free survival of 91% and 82%, respectively), suggesting that repotrectinib may delay or prevent the development of brain lesions. Overall, intracranial response rates with repotrectinib were numerically higher than those seen with entrectinib in the TKI-naïve setting and similar to those observed with lorlatinib following prior crizotinib treatment, though cross-trial comparisons should be interpreted with caution.^{8,16}

Repotrectinib had primarily grade 1–2 treatment-related adverse events. Dizziness was the most common (58%), but most events were low grade and manageable with dose reductions or interruptions; discontinuation of repotrectinib due to dizziness was not reported. Nervous system disorders such as dizziness and ataxia are well characterized consequences of TRK inhibition. Similar to entrectinib,¹⁷ repotrectinib inhibits TRKA/B/C receptors, which are involved in the development and maintenance of the nervous system.¹⁸ Overall, these neurologic adverse events were managed with supportive care measures according to the protocol recommendations and similar to previously published guidance.¹⁷

This study is limited by its single arm design and small patient numbers due to the rare population. Time-to-event efficacy end points and safety will continue to be followed to characterize long-term outcomes. Whereas other next-generation ROS1 inhibitors (e.g., taletrectinib, NVL-520) are in development,^{19,20} this registrational study of repotrectinib offers important insights into the activity of next-generation, CNS active ROS1 inhibitors.

In conclusion, repotrectinib demonstrated high response rates and durable activity in *ROS1*+ NSCLC, including patients with TKI-naïve and TKI-pretreated tumors, *ROS1* G2032R resistance mutations, and brain metastases. Repotrectinib was mainly associated with low grade adverse events. Side effects related to decreased TRK activity were expected, similar to that of other TKIs that inhibit TRK. Comparative studies may be needed to define the role of repotrectinib in the management sequence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We thank the patients and families who have made this study possible and the clinical study teams who participated. All authors contributed to and approved the manuscript; writing and editorial assistance were provided by Elaine Heatherington, PhD, of Bio Connections LLC, funded by Bristol Myers Squibb Company.

SOURCE OF SUPPORT

Turning Point Therapeutics, a wholly owned subsidiary of Bristol Myers Squibb Company, sponsored the study and funded writing and editorial support. Alexander Drilon was supported in part by the National Cancer Institute and National Institutes of Health (1R01CA273224-01, P30 CA008748). Matthew Krebs acknowledges support from National Institute for Health Research (NIHR) Manchester Biomedical Research Centre, NIHR Manchester Clinical Research Facility at The Christie and Manchester Experimental Cancer Medicine Centre (Manchester, UK).

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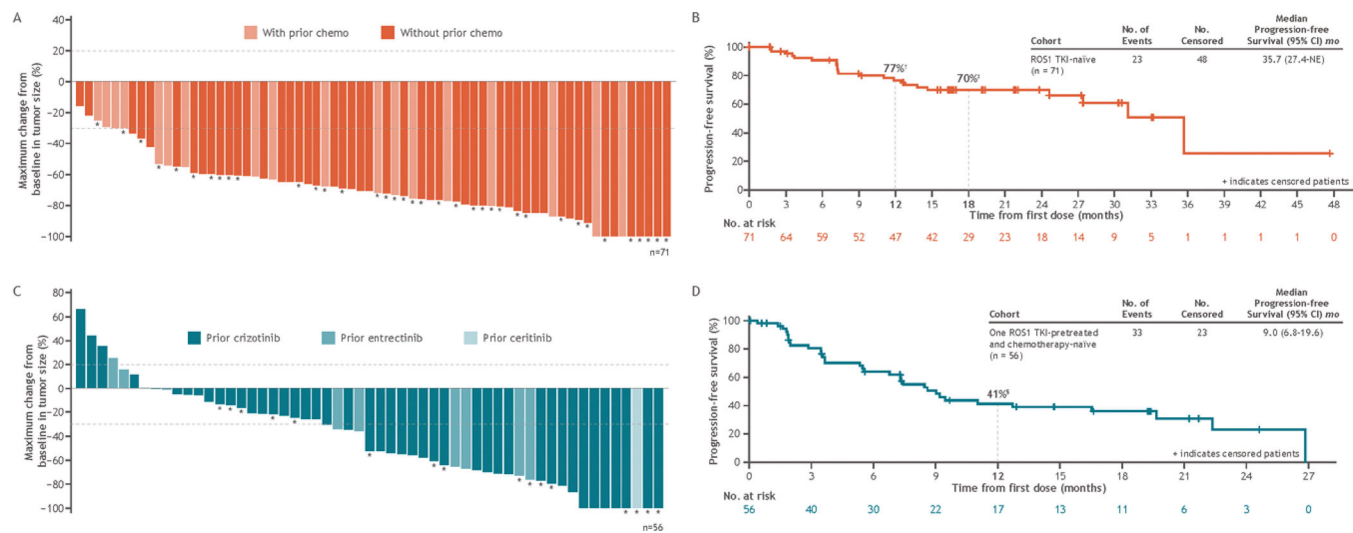


Figure 1. Efficacy of Repotrectinib Therapy in the Primary Efficacy Cohorts. Change in tumor burden (A) and progression-free survival (B) in the ROS1 TKI-naïve cohort. Change in tumor burden (C) and progression-free survival (D) in the one ROS1 TKI-pretreated and chemotherapy-naïve cohort. Waterfall plots only include patients with baseline and post-baseline target lesion measurements. * Treatment ongoing. † 95% CI, 66–87. ‡ 95% CI, 59–81. § 95% CI, 27–56.

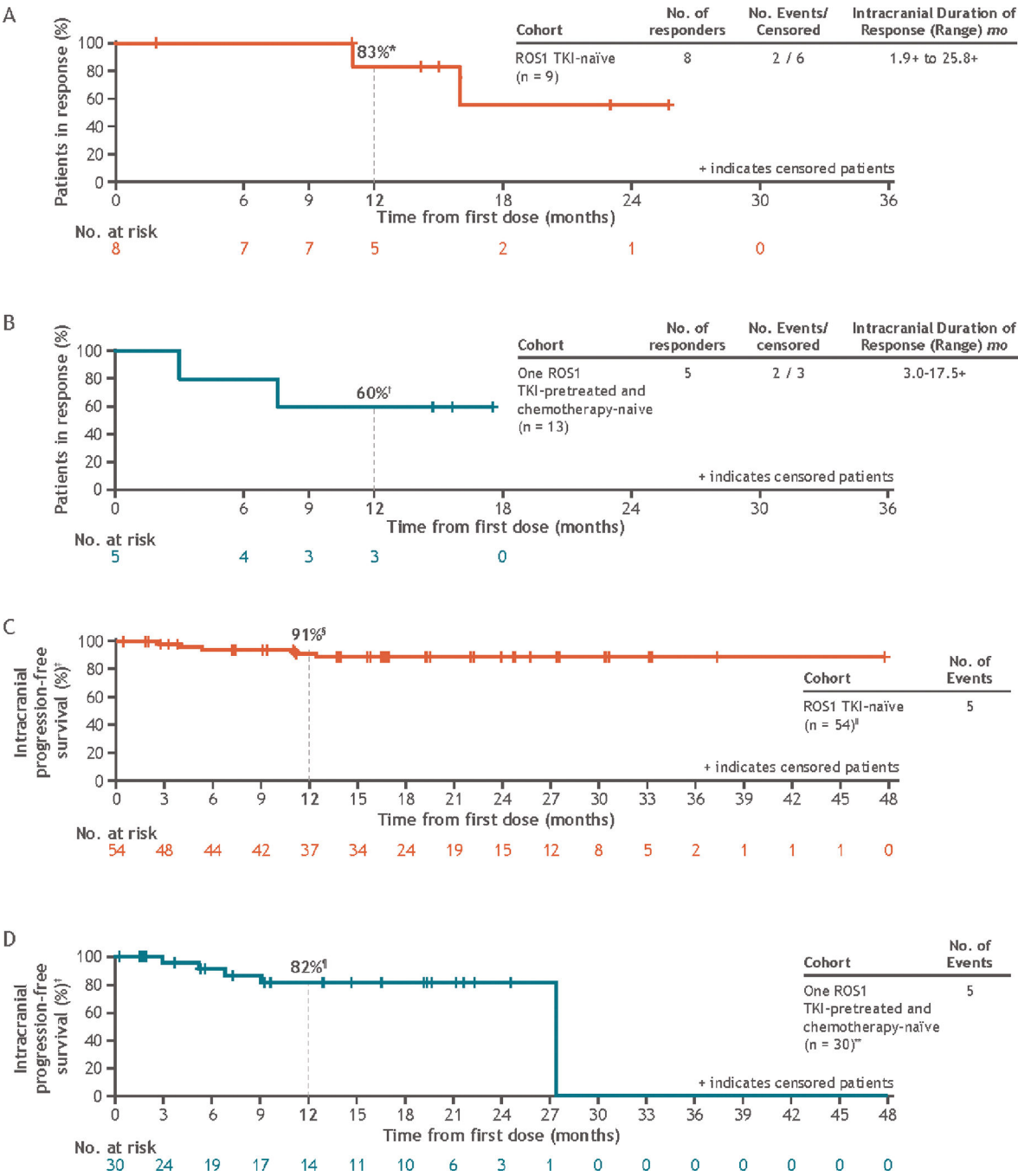


Figure 2. ROS1 G2032R and Intracranial Efficacy. Intracranial duration of response in patients with measurable baseline brain metastasis for the ROS1 TKI-naïve (A) and one ROS1 TKI-pretreated and chemotherapy-naïve (B) cohorts. Intracranial progression-free survival in patients without baseline brain metastases for the ROS1 TKI-naïve (C) and one ROS1 TKI-pretreated and chemotherapy-naïve (D) cohorts. * 95% CI, 54–100. † 95% CI, 17–100. ‡ Exploratory analysis of intracranial progression-free survival based on time of development of new brain lesions as assessed by

BICR. § 95% CI, 83–100. || Includes patients from phase 1 (n=6) and phase 2 (n=48). ¶ 95% CI, 65–98. ** Includes patients from phase 1 (n=3) and phase 2 (n=27).

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Table 1.

Baseline Patient Characteristics by Cohort in the Primary Efficacy Population

	ROS1 TKI-naïve (n=71)*	1 ROS1 TKI-pretreated and chemotherapy-naïve (n=56) ^{†,‡}
Age		
Median (range) — yr	57 (28–80)	57 (33–78)
≥18 to <65 — no. (%)	52 (73)	41 (73)
≥65 — no. (%)	19 (27)	15 (27)
Sex — no. (%)		
Female	43 (61)	38 (68)
Male	28 (39)	18 (32)
Region — no. (%)		
United States	11 (16)	17 (30)
Asia	41 (58)	23 (41)
Other [§]	19 (27)	16 (29)
ECOG performance status — no. (%)		
0	24 (34)	18 (32)
1	47 (66)	38 (68)
Metastatic disease stage — no. (%)		
Stage IV	67 (94)	55 (98)
Adenocarcinoma — no. (%)	69 (97)	53 (95)
Smoking history — no. (%)		
Never smoked	45 (63)	36 (64)
Current smoker	2 (3)	1 (2)
Former smoker	16 (22)	16 (29)
Baseline brain metastasis — no. (%) [¶]		
Yes	17 (24)	26 (46)
No	54 (76)	30 (54)
Prior lines of systemic therapy no. (%)		
0	51 (72)	0
1	16 (22)	56 (100)
2	2 (3)	0
≥3	2 (3)	0
Prior lines of chemotherapy with or without immunotherapy — no. (%)		Not applicable
0	51 (72)	
1	17 (24)	
2	2 (3)	
≥3	1 (1)	
Prior lines of immunotherapy alone — no. (%)		Not applicable

	ROS1 TKI-naïve (n=71) [*]	1 ROS1 TKI-pretreated and chemotherapy-naïve (n=56) ^{†,‡}
0	69 (97)	
1	2 (3)	
Prior ROS1 tyrosine kinase therapy — no. (%)		
Crizotinib	Not applicable	46 (82)
Entrectinib		9 (16)
Ceritinib		1 (2)

^{*}Phase 1, n=8; phase 2, n=63.

[†]Phase 1, n=3; and phase 2, n=53.

[‡]No prior lines of chemotherapy or immunotherapy are allowed.

[§]Includes Australia, Canada, and Europe.

[¶]Assessed by blinded independent central review.

Table 2.

Overall Efficacy Summary According to Blinded Independent Central Review

	ROS1 TKI-naïve (n=71)	1 ROS1 TKI-pretreated and chemotherapy-naïve (n=56)
Objective response rate [*]		
No. responders (CR + PR)	56	21
Percent (95% CI)	79 (68, 88)	38 (25, 52)
Best overall response [*] — no. (%)		
Complete response	7 (10)	3 (5)
Partial response	49 (69)	18 (32)
Stable disease	11 (16)	23 (41)
Progressive disease	2 (3)	9 (16)
Not evaluable	0	2 (4)
Median time to response (range) mo	1.8 (0.9–5.6)	1.8 (1.6–3.6)
Median duration of response (95% CI) — mo	34.1 (25.6, NE)	14.8 (7.6, NE)
Clinical benefit rate		
No. with clinical benefit	67	44
Percent (95% CI)	94 (86, 98)	79 (66, 88)
Median progression-free survival (95% CI) — mo	35.7 (27.4, NE)	9.0 (6.8, 19.6)
Median overall survival (95% CI) mo	NE (44.4, NE)	25.1 (17.8, NE)
Intracranial objective response rate [†]		
No. patients with measurable baseline brain metastases	9 ^{‡,§}	13 [¶]
No. patients with response	8	5
Intracranial response % (95% CI)	89 (52, 100)	38 (14, 68)
Complete response	1 (11)	0
Partial response	7 (78)	5 (38)
Median intracranial duration of response (95% CI) — mo	NE (16.0, NE)	NE (3.0, NE)

Clinical benefit rate was a prespecified secondary endpoint as assessed by BICR per RECIST v1.1. It was defined as the proportion of patients with a best overall response of confirmed CR, confirmed PR, or stable disease. CR denotes complete response; NE denotes not estimable; PR denotes partial response; TKI denotes tyrosine kinase inhibitor.

^{*} Per RECIST v1.1.

[†] Per modified RECIST v1.1.

[‡] One patient was not evaluable due to no post-baseline scan.

[§] Two of two patients with prior intervention on central nervous system lesions within 60 days had a partial response.

[¶] Two of seven patients with prior intervention on central nervous system lesions within 60 days had a partial response.

Table 3.

Adverse Events Reported with Repotrectinib at the Recommended Phase 2 Dose

Event, n (%)	Treatment-Emergent Adverse Events (N=426)		Treatment-Related Adverse Events (N=426)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
<i>no. of patients (%)</i>				
Any adverse event	422 (99)	216 (51)	409 (96)	122 (29)
Any grade adverse event occurring in ≥15% of patients				
Dizziness	264 (62)	11 (3)	245 (58)	11 (3)
Dysgeusia	224 (53)	0	213 (50)	0
Constipation	162 (38)	1 (<1)	111 (26)	0
Anemia	160 (38)	33 (8)	111 (26)	16 (4)
Paresthesia	143 (34)	3 (1)	126 (30)	3 (1)
Dyspnea	117 (28)	27 (6)*	36 (8)	2 (1)
Alanine aminotransferase increase	99 (23)	8 (2)	76 (18)	6 (1)
Fatigue	95 (22)	4 (1)	70 (16)	3 (1)
Ataxia	90 (21)	1 (<1)	87 (20)	0
Aspartate aminotransferase increase	89 (21)	9 (2)	75 (18)	6 (1)
Nausea	85 (20)	3 (1)	51 (12)	2 (1)
Muscular weakness	85 (20)	8 (2)	59 (14)	6 (1)
Headache	79 (18)	0	42 (10)	0
Blood creatine phosphokinase increase	75 (18)	15 (4)	72 (17)	15 (4)
Weight increase	67 (16)	11 (3)	49 (12)	7 (2)
Memory impairment	65 (15)	1 (<1)	54 (13)	1 (<1)
Cough	64 (15)	1 (<1)	10 (2)	0
	Any Grade Treatment-Emergent Adverse Events		Any Grade Treatment-Related Adverse Events	
Discontinuation of therapy	31 (7)		14 (3)	
Leading to dose reduction	163 (38)		149 (35)	
Leading to dose interruption	213 (50)		150 (35)	
Serious adverse event	147 (34)		38 (9)	

Event, n (%)	Treatment-Emergent Adverse Events (N=426)		Treatment-Related Adverse Events (N=426)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatal adverse event	19 (4)		0	

Adverse events were reported with the use of the Medical Dictionary for Regulatory Activities, version 21.0, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

* Two patients (<1%) had grade 5 dyspnea.