# Taletrectinib in *ROS1*+ Non–Small Cell Lung Cancer: TRUST

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## ABSTRACT

**PURPOSE** Taletrectinib is an oral, potent, CNS-active, selective, next-generation ROS1 tyrosine kinase inhibitor (TKI). We report integrated efficacy and safety from registrational taletrectinib studies in *ROS1*+ non–small cell lung cancer.

**METHODS** TRUST-I and TRUST-II were phase II, single-arm, open-label, nonrandomized, multicenter trials. Efficacy outcomes were pooled from TRUST-I and TRUST-II pivotal cohorts. The safety population comprised all patients treated with once-daily oral taletrectinib 600 mg pooled across the taletrectinib clinical program. The primary end point was independent review committee–assessed confirmed objective response rate (cORR). Secondary outcomes included intracranial (IC)-ORR, progression-free survival (PFS), duration of response (DOR), and safety.

**RESULTS** As of June 7, 2024, the efficacy-evaluable population included 273 patients in TRUST-I and TRUST-II. Among TKI-naïve patients (n = 160), the cORR was 88.8% and the IC-cORR was 76.5%; in TKI-pretreated patients (n = 113), the cORR was 55.8% and the IC-cORR was 65.6%. In TKI-naïve patients, the median DOR and median PFS were 44.2 and 45.6 months, respectively. In TKI-pretreated patients, the median DOR and median PFS were 16.6 and 9.7 months. The cORR in patients with G2032R mutation was 61.5% (8 of 13). Among 352 patients treated with taletrectinib 600 mg once daily, the most frequent treatment-emergent adverse events (TEAEs) were GI events (88%) and elevated AST (72%) and ALT (68%); most were grade 1. Neurologic TEAEs were infrequent (dizziness, 21%; dysgeusia, 15%) and mostly grade 1. TEAEs leading to discontinuations (6.5%) were low.

**CONCLUSION** Taletrectinib showed a high response rate with durable responses, robust IC activity, prolonged PFS, favorable safety, and low rates of neurologic adverse events in TKI-naïve and pretreated patients.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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## INTRODUCTION

Proto-oncogene tyrosine-protein kinase 1 (*ROS1*) gene fusions, first reported in 2007,[1,2] are oncogenic molecular alterations resulting in constitutive activation of the ROS1 kinase domain and drive persistent downstream signaling and dysregulated cell differentiation, proliferation, and survival. These *ROS1* fusions are rare genetic events reported in multiple solid tumors, including non–small cell lung cancer (NSCLC), where the prevalence is 0.9% to 2.6%.[1,3-5] Patients with *ROS1* fusion–positive (*ROS1*+) NSCLC tend to be female, are younger than patients without driver alterations, are diagnosed at an advanced stage (III-IV), have adenocarcinoma, and most are never smokers.[1] Approximately one third of patients with *ROS1*+ NSCLC have a brain metastasis at diagnosis, which can be as high as 50% in previously treated patients.[1,30]

ROS1 tyrosine kinase inhibitors (TKIs) transformed clinical outcomes for *ROS1*+ NSCLC; however, patients treated with first-generation TKIs progress because of off-target bypass pathway activation, leading to refractory disease, development of on-target acquired resistance mutations such as G2032R, or brain metastases.[1,6] Currently, three TKIs are approved by the US Food and Drug Administration (FDA) for *ROS1*+ NSCLC: crizotinib, entrectinib, and repotrectinib.[7-9] While a higher objective response rate (ORR) and longer median progression-free survival (PFS) were observed with first-line crizotinib versus chemotherapy (CT), CNS metastases developed in nearly 50% of patients with *ROS1*+ NSCLC.[10-13] Entrectinib was designed to cross the blood-brain barrier, but overall responses were marginal in patients with previous CNS progression (intracranial [IC]-ORR: 11%) and against the most common acquired resistance mutation after crizotinib treatment, G2032R, which occurs

## CONTEXT

**Key Objective**

To examine what role taletrectinib, a next-generation ROS1 tyrosine kinase inhibitor, may play in the treatment of advanced ROS1+ non–small cell lung cancer (NSCLC) by presenting the integrated analysis from two pivotal phase II studies: TRUST-I (ClinicalTrials.gov identifier: NCT04395677) and TRUST-II (ClinicalTrials.gov identifier: NCT04919811).

**Knowledge Generated**

Regardless of previous systemic therapies, taletrectinib demonstrated high and durable responses; prolonged progression-free survival; robust activity against intracranial lesions and acquired mutations, including G2032R; and favorable safety with low incidence of neurologic adverse events. Consistent responses and safety results were observed regardless of race or geographic region.

**Relevance *(T.E. Stinchcombe)***

Taletrectinib will likely become the preferred treatment option for advanced ROS1+ NSCLC.*

*Relevance section written by *JCO* Associate Editor Thomas E. Stinchcombe, MD.

in 30% to 40% of patients.[8,14,15] Repotrectinib, recently FDA-approved for advanced *ROS1*+ NSCLC,[9] has CNS activity and was designed to be effective against ROS1 resistance mutations.[16,17] While active against G2032R and brain metastases, a high incidence and wide spectrum of neurologic adverse events (AEs) were observed in most patients receiving repotrectinib.[9,17] Zidesamtinib, another next-generation ROS1 TKI, is being evaluated in *ROS1*+ solid tumors including NSCLC.[18] Unmet needs remain for efficacious and well-tolerated treatments for patients with *ROS1*+ NSCLC that produce strong overall and IC responses, prolong disease control, overcome acquired on-target resistance mutations, and have limited neurologic side effects.

Taletrectinib is an oral, CNS-active, next-generation ROS1 TKI with 11- to 20-fold selectivity over TrKB, which may translate into lower rates of, less severe, or limited spectrum of neurologic AEs.[19,20] The recommended phase II dose (600 mg once daily) was established in two phase I trials conducted in the United States and Japan[21,22] and confirmed during the safety lead-in of TRUST-I.[20] A pooled population pharmacokinetics (PK) analysis indicated that population PK of taletrectinib is similar in US and Japanese phase I studies.[21]

An integrated analysis using registrational cohorts from the pivotal phase II regional TRUST-I (ClinicalTrials.gov identifier: NCT04395677) and global TRUST-II (ClinicalTrials.gov identifier: NCT04919811) trials was performed to increase the number of patients and provide a more reliable estimation of treatment effects, as well as examine if the efficacy and safety results observed in TRUST-I[20] were generalizable to a global population of patients with *ROS1*+ NSCLC. This integrated analysis is feasible because both studies had similar pivotal study designs, inclusion and exclusion criteria, and primary and secondary end points. In addition, the efficacy and safety assessment methods and their schedules were identical, and statistical approaches were consistent between these studies.[19,20] In this integrated analysis, we show that the efficacy and safety results with taletrectinib observed in TRUST-I[20] are generalizable to a global population of patients with *ROS1*+ NSCLC.

## METHODS

### Study Design and Treatment

The design of TRUST-I was published previously.[20,22] Briefly, TRUST-I is an open-label, single-arm, nonrandomized study of taletrectinib for locally advanced or metastatic *ROS1*+ NSCLC in China with two cohorts (Appendix Fig A1A, online only). Cohort 1 enrolled TKI-naïve patients, and cohort 2 enrolled patients who failed previous crizotinib, the only ROS1 TKI approved in China during this trial. TRUST-II is a global, multicenter, open-label, single-arm, nonrandomized study of taletrectinib (Appendix Fig A1B). Among TRUST-II cohorts, cohorts 1 (TKI-naïve *ROS1*+ NSCLC) and 2 (pretreated with one previous approved ROS1 TKI [crizotinib or entrectinib]) served as registrational cohorts. TKI-naïve or TKI-pretreated patients in both studies might have received ≤one previous line of systemic CT. Taletrectinib 600 mg was administered orally once daily in 21-day treatment cycles until disease progression, unacceptable toxicity, death, or consent withdrawal.

### Patients

Eligibility criteria across pivotal cohorts were mostly similar. Eligible adults (defined by local regulations) had advanced NSCLC, ≥one measurable baseline lesion per RECIST version 1.1 (v1.1), and locally documented evidence of *ROS1* gene fusion using a validated assay by a local laboratory. Brain metastases were allowed if patients were asymptomatic or

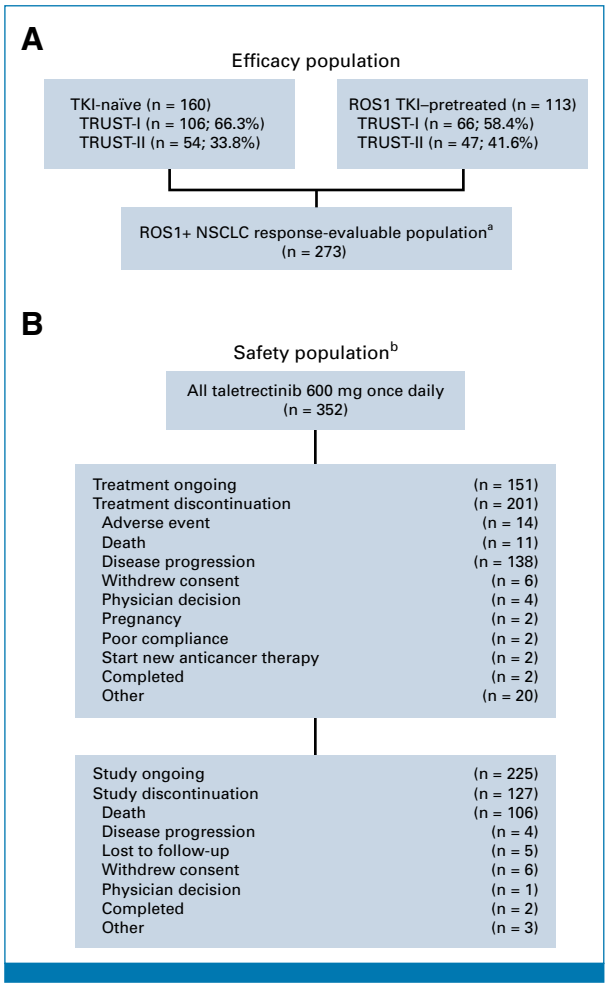


**FIG 1.** Analysis populations. Data cutoff: June 7, 2024. Patient flowcharts in the (A) efficacy and (B) safety populations. [a]REP included patients with *ROS1*+ NSCLC with ≥one measurable baseline lesion per RECIST v1.1 by IRC receiving ≥one dose of taletrectinib. One patient from TRUST-I was excluded from the REP because of a secondary malignancy. [b]The integrated safety population described reflects exposure to taletrectinib as a single agent dosed at 600 mg orally once daily until disease progression or unacceptable toxicity in 352 patients with *ROS1*+ NSCLC (N = 337) and other solid tumors (n = 15). IRC, independent review committee; NSCLC, non–small cell lung cancer; REP, response-evaluable population; TKI, tyrosine kinase inhibitor.

previously treated and clinically stable; radiotherapy, if given, must have been completed ≥14 days before dosing. Other inclusion criteria were an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; adequate hepatic, renal, and bone marrow function; and QT interval corrected for heart rate by Fridericia's formula interval within 470 ms. Previous small-molecule anticancer therapies (eg, previous TKIs) must have washed out for ≥2 weeks or five half-lives, whichever was shorter. AEs because of previous therapy must have been resolved to Common Terminology Criteria for Adverse Events grade 1 or to baseline. Patients with active infection, including active hepatitis B or C and history of pneumonitis or interstitial lung disease, were excluded. For geographic comparisons, Western countries included those in North America and Europe.

## Assessments

Systemic tumor assessments were evaluated using RECIST v1.1 criteria and brain metastases with modified RECIST (mRECIST) v1.1.[23] Contrast-enhanced computed tomography of the chest, abdomen, and pelvis was required at baseline and during the treatment period starting at C3D1, with a frequency of once every two treatment cycles for the first eight treatment cycles, then every three cycles from cycles 9 to 26, and every four cycles thereafter. Baseline brain magnetic resonance imaging with gadolinium was required for all patients. If baseline brain metastases were present, brain imaging continued during treatment at the same schedule as systemic tumor assessment; brain imaging was performed as clinically indicated if there were no brain baseline metastases.

Safety assessments were performed in all patients receiving ≥one dose of taletrectinib 600 mg once daily across the taletrectinib clinical program and included physical examinations, evaluation of vital signs, clinical laboratory tests, electrocardiograms, and treatment-emergent AEs (TEAEs; grading per National Cancer Institute Common Terminology Criteria for Adverse Events, v5.0).

## End Points

The primary efficacy end point in both TRUST-I and TRUST-II was independent review committee (IRC)–assessed confirmed ORR (cORR) per RECIST v1.1. Secondary efficacy end points included disease control rate (DCR), duration of response (DOR), time to response (TTR), and PFS. In patients with measurable baseline brain metastases, confirmed IC-ORR and DCR were assessed by IRC per mRECIST v1.1. Exploratory end points included efficacy in predefined subgroups. Safety end points included the incidence, severity, and duration of AEs; relatedness to study drug; serious AEs; and AEs of special interest, including reporting of Hy's Law.[24,25]

## Statistical Analysis

The response-evaluable population (REP) included patients with *ROS1*+ NSCLC with ≥one measurable baseline lesion per RECIST V1.1 by IRC receiving ≥one dose of taletrectinib. The pooled safety population included all patients receiving taletrectinib 600 mg once daily until disease progression or unacceptable toxicity across the safety population (TRUST-I, TRUST-II, 1 phase II trial in neurotrophic tyrosine receptor kinase+ tumors in China [C205; ClinicalTrials.gov identifier: NCT04617054] and one completed phase I trial conducted in Japan [J102; ClinicalTrials.gov identifier: NCT02675491]).[22] Corresponding 95% CIs were calculated using the Clopper-Pearson method. cORR was defined as the proportion of patients with IRC-assessed best overall responses (BORs), which included

**TABLE 1.** Baseline Demographic and Disease Characteristics (response-evaluable population)

| Characteristic | TKI-Naïve (n = 160) | ROS1 TKI–Pretreated (n = 113) | Overall (n = 273) |
|---|---|---|---|
| Age, years, median (minimum-maximum) | 57.0 (26-82) | 53.0 (27-79) | 56.0 (26-82) |
| Female sex, No. (%) | 89 (55.6) | 67 (59.3) | 156 (57.1) |
| Smoking status, No. (%) | | | |
| Never smoker | 105 (65.6) | 77 (68.1) | 182 (66.7) |
| Former smoker | 47 (29.4) | 34 (30.1) | 81 (29.7) |
| Current smoker | 8 (5.0) | 2 (1.8) | 10 (3.7) |
| Geographic region, No. (%) | | | |
| Western | 21 (13.1) | 26 (23.0) | 47 (17.2) |
| Non-Western | 139 (86.9) | 87 (77.0) | 226 (82.8) |
| ECOG PS, No. (%) | | | |
| 0 | 41 (25.6) | 40 (35.4) | 81 (29.7) |
| 1 | 119 (74.4) | 73 (64.6) | 192 (70.3) |
| Disease stage at enrollment, No. (%) | | | |
| III | 14 (8.8) | 3 (2.7) | 17 (6.2) |
| IV | 146 (91.3) | 110 (97.3) | 256 (93.8) |
| Histology, No. (%) | | | |
| Adenocarcinoma | 155 (96.9) | 107 (94.7) | 262 (96.0) |
| Previous chemotherapy, No. (%) | | | |
| Yes | 32 (20.0) | 42 (37.2) | 74 (27.1) |
| No | 128 (80.0) | 71 (62.8) | 199 (72.9) |
| Brain metastasis at baseline (mRECIST v1.1), No. (%) | | | |
| No | 123 (76.9) | 58 (51.3) | 181 (66.3) |
| Yes | 37 (23.1) | 55 (48.7) | 92 (33.7) |
| Measurable | 17 (10.6) | 32 (28.3) | 49 (17.9) |
| Nonmeasurable | 20 (12.5) | 23 (20.4) | 43 (15.8) |
| Patients pretreated with previous TKI therapy, No. (%) | | | |
| Entrectinib | Not applicable | 10 (8.8) | Not applicable |
| Crizotinib | Not applicable | 103 (91.2) | Not applicable |
| G2032R mutation at baseline, No. (%) | Not applicable | | Not applicable |
| Yes | Not applicable | 13 (11.5) | Not applicable |
| No | Not applicable | 19 (61.8) | Not applicable |
| Unavailable | Not applicable | 81 (71.7) | Not applicable |
| Study ID, No. (%) | | | |
| TRUST-I | 106 (66.3) | 66 (58.4) | 172 (63.0) |
| TRUST-II | 54 (33.8) | 47 (41.6) | 101 (37.0) |

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ID, identification; mRECIST, modified RECIST; TKI, tyrosine kinase inhibitor.

confirmed complete response (CR) and partial response (PR); DCR was defined as the proportion of patients with IRC-assessed BORs including CR, PR, and stable disease (SD). DOR was defined as time from first documented CR/PR to first documented progressive disease (PD) or death because of any cause for patients with confirmed objective responses; patients not experiencing PD or death were censored at the time of last tumor assessment. PFS was defined as time from first taletrectinib dose to first PD or death because of any cause, whichever occurred first. Patients not experiencing PD or death were censored at their last tumor assessment; PFS was considered to have occurred on the date of death in patients who died before documented radiographic progression. The Kaplan-Meier method was used to estimate PFS and DOR time curves; corresponding 95% CIs were determined using Greenwood's formula. Median durations of PFS and DOR were reported with corresponding Brookmeyer and Crowley 95% CIs.

## Study Oversight

These studies were conducted in accordance with international consensus ethical principles, including the Declaration of Helsinki, Council for International Organizations of

**TABLE 2.** Summary of Independent Review Committee–Assessed Responses Among Response-Evaluable Patients

| Category | TKI-Naïve (n = 160) | ROS1 TKI–Pretreated (n = 113) |
|---|---|---|
| BOR, No. | | |
| CR | 8 | 5 |
| PR | 134 | 58 |
| SD | 10 | 36 |
| PD | 5 | 8 |
| Not evaluable | 3 | 6 |
| cORR, No. (%) | 142 (88.8) | 63 (55.8) |
| Two-sided 95% CI[a] | 82.8 to 93.2 | 46.1 to 65.1 |
| DCR, No. (%) | 152 (95.0) | 99 (87.6) |
| Two-sided 95% CI[a] | 90.4 to 97.8 | 80.1 to 93.1 |
| Median DOR, months (95% CI) | 44.2 (30.4 to NR) | 16.6 (10.6 to 27.3) |
| Median time to response, months (95% CI) | 1.4 (1.4 to 1.4) | 1.4 (1.4 to 1.4) |
| Patients with measurable baseline brain metastasis (mRECIST v1.1) | n = 17 | n = 32 |
| BOR, No. | | |
| CR | 2 | 1 |
| PR | 11 | 20 |
| SD | 2 | 9 |
| PD | 1 | 1 |
| Not evaluable | 1 | 1 |
| IC ORR, No. (%) | 13 (76.5) | 21 (65.6) |
| Two-sided 95% CI[a] | 50.1 to 93.2 | 46.8 to 81.4 |
| DCR, No. (%) | 15 (88.2) | 30 (93.8) |
| Two-sided 95% CI[a] | 63.6 to 98.5 | 79.2 to 99.2 |
| IC DOR, months (95% CI) | 14.7 (4.2-30.2) | 11.9 (6.9-23.4) |
| Patients with G2032R mutation at baseline | Not applicable | n = 13 |
| BOR, No. | | |
| CR | Not applicable | 0 |
| PR | Not applicable | 8 |
| SD | Not applicable | 4 |
| PD | Not applicable | 1 |
| Not evaluable | Not applicable | 0 |
| cORR, No. (%) | Not applicable | 8 (61.5) |
| Two-sided 95% CI[a] | Not applicable | 31.6 to 86.1 |

Abbreviations: BOR, best overall response; cORR, confirmed ORR; CR, complete response; DCR, disease control rate; DOR, duration of response; IC, intracranial; mRECIST, modified RECIST; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.
[a]Clopper and Pearson methods.

Medical Sciences, applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice, and local regulations. The protocol was approved by institutional review boards and independent ethics committees at each participating trial site. All patients provided written informed consent before enrollment.

## RESULTS

### Patient Characteristics

As of June 7, 2024, 273 patients with *ROS1*+ NSCLC were enrolled and included in the pooled efficacy analysis of the REP (Fig 1A). Among 160 TKI-naïve patients, 106 were from TRUST-I (66.3%) and 54 (33.8%) were from TRUST-II; in 113 TKI-pretreated patients, 66 were from TRUST-I (58.4%) and 47 were from TRUST-II (41.6%). Among the REP (n = 273), the median age was 56.0 years, 57.1% was female, 66.7% had never smoked, approximately 70% had an ECOG PS of 1, and most patients had stage IV adenocarcinoma; geographically, approximately one fifth of patients (17%) were from Western countries (Table 1). In the pooled TKI-naïve population (n = 160), 20.0% had previous CT and 23.1% had baseline brain metastasis. In the pooled TKI-pretreated population (n = 113), 37.2% had previous CT and 48.7% had baseline brain metastasis. Over 90% of TKI-pretreated patients received previous crizotinib and approximately 9% received previous entrectinib.

### Efficacy in Response-Evaluable Patients

Among response-evaluable TKI-naïve patients (n = 160), the IRC-assessed cORR was 88.8% (95% CI: 82.8, 93.2), with eight achieving CR and 134 PR (Table 2; Fig 2A; Appendix Fig A2A); the DCR was 95.0% (95% CI, 90.4 to 97.8). For patients who had previous CT (n = 32), the ORR was 87.5%, and for those without (n = 128), the ORR was 89.1% (Appendix Table A1). With a median follow-up of 21.2 months, the median DOR in patients with confirmed responses was 44.2 months (95% CI, 30.4 to not reached [NR]; Fig 3A). The estimated 36-month DOR rate was 57.7% (95% CI, 45.0 to 68.5). The median TTR was 1.4 months (95% CI, 1.4 to 1.4). The median PFS was 45.6 months (95% CI, 29.0 to NR; Fig 3B); the estimated 36-month PFS rate was 52.6% (95% CI, 41.0 to 62.9). Median overall survival (OS) was not reached; the estimated 36-month OS rate was 66.3% (95% CI, 55.3 to 75.2).

Among response-evaluable TKI-pretreated patients (n = 113), the IRC-assessed cORR was 55.8% (95% CI, 46.1 to 65.1), with five achieving CR and 58 achieving PR (Table 2; Fig 2B; Appendix Fig A2B); the DCR was 87.6% (95% CI, 80.1 to 93.1). Specifically, the cORR for patients who had previous crizotinib (n = 103) was 53.4% and 80.0% for previous entrectinib (n = 10). For patients who had previous CT (n = 42), the cORR was 59.5%, and for those without (n = 71), the cORR was 53.5% (Appendix Table A1). With a median follow-up of 21.0 months, the median DOR in patients with confirmed responses was 16.6 months (95% CI, 10.6 to 27.3; Fig 3C). The estimated 12-month DOR rate was 61.1% (95% CI, 46.3 to 73.1). The median TTR was 1.4 months (95% CI, 1.4 to 1.4).

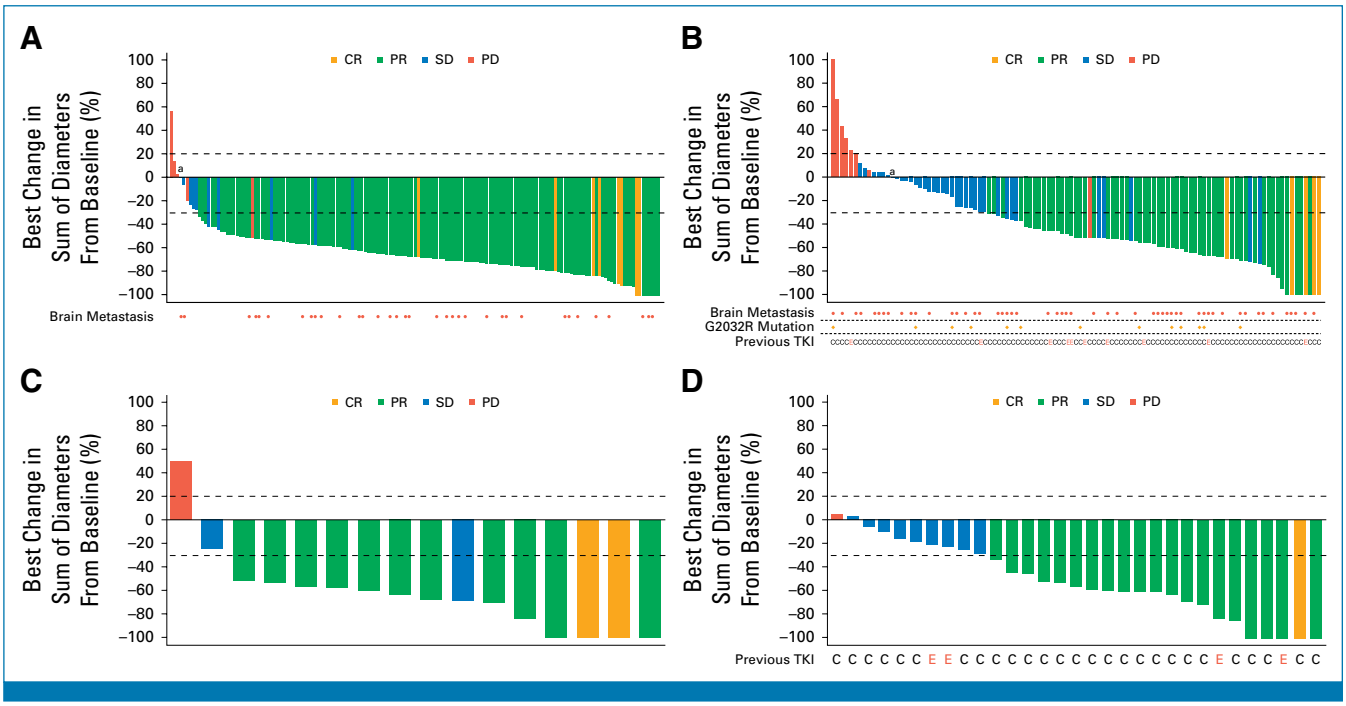


**FIG 2.** IRC-assessed BOR of taletrectinib in TKI-naïve and TKI-pretreated patients with *ROS1*+ NSCLC. Overall best percent change in the sum of diameters of target lesions from baseline in (A) TKI-naïve (n = 160; three patients with confirmed BOR as not evaluable are not displayed in the waterfall plot) and (B) TKI-pretreated (n = 113; six patients with confirmed BOR as not evaluable are not displayed in the waterfall plot) patients and IC best percent change in the sum of diameters of IC measurable lesions from baseline in (C) TKI-naïve (n = 17; one patient confirmed with BOR as not evaluable is not displayed in the waterfall plot) and (D) TKI-pretreated (n = 32; one patient confirmed with BOR as not evaluable is not displayed in the waterfall plot) patients. [a]One patient had a best percent change of 0 and BOR as SD. BOR, best overall response; CR, complete response; IC, intracranial; IRC, independent review committee; NSCLC, non–small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

The median PFS was 9.7 months (95% CI, 7.4 to 12.0; Fig 3D); the estimated 12-month PFS rate was 39.7% (95% CI, 29.6 to 49.6). Median OS was not reached; the estimated 12-month OS rate was 77.5% (95% CI, 68.1 to 84.5).

### Efficacy in Patients With Measurable Brain Metastases

In 17 TKI-naïve patients with measurable baseline brain metastases, the IC-ORR was 76.5% (95% CI, 50.1 to 93.2) and the IC-DCR was 88.2% (95% CI, 63.6 to 98.5; Table 2; Fig 2C). With a median follow-up of 22.6 months for TKI-naïve patients, the IC-DOR was 14.7 months (95% CI, 4.2 to 30.2). In 32 TKI-pretreated patients with measurable baseline brain metastases, the IC-ORR was 65.6% (95% CI, 46.8 to 81.4) and the IC-DCR was 93.8% (95% CI, 79.2 to 99.2; Table 2; Fig 2D). With a median follow-up of 19.6 months for TKI-pretreated patients, the IC-DOR was 11.9 months (95% CI, 6.9 to 23.5).

### Efficacy in Patients With G2032R Acquired Resistance Mutations

Among 32 patients with rebiopsy samples after failure of a previous line of crizotinib or entrectinib, 13 patients (41%) had a baseline G2032R mutation. Of these patients, eight (61.5% [95% CI, 31.6 to 86.1]) had responses.

### Subgroup Analyses

Across the pooled TKI-naïve and TKI-pretreated patient populations, similar high ORRs were observed regardless of age, sex, ECOG PS, geographic region, race, or presence/absence of baseline brain metastasis (Appendix Fig A3).

### Safety

Safety was evaluated in 352 patients receiving once-daily oral taletrectinib 600 mg (Fig 1B). The most common TEAEs were elevated AST (72%), elevated ALT (68%), diarrhea (64%), nausea (46%), and vomiting (44%); most AST and ALT elevations were either grade 1 or 2, and most GI-related AEs were grade 1 (Table 3; Appendix Table A2). Neurologic TEAEs occurring in ≥10% of patients were dizziness (21%), dysgeusia (15%), and headache (11%); most were grade 1. TEAEs leading to dose reductions occurring in ≥5% of patients included increased ALT (9%) and increased AST (5%). Serious TEAEs occurred in 30% of patients, and related serious TEAEs occurred in 7.7%. TEAEs leading to treatment discontinuation were reported by 7% of patients (3% were treatment-related); only pneumonia (n = 3), interstitial lung disease (n = 2), and hepatic function abnormal (n = 2) occurred in ≥one patient. The most common treatment-related AEs were increased AST (70%), increased ALT

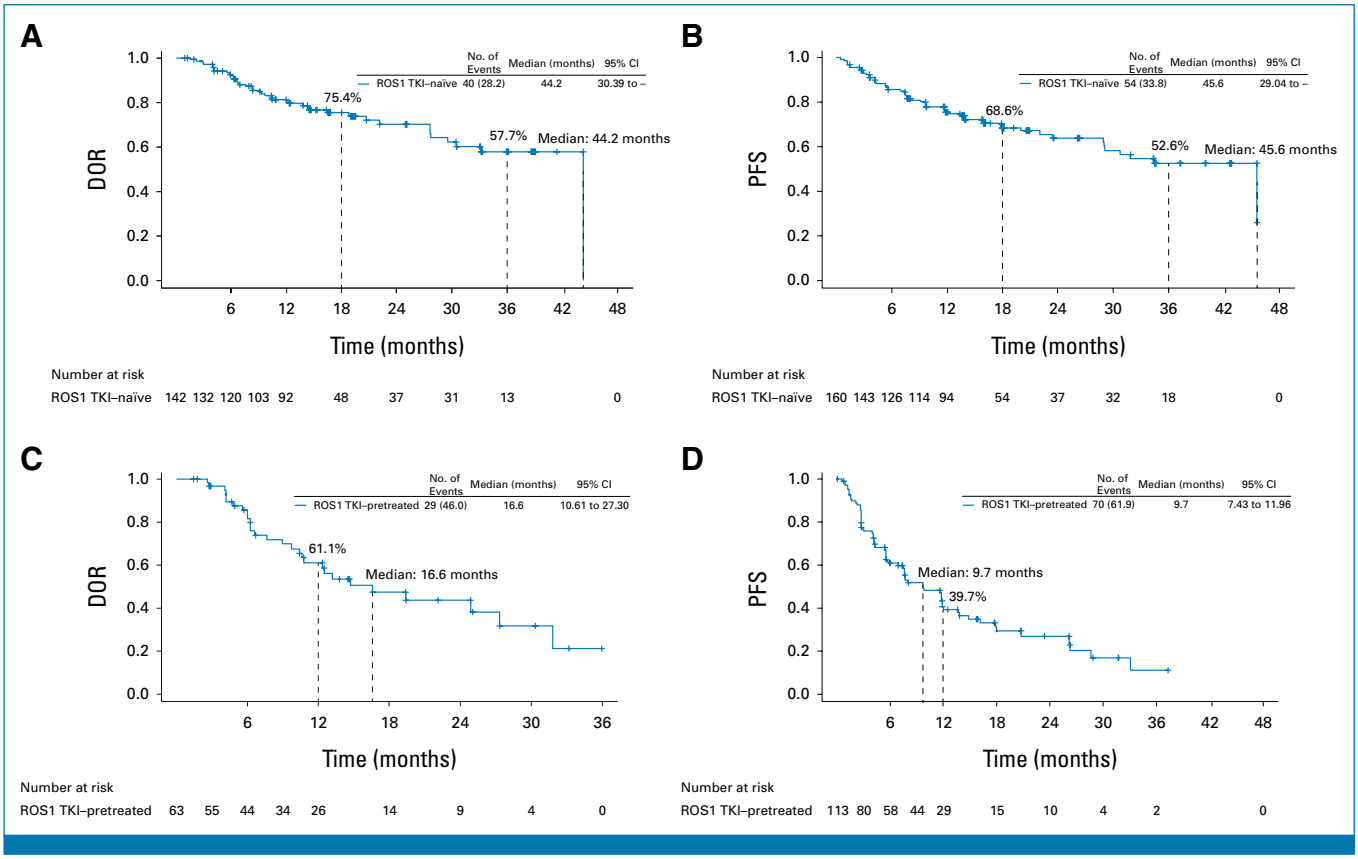


**FIG 3.** DOR and PFS by IRC assessment of taletrectinib in TKI-naïve and TKI-pretreated patients with ROS1+ NSCLC. (A) DOR in TKI-naïve patients, (B) PFS in TKI-naïve patients, (C) DOR in TKI-pretreated patients, and (D) PFS in TKI-pretreated patients. DOR, duration of response; IRC, independent review committee; NSCLC, non–small cell lung cancer; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

(67%), diarrhea (61%), nausea (44%), and vomiting (41%); most of these events were grade 1 (Table 3; Appendix Table A3). Treatment-related fatal events occurred in three patients (all from TRUST-I): two TKI-naïve (hepatic failure and pneumonia, n = 1 each) and one TKI-pretreated patient (hepatic function abnormal).

## DISCUSSION

Taletrectinib induced robust cORR (88.8%) and DOR (44.2 months) in TKI-naïve patients and led to durable outcomes in most patients with advanced *ROS1*+ NSCLC. Taletrectinib reported a median PFS of 45.6 months in TKI-naïve patients. In patients pretreated with crizotinib or entrectinib, taletrectinib demonstrated robust and durable responses (ORR, 55.8%; median DOR, 16.6 months) and a median PFS of 9.7 months.

Responses were seen regardless of race, region of the world, or whether patients had previous systemic therapies. These results indicate that taletrectinib provides clinically meaningful tumor shrinkage and prolonged disease control as a treatment option for advanced *ROS1*+ NSCLC regardless of treatment history. Moreover, the data suggest that the results are applicable globally to patients with advanced or metastatic *ROS1*+ NSCLC.

While cross-trial comparisons should be interpreted cautiously, the results presented here compare favorably with other available ROS1 TKIs in TKI-naïve patients for observed response rates (crizotinib: 72%; entrectinib: 68%; repotrectinib: 79%), median DOR (crizotinib: 24.7 months; entrectinib: 20.5 months; repotrectinib: 34.1 months), and median PFS (crizotinib: 19.3 months; entrectinib: 15.7 months; repotrectinib: 35.7 months).[11,15,17] In patients treated with repotrectinib who had previous crizotinib, entrectinib, or ceritinib, the ORR was 38%, the median DOR was 14.8 months, and the median PFS was 9.0 months.[17]

Brain metastases are a common treatment challenge in *ROS1*+ NSCLC.[1,13,15] IC responses in TKI-pretreated patients were clinically meaningful, with most patients responding (IC-ORR of 65.6% *v* 38% with repotrectinib), including one achieving CR.[17] In addition, two of the 21 TKI-pretreated patients experiencing an IC response had received previous entrectinib (Fig 2D), demonstrating CNS benefit despite previous exposure to CNS-penetrant therapy. These results indicate that taletrectinib can effectively treat CNS lesions regardless of previous exposure to first-generation TKIs.

TKI resistance, whether on-target or off-target, invariably develops in *ROS1*+ NSCLC, with most crizotinib and

**TABLE 3.** Summary of TEAEs and Treatment-Related AEs in Patients Treated With Once-Daily Taletrectinib 600 mg

| | TEAEs, No. (%) | | Treatment-Related AEs, No. (%) | |
|---|---|---|---|---|
| Category | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| Patients with ≥one event | 351 (99.7) | 181 (51.4) | 349 (99.1) | 116 (33.0) |
| Events reported in ≥15% of patients | | | | |
| Increased AST | 253 (71.9) | 26 (7.4) | 247 (70.2) | 22 (6.3) |
| Increased ALT | 238 (67.6) | 35 (9.9) | 234 (66.5) | 31 (8.8) |
| Diarrhea | 224 (63.6) | 7 (2.0) | 216 (61.4) | 11 (3.1) |
| Nausea | 163 (46.3) | 5 (1.4) | 156 (44.3) | 4 (1.1) |
| Vomiting | 153 (43.5) | 6 (1.7) | 145 (41.2) | 2 (0.6) |
| Anemia | 129 (36.6) | 12 (3.4) | 112 (31.8) | 9 (2.6) |
| Dizziness | 75 (21.3) | 1 (0.3) | 55 (15.6) | 1 (0.3) |
| Constipation | 73 (20.7) | 0 | 48 (13.6) | 0 |
| Increased blood bilirubin | 65 (18.5) | 4 (1.1) | 61 (17.3) | 3 (0.9) |
| QT prolongation | 65 (18.5) | 12 (3.4) | 63 (17.9) | 12 (3.4) |
| Increased blood creatinine | 63 (17.9) | 0 | 55 (15.6) | 0 |
| Decreased neutrophil count | 61 (17.3) | 17 (4.8) | 58 (16.5) | 16 (4.5) |
| Decreased appetite | 59 (16.8) | 1 (0.3) | 55 (15.6) | 1 (0.3) |
| Decreased WBC count | 59 (16.8) | 6 (1.7) | 57 (16.2) | 6 (1.7) |
| Increased blood creatine phosphokinase | 56 (15.9) | 7 (2.0) | 50 (14.2) | 4 (1.1) |
| Dysgeusia | 53 (15.1) | 0 | 53 (15.1) | 0 |
| Events leading to dose interruption | 143 (40.6) | 83 (23.6) | 96 (27.3) | 49 (13.9) |
| Events leading to dose reduction | 102 (29.0) | 62 (17.6) | 97 (27.6) | 61 (17.3) |
| Events leading to treatment discontinuation | 23 (6.5) | 18 (5.1) | 9 (2.6) | 6 (1.7) |

NOTE. Worst grade per patient, system organ class, or preferred term is reported. National Cancer Institute Common Terminology Criteria for Adverse Events v5.0 was used for C203, C205, and G208; National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 was used for J102.
Abbreviations: AEs, adverse events; TEAEs, treatment-emergent AEs.

entrectinib–treated patients progressing within 2 years.[1,13,15] *ROS1* G2032R, the most common acquired resistance mutation, sterically interferes with TKI binding, leading to on-target resistance.[6] While crizotinib and entrectinib are not effective against this mutation,[6] taletrectinib demonstrated activity in 13 TKI-pretreated patients with baseline G2032R mutations (ORR, 61.5%). These data are comparable with responses seen with repotrectinib (ORR, 59%),[17] suggesting that taletrectinib is a potential treatment option for patients with an *ROS1* G2032R mutation.

Consistent response rates with taletrectinib were observed between patients enrolled from Western and non-Western regions, and among White and Asian patients, suggesting that the clinical benefit of taletrectinib is applicable globally. In accordance with similar PK data in patients in Japan and the United States,[21] similar response rates and safety profiles were also observed in TKI-naïve patients from a global or Asian population of patients receiving crizotinib,[11,26] entrectinib,[15,27] and repotrectinib[17,28] and in TKI-pretreated patients receiving repotrectinib.[17,28]

The tolerability of ROS1 inhibitors is an important criterion for treatment choice, given the usually prolonged duration of treatment, and varies in terms of specificity and severity of AEs.[29] Crizotinib was the first approved ROS1 TKI but has limited CNS penetration and is not active against G2032R.[6,11] Crizotinib demonstrated a similar frequency of elevated transaminases (increased ALT: 79%; increased AST: 66%), GI events (diarrhea: 61%; vomiting: 46%), and neurologic treatment-related AEs (dysgeusia: 26%; headache: 22%; dizziness: 18%).[7] Rates of constipation (43%), edema (43%), and vision disorders (71%) were higher with crizotinib.[7]

Entrectinib, the second approved ROS1 TKI, had improved CNS penetration and activity compared with crizotinib but demonstrated higher rates of neurologic events (dysgeusia: 44%; dizziness: 38%; dysesthesia: 34%; cognitive impairment: 27%) than taletrectinib.[6,8,15]

Repotrectinib, a next-generation ROS1 TKI recently approved for the treatment of advanced or metastatic *ROS1*+ NSCLC, demonstrated IC activity and is active against *ROS1* G2032R.[17] Compared with taletrectinib, rates of dose reductions were higher with repotrectinib (38%).[17] Rates of neurologic treatment-related AEs were generally higher than those observed with taletrectinib (dizziness: 65%; ataxia: 28%; cognitive impairment: 25%).[9]

Overall, taletrectinib demonstrated a favorable tolerability and safety profile in patients with advanced *ROS1*+ NSCLC and other solid tumors treated at 600 mg once daily (N = 352).[22] Rates of treatment discontinuations (6.5%) were low. Many of the most common AEs were based on laboratory results without clinical symptoms, with the exception of GI and neurologic events. However, most neurologic events observed with taletrectinib were grade 1. As previously reported, the selectivity of taletrectinib for ROS1 over TrKB may explain the lower rates and narrower spectrum of neurologic side effects versus other ROS1 TKIs.[20] With a side effect profile consisting mainly of increased liver enzymes and low-grade GI toxicity rather than neurologic toxicities, taletrectinib may offer an improved safety profile for long-term use versus other therapeutic options.

Limitations of this integrated analysis include the limited number of TKI-pretreated patients with baseline mutation status (71.7% unavailable) and follow-up biopsies because of the challenge of obtaining additional biopsies at disease progression. Depending on the tumor location and the health status of the patient, obtaining an adequate rebiopsy sample was not always possible, thus limiting the availability of translational data such as the rates of development of and efficacy against resistance mutations.

In this integrated analysis from TRUST-I and TRUST-II, taletrectinib demonstrated high and durable overall and IC response rates and prolonged PFS in both TKI-naïve and TKI-pretreated patients, with activity against G2032R acquired resistance mutations, establishing taletrectinib as a potential best-in-class ROS1 TKI for advanced *ROS1*+ NSCLC. This integrated analysis further validated the efficacy and safety profile of taletrectinib from the TRUST-I trial and confirmed that the results were generalizable to the global population of patients with *ROS1*+ NSCLC. Additional follow-up on long-term survival is ongoing. The safety and efficacy of taletrectinib will be directly compared with those of crizotinib in an ongoing phase III randomized trial in TKI-naïve patients with locally advanced or metastatic *ROS1*+ NSCLC (ClinicalTrials.gov identifier: NCT06564324).


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**Taletrectinib in *ROS1*+ Non–Small Cell Lung Cancer: TRUST**

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## APPENDIX

**TABLE A1.** Independent Review Committee–Assessed Responses Among Treatment-Naïve and Pretreated Patients With and Without Previous Chemotherapy

| Category | TKI-Naïve | | | ROS1 TKI–Pretreated | | |
|---|---|---|---|---|---|---|
| | Previous Chemotherapy (n = 32) | No Previous Chemotherapy (n = 128) | All Naïve (n = 160) | Previous Chemotherapy (n = 42) | No Previous Chemotherapy (n = 71) | All Naïve (n = 113) |
| Best overall response, no. (%) | | | | | | |
| Complete response | 2 (6.3) | 6 (4.7) | 8 (5.0) | 3 (7.1) | 2 (2.8) | 5 (4.4) |
| Partial response | 26 (81.3) | 108 (84.4) | 134 (83.8) | 22 (52.4) | 36 (50.7) | 58 (51.3) |
| Stable disease | 2 (6.3) | 8 (6.3) | 10 (6.3) | 9 (21.4) | 27 (38.0) | 36 (31.9) |
| Progressive disease | 2 (6.3) | 3 (2.3) | 5 (3.1) | 4 (9.5) | 4 (5.6) | 8 (7.1) |
| Not evaluable | 0 | 3 (2.3) | 3 (1.9) | 4 (9.5) | 2 (2.8) | 6 (5.3) |
| Confirmed objective response rate, % (95% CI) | 87.5 (71.0 to 96.4) | 89.1 (82.3 to 93.9) | 88.8 (82.8 to 93.2) | 59.5 (43.3 to 74.4) | 53.5 (41.3 to 65.5) | 55.8 (46.1 to 65.1) |
| Disease control rate, % (95% CI) | 93.8 (79.2 to 99.2) | 95.3 (90.1 98.3) | 95.0 (90.4 to 97.8) | 81.0 (65.9 to 91.4) | 91.5 (82.5 to 96.8) | 87.6 (80.1 to 93.1) |

Abbreviation: TKI, tyrosine kinase inhibitor.

**TABLE A2.** Treatment-Emergent Adverse Events Reported in Patients Treated With Once-Daily Taletrectinib 600 mg (n = 352)

| Category | Grade 1, No. (%) | Grade 2, No. (%) | Grade 3, No. (%) | Grade 4, No. (%) | Grade 5, No. (%) | Any Grade, No. (%) |
|---|---|---|---|---|---|---|
| Patients with ≥one event | 34 (9.7) | 136 (38.6) | 138 (39.2) | 15 (4.3) | 28 (8.0) | 351 (99.7) |
| Events reported in ≥15% of patients | | | | | | |
| Diarrhea | 175 (49.7) | 42 (11.9) | 7 (2.0) | 0 | 0 | 224 (63.6) |
| Increased AST | 168 (47.7) | 59 (16.8) | 26 (7.4) | 0 | 0 | 253 (71.9) |
| Increased ALT | 142 (40.3) | 61 (17.3) | 34 (9.7) | 1 (0.3) | 0 | 238 (67.6) |
| Nausea | 125 (35.5) | 33 (9.4) | 5 (1.4) | 0 | 0 | 163 (46.3) |
| Vomiting | 116 (33.0) | 31 (8.8) | 6 (1.7) | 0 | 0 | 153 (43.5) |
| Anemia | 76 (21.6) | 41 (11.6) | 12 (3.4) | 0 | 0 | 129 (36.6) |
| Dizziness | 68 (19.3) | 6 (1.7) | 1 (0.3) | 0 | 0 | 75 (21.3) |
| Constipation | 62 (17.6) | 11 (3.1) | 0 | 0 | 0 | 73 (20.7) |
| Increased blood bilirubin | 48 (13.6) | 13 (3.7) | 3 (0.9) | 1 (0.3) | 0 | 65 (18.5) |
| QT prolongation | 44 (12.5) | 9 (2.6) | 12 (3.4) | 0 | 0 | 65 (18.5) |
| Increased blood creatinine | 52 (14.8) | 11 (3.1) | 0 | 0 | 0 | 63 (17.9) |
| Decreased neutrophil count | 30 (8.5) | 14 (4.0) | 12 (3.4) | 5 (1.4) | 0 | 61 (17.3) |
| Decreased appetite | 44 (12.5) | 14 (4.0) | 1 (0.3) | 0 | 0 | 59 (16.8) |
| Decreased WBC count | 33 (9.4) | 20 (5.7) | 6 (1.7) | 0 | 0 | 59 (16.8) |
| Increased blood creatine phosphokinase | 36 (10.2) | 13 (3.7) | 6 (1.7) | 1 (0.3) | 0 | 56 (15.9) |
| Dysgeusia | 45 (12.8) | 8 (2.3) | 0 | 0 | 0 | 53 (15.1) |
| Events leading to dose interruption | 11 (3.1) | 49 (13.9) | 77 (21.9) | 5 (1.4) | 1 (0.3) | 143 (40.6) |
| Events leading to dose reduction | 7 (2.0) | 33 (9.4) | 59 (16.8) | 3 (0.9) | 0 | 102 (29.0) |
| Events leading to treatment discontinuation | 0 | 5 (1.4) | 13 (3.7) | 0 | 5 (1.4) | 23 (6.5) |

NOTE. Worst grade per patient, system organ class, or preferred term is reported. National Cancer Institute Common Terminology Criteria for Adverse Events v5.0 was used for C203, C205, and G208; National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 was used for J102.

**TABLE A3.** Treatment-Related Adverse Events Reported in Patients Treated With Once-Daily Taletrectinib 600 mg (n = 352)

| Category | Grade 1, No. (%) | Grade 2, No. (%) | Grade 3, No. (%) | Grade 4, No. (%) | Grade 5, No. (%) | Any Grade, No. (%) |
|---|---|---|---|---|---|---|
| Patients with ≥one event | 72 (20.5) | 161 (45.7) | 102 (29.0) | 11 (3.1) | 3 (0.9) | 349 (99.1) |
| Events reported in ≥15% of patients | | | | | | |
| Increased AST | 166 (47.2) | 59 (16.8) | 22 (6.3) | 0 | 0 | 247 (70.2) |
| Increased ALT | 143 (40.6) | 60 (17.0) | 30 (8.5) | 1 (0.3) | 0 | 234 (66.5) |
| Diarrhea | 170 (48.3) | 39 (11.1) | 7 (2.0) | 0 | 0 | 216 (61.4) |
| Nausea | 124 (35.2) | 28 (8.0) | 4 (1.1) | 0 | 0 | 156 (44.3) |
| Vomiting | 112 (31.8) | 31 (8.8) | 2 (0.6) | 0 | 0 | 145 (41.2) |
| Anemia | 70 (19.9) | 33 (9.4) | 9 (2.6) | 0 | 0 | 112 (31.8) |
| QT prolongation | 42 (11.9) | 9 (2.6) | 12 (3.4) | 0 | 0 | 63 (17.9) |
| Increased blood bilirubin | 47 (13.4) | 11 (3.1) | 2 (0.6) | 1 (0.3) | 0 | 61 (17.3) |
| Decreased neutrophil count | 28 (8.0) | 14 (4.0) | 11 (3.1) | 5 (1.4) | 0 | 58 (16.5) |
| Decreased WBC count | 33 (9.4) | 18 (5.1) | 6 (1.7) | 0 | 0 | 57 (16.2) |
| Dizziness | 51 (14.5) | 3 (0.9) | 1 (0.3) | 0 | 0 | 55 (15.6) |
| Increased blood creatinine | 48 (13.6) | 7 (2.0) | 0 | 0 | 0 | 55 (15.6) |
| Decreased appetite | 42 (11.9) | 12 (3.4) | 1 (0.3) | 0 | 0 | 55 (15.6) |
| Dysgeusia | 45 (12.8) | 8 (2.3) | 0 | 0 | 0 | 53 (15.1) |
| Events leading to dose interruption | 8 (2.3) | 39 (11.1) | 46 (13.1) | 3 (0.9) | 0 | 96 (27.3) |
| Events leading to dose reduction | 6 (1.7) | 30 (8.5) | 58 (16.5) | 3 (0.9) | 0 | 97 (27.6) |
| Events leading to treatment discontinuation | 0 | 3 (0.9) | 6 (1.7) | 0 | 0 | 9 (2.6) |

NOTE. Worst grade per patient, system organ class, or preferred term is reported. National Cancer Institute Common Terminology Criteria for Adverse Events v5.0 was used for C203, C205, and G208; National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 was used for J102.

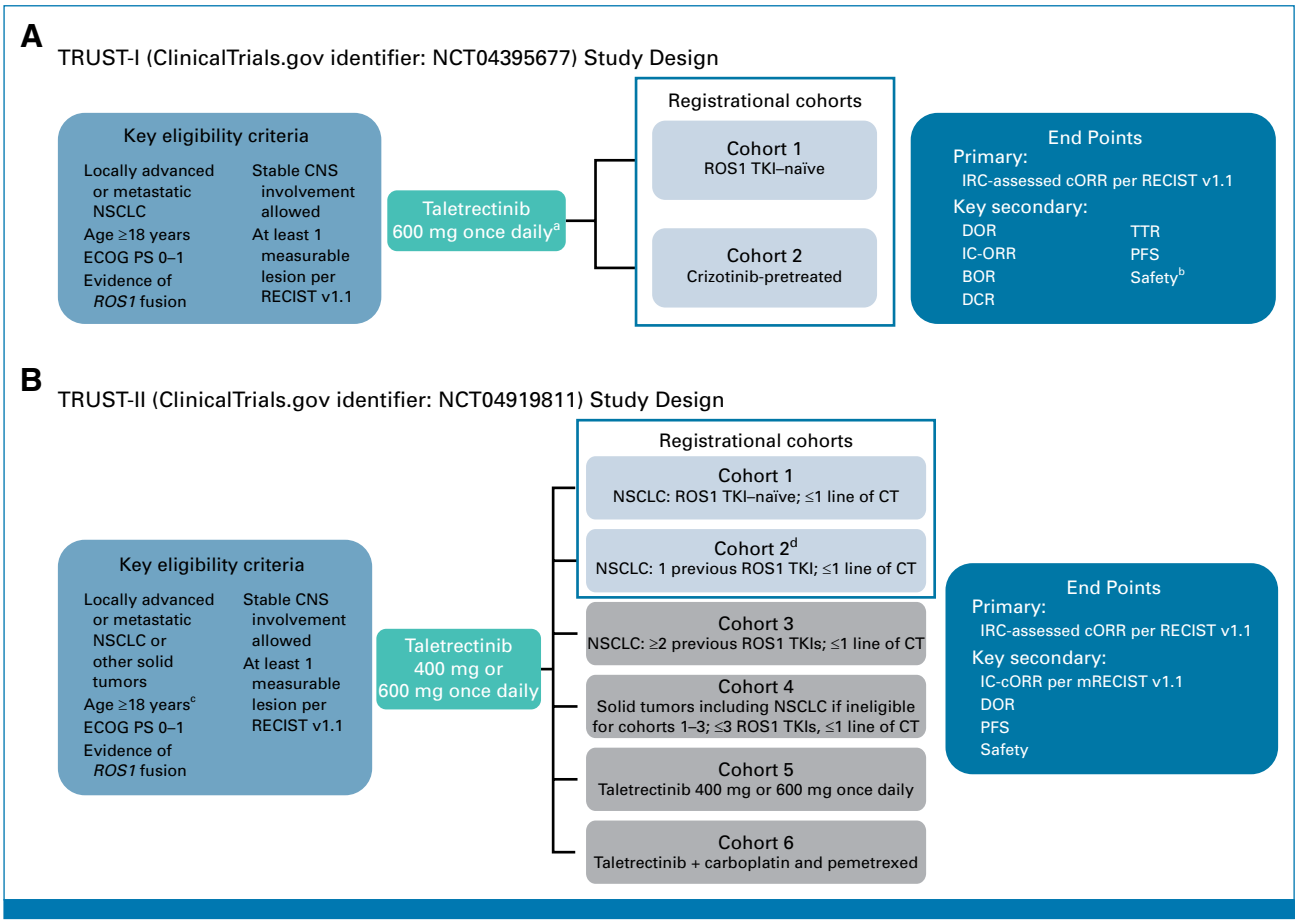


**FIG A1.** Study designs of (A) TRUST-I (ClinicalTrials.gov identifier: NCT04395677) and (B) TRUST-II (ClinicalTrials.gov identifier: NCT04919811). [a]A dose-confirmation lead-in stage evaluated the safety of taletrectinib 400 mg once daily (n = 3) and 600 mg once daily (n = 3). [b]Safety was analyzed in patients receiving ≥one dose of taletrectinib until 30 days after the last dose of taletrectinib or the start date of new anticancer therapy minus 1 day, whichever occurred first. [c]Or ≥20 years, as required by local regulations. [d]One previous ROS1 TKI (crizotinib or entrectinib). BOR, best overall response; cORR, confirmed ORR; CT, chemotherapy; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, intracranial; IRC, independent review committee; mRECIST, modified RECIST; NSCLC, non–small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; TTR, time to response; TKI, tyrosine kinase inhibitor.

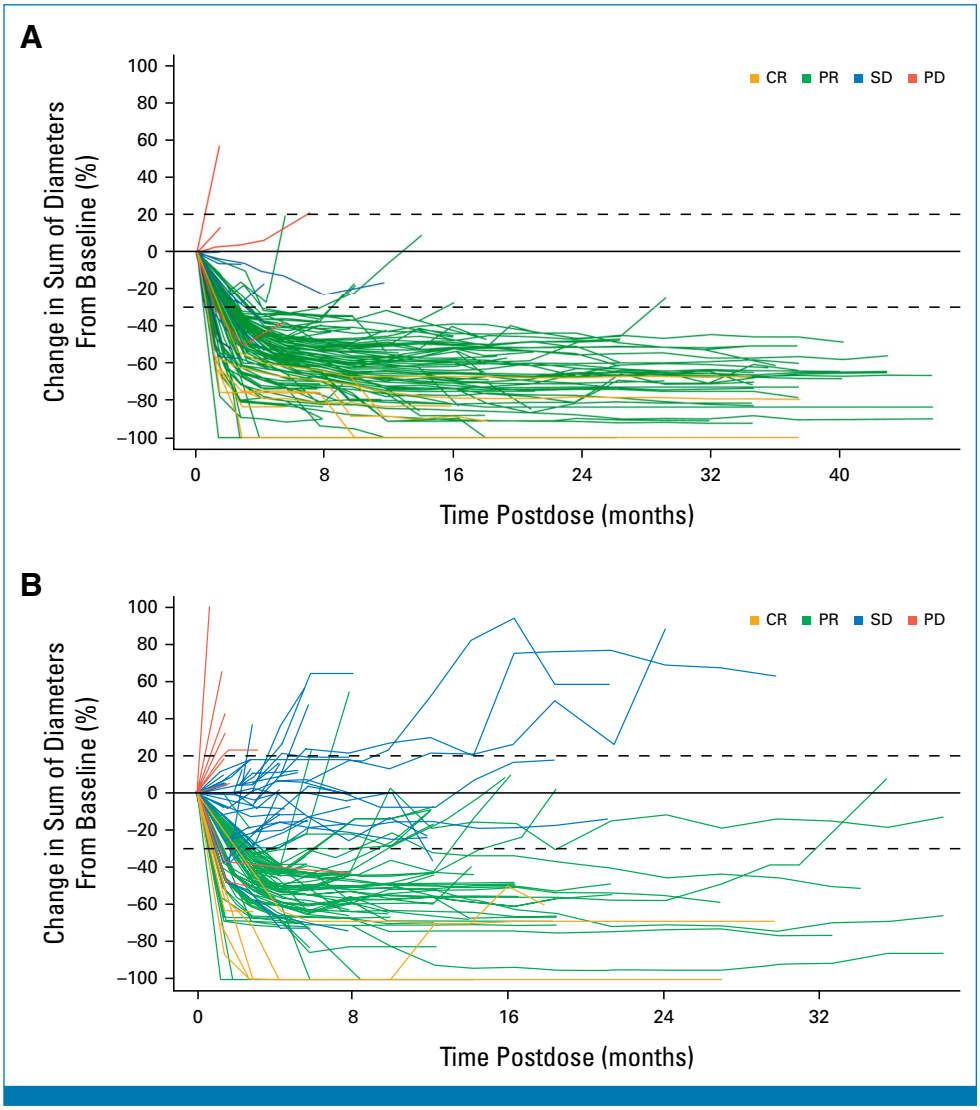


**FIG A2.** Change in size of target lesions relative to baseline over time in (A) TKI-naïve and (B) TKI-pretreated patients. Reduction in target lesion size over time in (A) TKI-naïve patients (three patients had confirmed BOR as not evaluable and are not displayed) and (B) TKI-pretreated patients (the target lesion sum of diameters from baseline of one patient had increased 136.5%, which was cut at 100% in the figure because of page size limit; six patients had confirmed BOR as not evaluable and are not displayed in the spider plot). BOR, best overall response; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

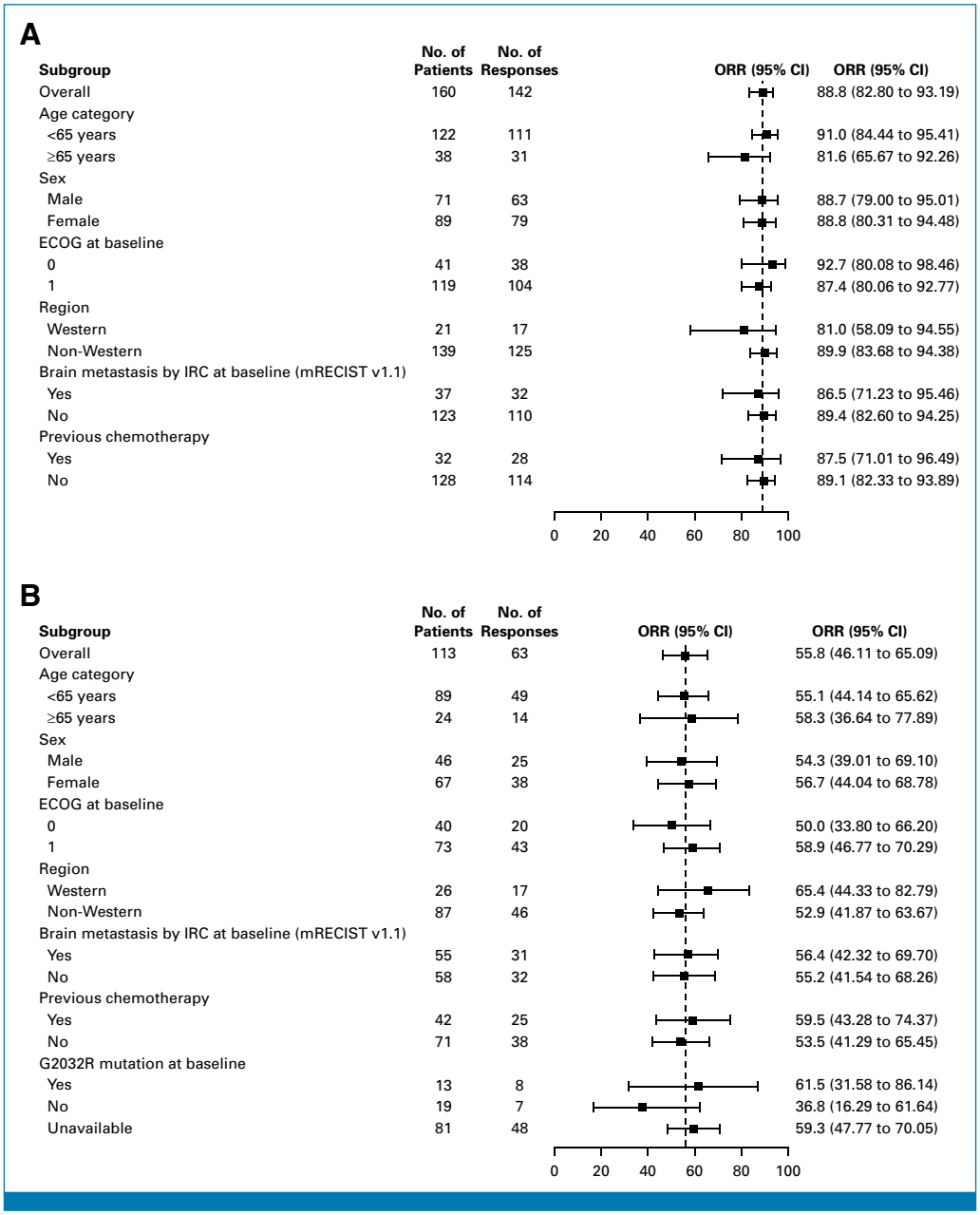


**FIG A3.** Responses per IRC by subgroup in the response-evaluable population in (A) TKI-naïve and (B) TKI-pretreated patients. ORR in (A) TKI-naïve patients and (B) TKI-pretreated patients. ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee; mRECIST, modified RECIST; ORR, objective response rate; TKI, tyrosine kinase inhibitor.