2024 ASCO® ANNUAL MEETING

EFFICACY AND SAFETY OF TALETRECTINIB IN PATIENTS WITH ADVANCED OR METASTATIC ROS1+ NON-SMALL CELL LUNG CANCER: THE PHASE 2 TRUST-I STUDY

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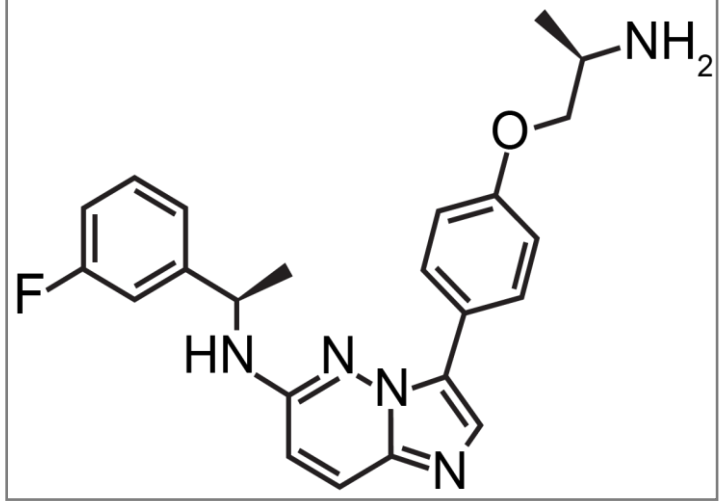
Conflicts of Interest

I have no conflict of interest to declare.

TRUST-I (NCT04395677): Phase 2 Trial of Taletrectinib in ROS1+ NSCLC

Taletrectinib



- For patients with ROS1-positive (ROS1+) NSCLC, ROS1 tyrosine kinase inhibitors (TKIs) are the current standard of care[1]
  - However, most patients progress within 2 years due to acquired resistance mutations (ie, G2032R) or brain metastases[1]
- Taletrectinib is a next-generation, potent, CNS-active, and selective ROS1 TKI specifically designed to:[2,3]
  - Improve efficacy and safety in ROS1+ NSCLC
  - Effectively treat CNS metastases
  - Overcome acquired resistance
  - Reduce neurological side effects with selectivity for ROS1 over tyrosine receptor kinase B (TrkB)
- We report updated data from the pivotal TRUST-I (NCT04395677) study in China, one of the largest clinical trials to date conducted in people living with ROS1+ NSCLC

1. Gendarme S et al. *Curr Oncol.* 2022;29:641-658. **2.** Nagasaka M et al. *Future Oncol.* 2023;19(2):123-135. **3.** Katayama R et al. *Nat Comm.* 2019;10(1):3604.
CNS, central nervous system; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

TRUST-I (NCT04395677): Phase 2 Trial of Taletrectinib in ROS1+ NSCLC

Key Eligibility Criteria

Inclusion Criteria:
- Locally advanced or metastatic NSCLC
- Age ≥18 years
- ECOG PS 0-1
- Evidence of ROS1 fusion in tumor tissue

Cohort A: ROS1 TKI naive
Taletrectinib 600 mg QD[b]

Cohort B: Crizotinib pretreated
Taletrectinib 600 mg QD[b]

Endpoints

Primary:
- IRC-assessed cORR per RECIST v1.1

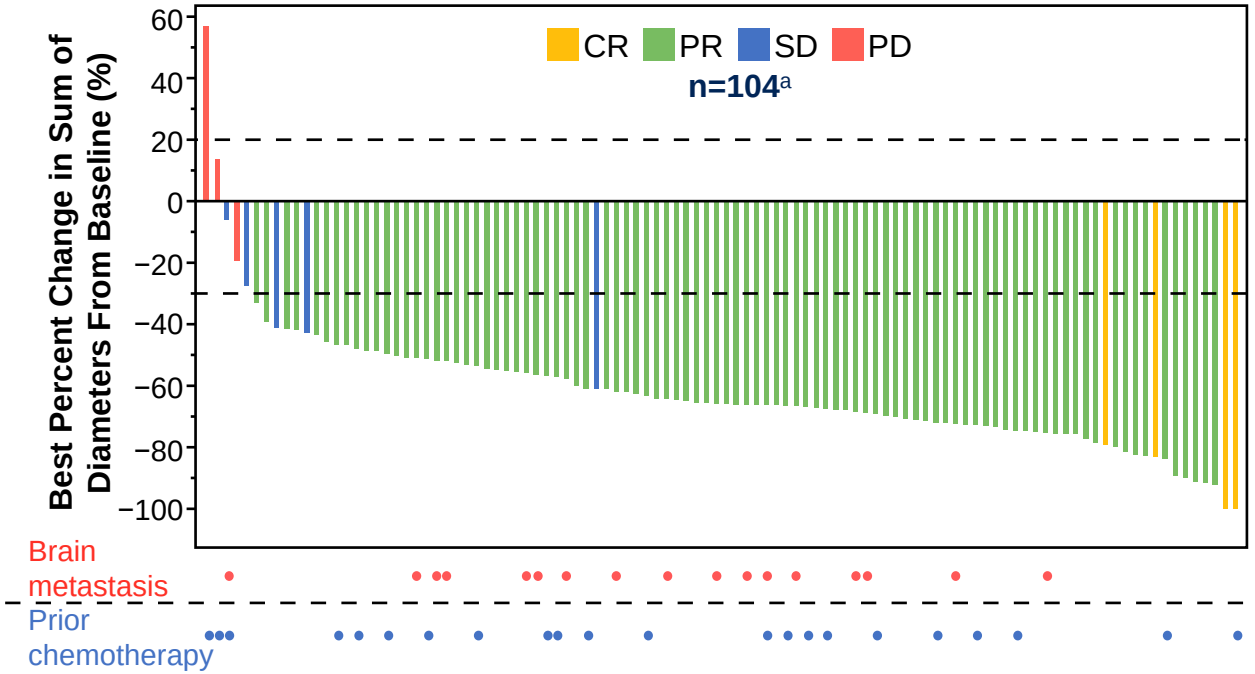
Secondary:
- DOR
- IC-ORR
- BOR
- DCR
- TTR
- PFS
- Safety[a]

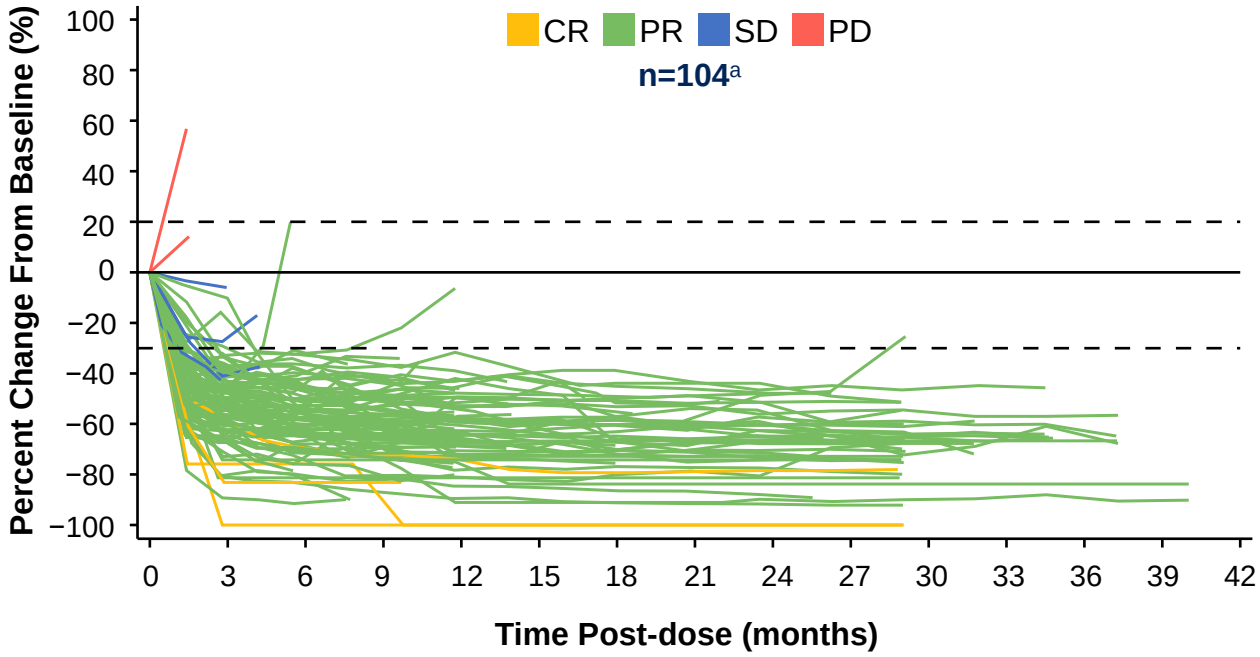
Category	TKI Naive n=106	Crizotinib Pretreated n=67	Overall n=173
Median age, years (range)	56.0 (26–78)	51.0 (31–77)	55.0 (26–78)
Female, n (%)	59 (55.7)	41 (61.2)	100 (57.8)
ECOG PS 0/1, n (%)	20 (18.9)/86 (81.1)	19 (28.4)/48 (71.6)	39 (22.5)/134 (77.5)
Stage IV disease	97 (91.5)	65 (97.0)	162 (93.6)
Prior anticancer chemotherapy, n (%)	22 (20.8)	23 (34.3)	45 (26.0)
Never smoker	78 (73.6)	49 (73.1)	127 (73.4)
Brain metastasis, n (%)	18 (17.0)	28 (41.8)	46 (26.6)

[a]Safety was analyzed in patients receiving ≥1 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.
[b]A dose confirmation lead-in stage evaluated the safety of taletrectinib 400 mg QD (n=3) and 600 mg QD (n=3).
BOR, best overall response; cORR, confirmed objective response rate; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, intracranial; IRC, independent review committee; NSCLC, non-small cell lung cancer; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; TTR, time to response.

Taletrectinib: Efficacy in ROS1+ TKI-Naive NSCLC

Responses	TKI Naive n=106
IRC-assessed cORR, % (95% CI)	90.6 (83.33, 95.38)
DCR, % (95% CI)	95.3 (89.33, 98.45)
Median TTR, months (95% CI)	1.4 (1.38, 1.41)

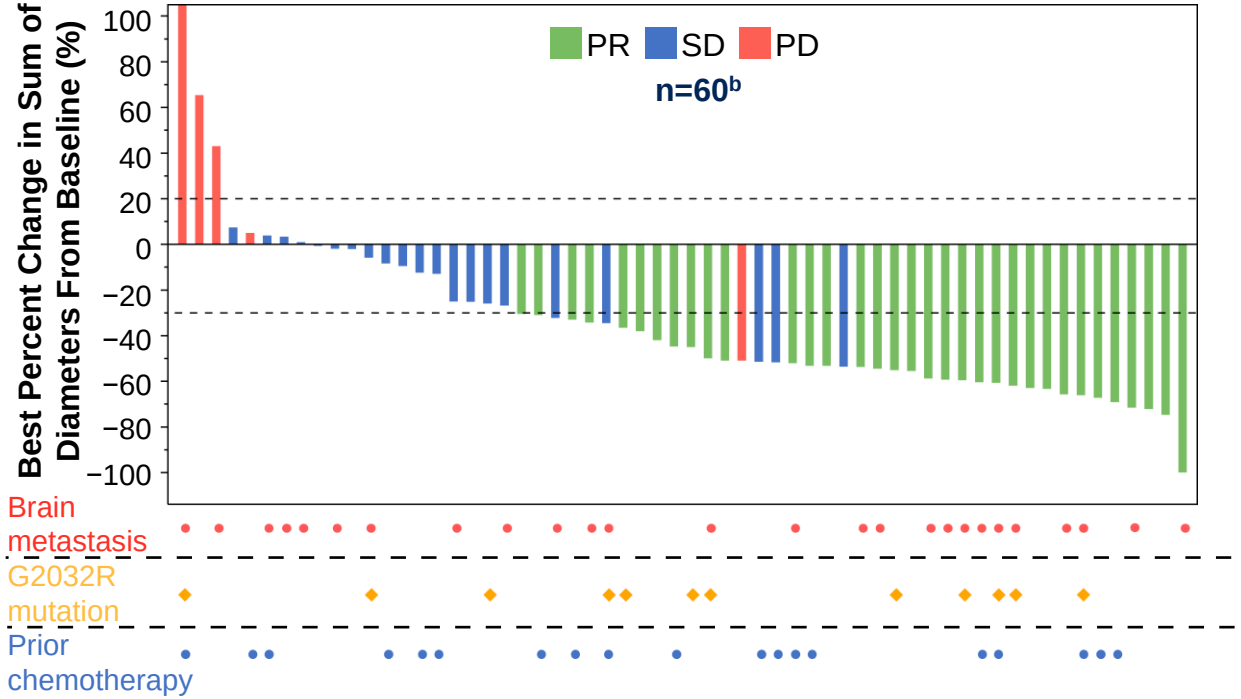


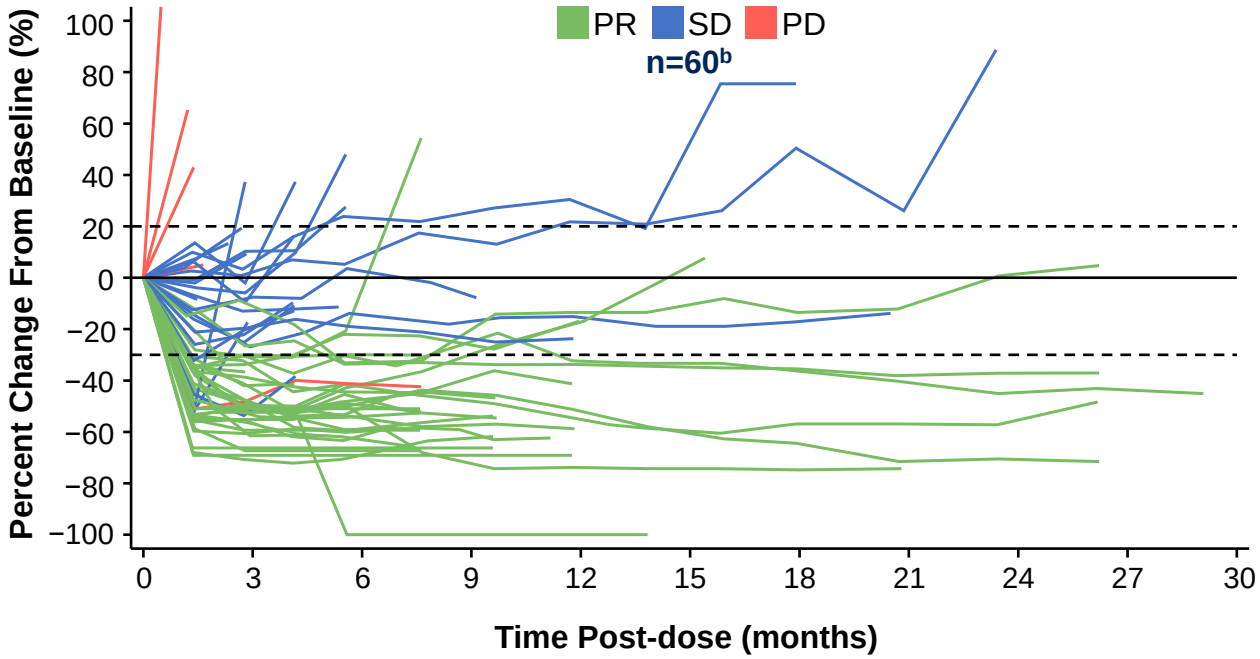


Data cutoff: November 29, 2023. [a]Two patients with confirmed BOR as not evaluable are not displayed in the waterfall and spider plots.
BOR, best overall response; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; IRC, independent review committee; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; TTR, time to response.

Taletrectinib: Efficacy in ROS1+ Crizotinib-Pretreated NSCLC

Responses	Crizotinib Pretreated n=66[a]
IRC-assessed cORR, % (95% CI)	51.5 (38.88, 64.01)
DCR, % (95% CI)	83.3 (72.13, 91.38)
Median TTR, months (95% CI)	1.4 (1.38, 1.41)
cORR: G2032R mutations, % (n/N)	66.7 (8/12)





Data cutoff: November 29, 2023. [a]One patient was excluded from the response-evaluable population in the crizotinib-pretreated group due to the presence of secondary cancer. [b]Six patients with confirmed BOR as not evaluable are not displayed in the waterfall and spider plots.

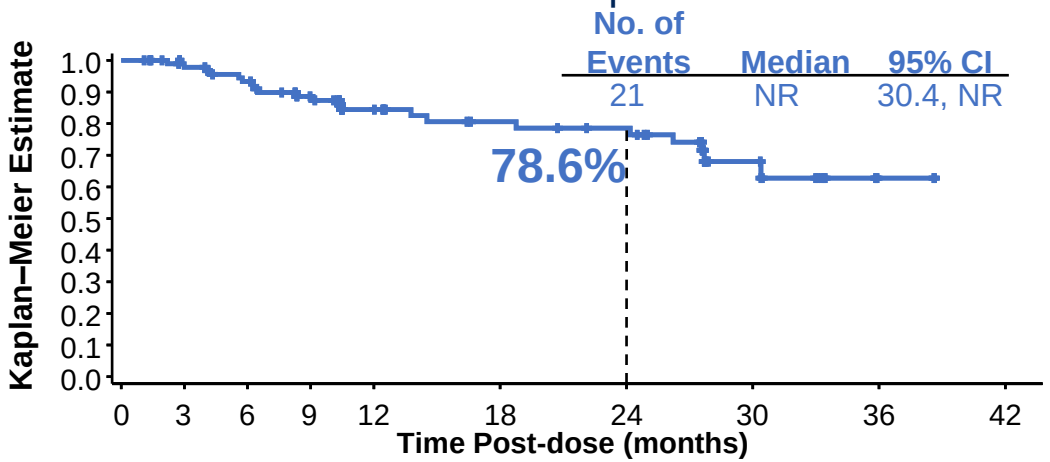
BOR, best overall response; cORR, confirmed objective response rate; DCR, disease control rate; IRC, independent review committee; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; TTR, time to response.

Taletrectinib: Duration of Response and Progression-Free Survival

TKI Naive (n=106)

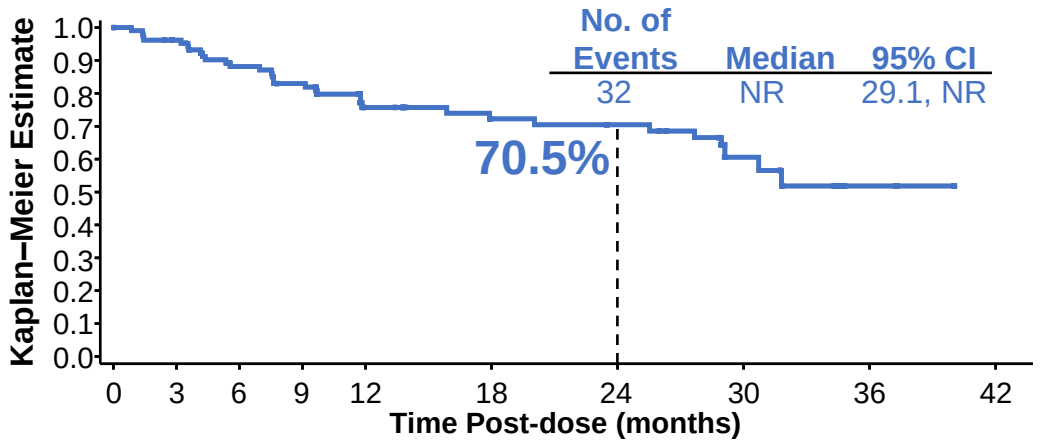
Median follow-up: 23.5 mo

DOR



Number at risk 96 89 82 70 50 40 37 14 2
TKI naive

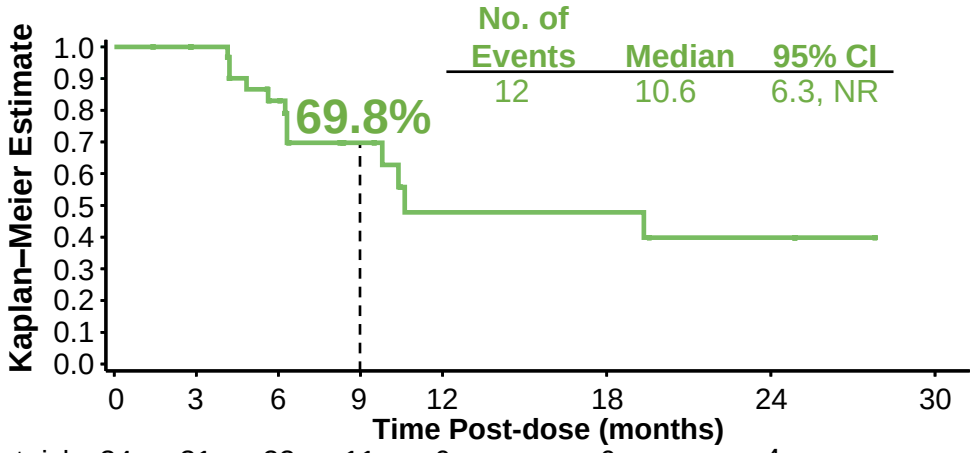
PFS



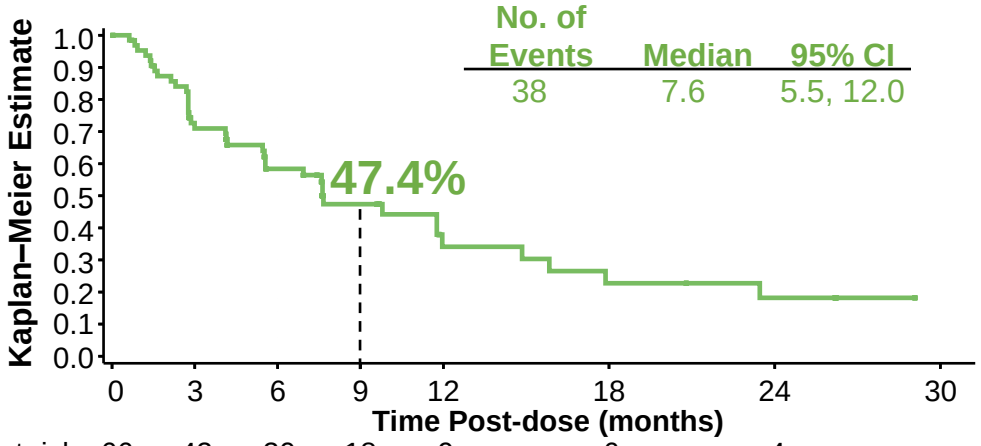
Number at risk 106 98 85 79 50 40 37 15 5
TKI naive

Crizotinib Pretreated (n=66)

Median follow-up: 9.7 mo



Number at risk 34 31 22 11 6 6 4
crizotinib pretreated

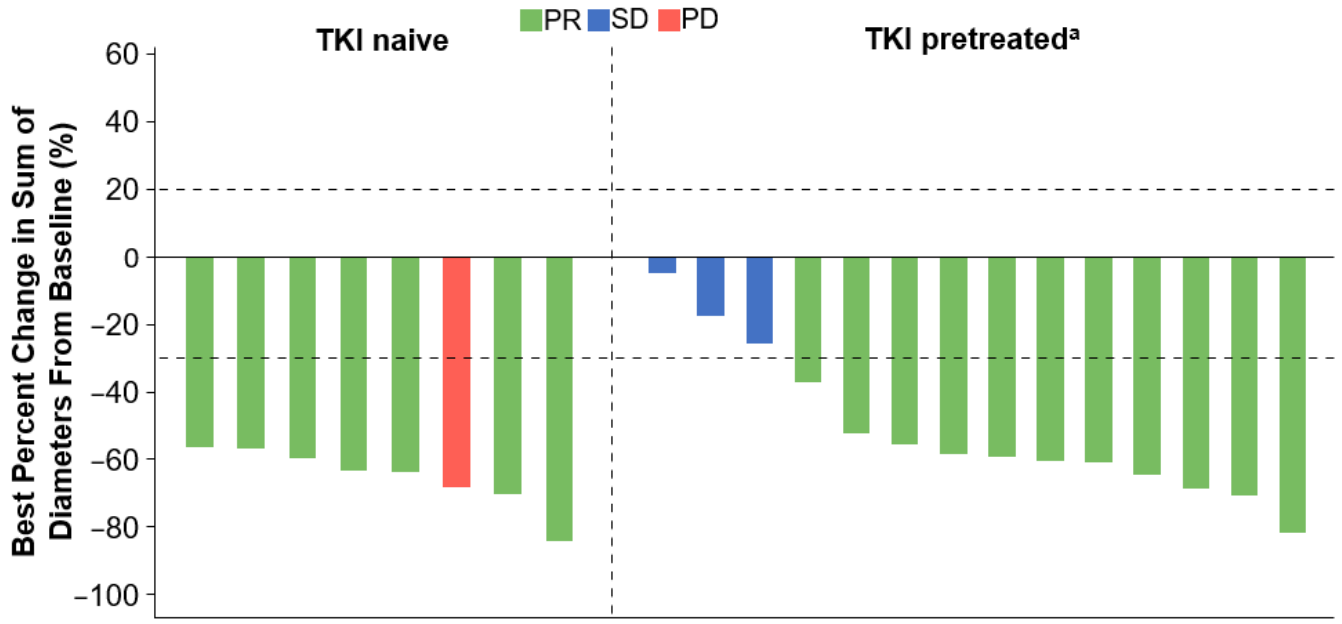


Number at risk 66 42 30 18 9 6 4
crizotinib pretreated

Data cutoff: November 29, 2023. DOR, duration of response; NR, not reached; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Taletrectinib: Responses in Measurable Baseline Brain Metastases

Responses	TKI Naive n=8	Crizotinib Pretreated n=15
IC-cORR, % (95% CI)	87.5 (47.35, 99.68)	73.3 (44.90, 92.21)
DCR, % (95% CI)	100.0 (63.06, 100.0)	93.3 (68.05, 99.83)



Data cutoff: November 29, 2023. [a]One patient with confirmed best overall response as not evaluable is not displayed in the waterfall plot.
cORR, confirmed objective response rate; DCR, disease control rate; IC, intracranial; IRC, independent review committee; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

Taletrectinib Safety: TEAEs in ≥15% of Patients[a] (N=173)

	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5[b] n (%)	Any grade n (%)
Increased AST	92 (53.2)	26 (15.0)	14 (8.1)	0	0	132 (76.3)
Diarrhea	99 (57.2)	16 (9.2)	6 (3.5)	0	0	121 (69.9)
Increased ALT	79 (45.7)	29 (16.8)	8 (4.6)	1 (0.6)	0	117 (67.6)
Vomiting	75 (43.4)	16 (9.2)	1 (0.6)	0	0	92 (53.2)
Anemia	52 (30.1)	30 (17.3)	3 (1.7)	0	0	85 (49.1)
Nausea	64 (37.0)	8 (4.6)	1 (0.6)	0	0	73 (42.2)
Decreased neutrophil count	25 (14.5)	10 (5.8)	6 (3.5)	4 (2.3)	0	45 (26.0)
Abnormal hepatic function	21 (12.1)	8 (4.6)	14 (8.1)	0	1 (0.6)	44 (25.4)
Decreased WBC count	27 (15.6)	14 (8.1)	3 (1.7)	0	0	44 (25.4)
Increased blood bilirubin	34 (19.7)	6 (3.5)	2 (1.2)	1 (0.6)	0	43 (24.9)
Dizziness	36 (20.8)	3 (1.7)	1 (0.6)	0	0	40 (23.1)
Proteinuria	34 (19.7)	5 (2.9)	0	0	0	39 (22.5)
Increased weight	17 (9.8)	16 (9.2)	3 (1.7)	0	0	36 (20.8)
Increased blood creatinine	33 (19.1)	2 (1.2)	0	0	0	35 (20.2)
QT prolongation	26 (15.0)	4 (2.3)	5 (2.9)	0	0	35 (20.2)
Hypercholesterolemia	29 (16.8)	4 (2.3)	0	0	0	33 (19.1)
Hyperuricemia	30 (17.3)	2 (1.2)	0	0	0	32 (18.5)
Decreased weight	23 (13.3)	8 (4.6)	0	0	0	31 (17.9)
Constipation	28 (16.2)	2 (1.2)	0	0	0	30 (17.3)
Decreased appetite	26 (15.0)	3 (1.7)	0	0	0	29 (16.8)
Increased conjugated bilirubin	22 (12.7)	3 (1.7)	2 (1.2)	1 (0.6)	0	28 (16.2)
COVID-19	10 (5.8)	15 (8.7)	3 (1.7)	0	0	28 (16.2)
Pyrexia	23 (13.3)	3 (1.7)	1 (0.6)	0	0	27 (15.6)
Increased blood CPK	21 (12.1)	5 (2.9)	0	0	0	26 (15.0)
Hypertriglyceridemia	24 (13.9)	2 (1.2)	0	0	0	26 (15.0)

- Median exposure of taletrectinib was 12.2 months (range: 0.23–40.04)
- 40.5% (70/173) of patients had a TEAE leading to treatment interruption
- 19.1% (33/173) of patients had a TEAE leading to a dose reduction
- 5.2% (9/173) of patients had a TEAE leading to treatment discontinuation
- Rates of neurologic TEAEs were low (dizziness: 23%; dysgeusia: 10%) and mostly grade 1

Data cutoff: November 29, 2023. [a]Worst grade per patient is reported. [b]Taletrectinib-related grade 5 TEAEs occurred in 3 patients: 2 TKI naive (1 hepatic failure, 1 pneumonia) and 1 crizotinib pretreated (abnormal hepatic function).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatinine phosphokinase; TEAE, treatment-emergent adverse event; WBC, white blood cell.

Conclusions

- With long-term follow-up in the TRUST-I trial in China, taletrectinib continued to demonstrate meaningful efficacy in both TKI-naive and crizotinib-pretreated patients with ROS1+ NSCLC
  - High and durable responses were observed, including high intracranial ORR
  - Prolonged PFS was observed regardless of line of therapy
  - Taletrectinib demonstrated activity against acquired resistance mutations including G2032R
- Taletrectinib demonstrated a favorable safety profile
  - Rates of dose reduction and treatment discontinuation due to TEAEs continued to be low
  - The rate of neurologic TEAEs was low and most were grade 1
- The ongoing global pivotal phase 2 study, TRUST-II (NCT04919811), is further evaluating the efficacy and safety of taletrectinib in patients with ROS1+ NSCLC in the United States, Europe, and Asia[1]

NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; TEAE, treatment-emergent adverse event.

1. Nagasaka M et al. *Future Onocol.* 2023;19(2):123-135.

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Efficacy and Safety of Taletrectinib in Chinese Patients With ROS11 Non–Small Cell Lung Cancer: The Phase II TRUST-I Study

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Efficacy and Safety of Taletrectinib in Chinese Patients With ROS1+ Non–Small Cell Lung Cancer: The Phase II TRUST-I Study

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ABSTRACT

PURPOSE Taletrectinib, a highly potent, CNS-active, ROS1 tyrosine kinase inhibitor (TKI), has demonstrated high and durable response rates, high intracranial objective response rate (ORR), prolonged progression-free survival (PFS), and activity against G2032R with a favorable safety profile. We report outcomes from the pivotal TRUST-I study (ClinicalTrials.gov identifier: NCT04395677) of taletrectinib for ROS1+ non–small cell lung cancer in China.

METHODS TRUST-I evaluated TKI-naïve and crizotinib-pretreated patients. The primary end point was confirmed ORR (cORR) by independent review committee; key secondary end points included duration of response (DOR), PFS, and safety.

RESULTS As of November 2023, 173 patients were enrolled (median age, 55 years; 58% female; 73% never smoked; TKI naïve: n = 106; crizotinib pretreated: n = 67). In TKI-naïve patients, cORR and intracranial cORR were 91% and 88%, respectively, and 52% and 73% in crizotinib-pretreated patients. In TKI-naïve patients, median DOR and median PFS were not reached (NR) with 22.1-month and 23.5-month follow-up, respectively. In crizotinib-pretreated patients, the median DOR was 10.6 months (95% CI, 6.3 months to NR; 8.4-month follow-up), and the median PFS was 7.6 months (95% CI, 5.5 to 12.0 months; 9.7-month follow-up). Eight of 12 patients (67%) with G2032R mutations responded. The most frequent treatment-emergent adverse events (TEAEs) were increased AST (76%), diarrhea (70%), and increased ALT (68%), most of which were grade 1-2. Incidences of neurologic TEAEs were low (dizziness: 23%; dysgeusia: 10%) and mostly grade 1. Discontinuations (5%) and dose reductions (19%) due to TEAEs were low.

CONCLUSION Taletrectinib continues to show high and durable overall responses, prolonged PFS, robust activity against intracranial lesions and acquired resistance mutations including G2032R, and a favorable safety profile with a low incidence of neurologic TEAEs.

ACCOMPANYING CONTENT

Appendix

Protocol

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INTRODUCTION

Tumors positive for proto-oncogene tyrosine protein kinase-1 (ROS1) gene fusions account for 0.9%-2.6% of non–small cell lung cancers (NSCLCs); most are lung adenocarcinomas.[1] In ROS1-rearranged (ROS1+) NSCLC, gene rearrangements result in constitutive activation of the ROS1 kinase domain and downstream activation of various signaling pathways related to cell differentiation, proliferation, and survival.[1] *ROS1* rearrangements in NSCLC are generally mutually exclusive, as newly diagnosed patients typically test negative for other known oncogenic alterations such as *ALK* rearrangements and EGFR mutations.[1] Patients with ROS1+ NSCLC tend to be female, younger than patients with NSCLC without driver mutations, and most are never smokers.[1]

ROS1 tyrosine kinase inhibitors (TKIs) are current standard of care for ROS1+ NSCLC.[2] Crizotinib was the first TKI approved in multiple countries for treatment of metastatic ROS1+ NSCLC.[3] Despite initial responses (objective response rate [ORR], 72%)[4] to first-line crizotinib, most patients eventually relapse within 2 years because of emergence of acquired resistance mutations (ie, G2032R) or brain

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