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Characterization of the Safety Profile of Taletrectinib in Patients With Advanced ROS1+ Non-Small Cell Lung Cancer: Results From TRUST-I and TRUST-II

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Background

- Taletrectinib is a next-generation, CNS-active, selective ROS1 TKI approved in the US, Japan, and China for the treatment of patients with locally advanced/metastatic ROS1+ NSCLC[1–5]
- Taletrectinib demonstrated robust efficacy, including IC activity and efficacy against G2032R mutations, with a manageable safety profile in TKI-naïve and TKI-pretreated patients with ROS1+ NSCLC in the Phase 2 TRUST-I (NCT04395677) and TRUST-II (NCT04919811) studies[6]
- Here we report efficacy data from TRUST-I and TRUST-II and updated pooled safety data, with a focus on clinically impactful AEs

Abbreviations

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; IC, intracranial; IRC, independent review committee; mo, months; (m)RECIST v1.1, (modified) Response Evaluation Criteria in Solid Tumors version 1.1; NA, not available; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; QD, once daily; ROS1, ROS proto-oncogene 1; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor; TRK, tropomyosin receptor kinase; US, United States.

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Methods

- The study designs of TRUST-I and TRUST-II have been previously reported[6]
- The efficacy population included patients from TRUST-I and TRUST-II with ≥1 measurable lesion at baseline per RECIST v1.1 by IRC who started treatment on taletrectinib 600 mg QD
- The safety population included all patients with ROS1+ NSCLC from Phase 1 and 2 studies who received ≥1 dose(s) of taletrectinib 600 mg QD

Efficacy

Patient Demographics and Baseline Characteristics

Baseline Characteristics	TKI-Naïve (N=157)	TKI-Pretreated (N=113)[a]	Integrated Safety Population (N=349)
Median age, years (range)	57 (26–83)	53 (27–79)	56 (26–83)
Female, n (%)	87 (55.4)	67 (59.3)	197 (56.4)
Stage IV disease, n (%)	143 (91.1)	110 (97.3)	329 (94.3)
ECOG PS 1, n (%)	116 (73.9)	73 (64.6)	236 (67.6)
Never smoker, n (%)	102 (65.0)	78 (69.0)	NA
Prior chemotherapy, n (%)	30 (19.1)	42 (37.2)	117 (33.5)
Brain metastases,[b] n (%)	37 (23.6)	55 (48.7)	NA
Prior crizotinib / entrectinib, n (%)	–	103 (91.2) / 10 (8.8)	NA

[a]TKI-pretreated patients in the efficacy population received one prior TKI. [b]Assessed by IRC per mRECIST v1.1.

Efficacy Summary

Efficacy	TKI-Naïve (N=157) TRUST-I (n=103)[7]	TKI-Naïve (N=157) TRUST-II (n=54)[8]	TKI-Pretreated (N=113) TRUST-I (n=66)[7]	TKI-Pretreated (N=113) TRUST-II (n=47)[8]
Median follow-up, months (range)	40.9 (22.0–50.1)	20.5 (8.3–34.5)	35.1 (21.5–50.1)	20.4 (8.6–34.5)
ORR, % (95% CI)	90.3 (82.9–95.3)	85.2 (72.9–93.4)	51.5 (38.9–64.0)[a]	61.7 (46.4–75.5)
Median DOR,[b] months (95% CI)	NR (30.4–NR)	NR (20.6–NR)	13.2 (7.7–24.9)	19.4 (10.7–NR)
Median PFS, months (95% CI)	44.6 (30.7–NR)	NR (15.9–NR)	7.6 (5.5–12.0)	11.8 (7.7–20.6)
IC Efficacy[c]	**(n=8)**	**(n=9)**	**(n=16)**	**(n=16)**
IC-ORR, % (95% CI)	87.5 (47.4–99.7)	66.7 (29.9–92.5)	75.0 (47.6–92.7)	56.3 (29.9–80.3)

Data cutoff: October 28, 2024. [a]Responses were observed in 8/12 patients with G2032R mutations (ORR 66.7% [95% CI 34.9–90.1]). [b]DOR reported only for patients with a complete or partial tumor response. [c]Assessed by IRC per mRECIST v1.1 in patients with ≥1 measurable baseline brain metastasis.

Safety

TEAEs in the Integrated Safety Population

- As of October 28, 2024, the integrated safety population included 349 patients with ROS1+ NSCLC from Phase 1 and Phase 2 studies who received ≥1 dose(s) of taletrectinib 600 mg QD
- The most common (any grade) TEAEs were increased AST, increased ALT, diarrhea, nausea, and vomiting (**Supplement**)
  - Increased AST/ALT were mostly low grade and only led to treatment discontinuation in one patient; GI events were mostly Grade 1, occurred early during treatment and were transient (**Supplement**)
- TEAEs led to dose interruptions in 40.7% of patients, dose reductions in 28.9%, and treatment discontinuations in 7.2%
  - Dose reductions did not affect efficacy (**Supplement**)

Treatment-Related AEs Associated With TRK Inhibition

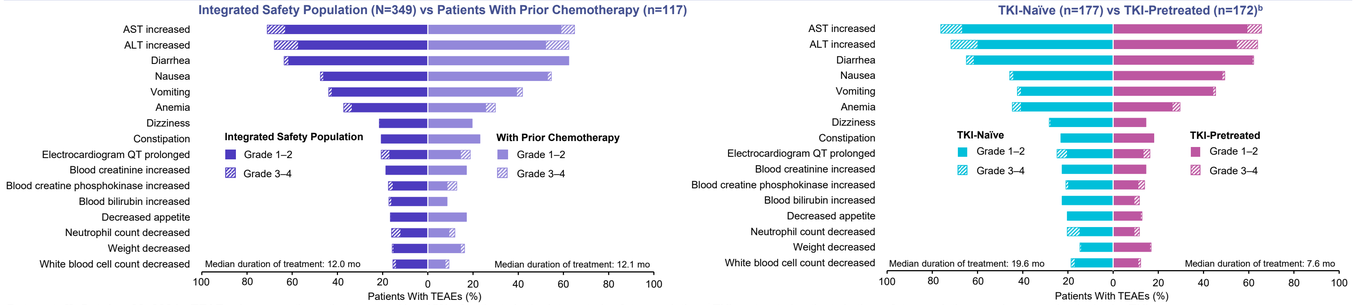
- Some ROS1 TKIs also inhibit TRK proteins, which can lead to neurologic toxicities that may impact patient quality of life[9]
- Taletrectinib was associated with low rates of neurologic treatment-related AEs, which were mostly Grade 1 and led to few dose reductions and no treatment discontinuations
  - TEAEs associated with TRK inhibition are included in the **Supplement**

Treatment-Related AEs Associated With TRK Inhibition (N=349)[a]

Treatment-Related AEs, n (%)	Any Grade	Grade 1	Grade 2	Grade 3	Dose Interruption	Dose Reduction	Treatment Discontinuation
Dizziness	53 (15.2)	49 (14.0)	3 (0.9)	1 (0.3)	2 (0.6)	1 (0.3)	0
Dysgeusia	51 (14.6)	44 (12.6)	7 (2.0)	0	1 (0.3)	1 (0.3)	0
Paresthesia[b]	35 (10.0)	31 (8.9)	3 (0.9)	1 (0.3)	2 (0.6)	2 (0.6)	0
Weight gain	15 (4.3)	10 (2.9)	4 (1.1)	1 (0.3)	0	0	0
Sleep disturbance[c]	12 (3.4)	12 (3.4)	0	0	0	0	0
Cognitive impairment[d]	3 (0.9)	3 (0.9)	0	0	0	0	0
Mood disorders[e]	1 (0.3)	1 (0.3)	0	0	0	0	0
Ataxia	0	0	0	0	0	0	0
Dysarthria	0	0	0	0	0	0	0

Data cutoff: October 28, 2024. [a]The inclusion of treatment-related AEs in the table is based on AEs commonly attributed to TRK inhibition by other ROS1/TRK inhibitors. Withdrawal pain has been associated with TRK inhibition. Clinical and nonclinical data do not suggest a risk of physical dependence and subsequent withdrawal symptoms with cessation of taletrectinib. [b]Grouped term for paresthesia, hyperesthesia, hypoesthesia, dysesthesia, and anesthesia. [c]Grouped term for somnolence, insomnia, and sleep disorder. [d]Grouped term for cognitive disorder, dementia, disturbance in attention, mental impairment, confusional state, delirium, memory impairment, and amnesia. [e]Grouped term for depression and anxiety.

TEAEs Were Similar Regardless of Receipt of Prior Anticancer Therapies[a]



Data cutoff: October 28, 2024. [a]TEAEs shown are those that occurred in ≥15% of patients in the integrated safety population. [b]TKI-pretreated patients in the safety population may have received ≥1 prior TKI.

Conclusions

- Taletrectinib demonstrated robust efficacy in both TKI-naïve and TKI-pretreated patients with advanced ROS1+ NSCLC
- The safety profile of taletrectinib was manageable, with low rates of dose reductions and discontinuations due to TEAEs, and was not affected by receipt of prior anticancer therapies
- Neurologic treatment-related AEs associated with TRK inhibition, which may impact patient quality of life, occurred infrequently with taletrectinib, were mostly Grade 1, and resulted in few dose reductions and no treatment discontinuations

Disclosures

The presenting author, Yasir Elamin, declares the following potential conflicts of interest: Advisory board: AstraZeneca, BluePrint Medicines, BMS, Catalyst Pharmaceuticals, Eli Lilly, Merus, Mirati Therapeutics, Novartis, Nuvation Bio, Sanofi, Spectrum, Taiho, Takeda, Turning Point Therapeutics; Funding to institution: AstraZeneca, BMS, Nuvation Bio, Spectrum, Taiho, Takeda

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TEAEs in ≥15% of Patients (N=349)[a]

Most Frequent TEAEs (≥15% of Patients), n (%)	Any Grade	Grade 1	Grade 2	Grade ≥3
Increased AST	248 (71.1)	161 (46.1)	59 (16.9)	28 (8.0)
Increased ALT	237 (67.9)	138 (39.5)	62 (17.8)	37 (10.6)
Diarrhea	222 (63.6)	174 (49.9)	41 (11.7)	7 (2.0)
Nausea	166 (47.6)	125 (35.8)	36 (10.3)	5 (1.4)
Vomiting	153 (43.8)	119 (34.1)	29 (8.3)	5 (1.4)
Anemia	130 (37.2)	77 (22.1)	40 (11.5)	13 (3.7)
Dizziness	75 (21.5)	65 (18.6)	9 (2.6)	1 (0.3)
Constipation	72 (20.6)	61 (17.5)	11 (3.2)	0
Electrocardiogram QT prolonged	72 (20.6)	49 (14.0)	10 (2.9)	13 (3.7)
Blood creatinine increased	65 (18.6)	54 (15.5)	11 (3.2)	0
Blood creatine phosphokinase increased	61 (17.5)	40 (11.5)	14 (4.0)	7 (2.0)
Blood bilirubin increased	60 (17.2)	43 (12.3)	13 (3.7)	4 (1.1)
Decreased appetite	58 (16.6)	40 (11.5)	17 (4.9)	1 (0.3)
Neutrophil count decreased	56 (16.0)	28 (8.0)	14 (4.0)	14 (4.0)
Weight decreased	55 (15.8)	27 (7.7)	26 (7.4)	2 (0.6)
White blood cell count decreased	54 (15.5)	31 (8.9)	18 (5.2)	5 (1.4)

Data cutoff: October 28, 2024.

[a]The safety population included patients with ROS1+ NSCLC who received ≥1 dose(s) of taletrectinib 600 mg QD from Phase 2 trials (TRUST-I and TRUST-II) and a Phase 1 trial (J102).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NSCLC, non-small cell lung cancer; QD, once daily; ROS1, ROS proto-oncogene 1; TEAE, treatment-emergent adverse event.

TEAEs of Clinical Interest (N=349)[a]

TEAE	Any Grade, n (%)	Grade ≥3, n (%)	Median Time to Onset, Days (IQR)	Median Time to Resolution, Days (IQR)	Dose Interruption, n (%)	Dose Reduction, n (%)	Treatment Discontinuation, n (%)
Increased AST	248 (71.1)	28 (8.0)	16 (8, 43)[b]	57 (31, 154)[b]	24 (6.9)	19 (5.4)	1 (0.3)
Increased ALT	237 (67.9)	37 (10.6)			24 (6.9)	31 (8.9)	
Diarrhea	222 (63.6)	7 (2.0)	2 (1, 16)	1 (1, 3)	7 (2.0)	9 (2.6)	0
Nausea	166 (47.6)	5 (1.4)	2 (1, 14)	4 (1, 61)	5 (1.4)	5 (1.4)	0
Vomiting	153 (43.8)	5 (1.4)	3 (1, 42)	1 (1, 3)	10 (2.9)	6 (1.7)	0
Dizziness	75 (21.5)	1 (0.3)	38 (3, 239)	3 (1, 42)	2 (0.6)	1 (0.3)	0
Dysgeusia	51 (14.6)	0	15 (6, 28)	248 (58, 570)	1 (0.3)	1 (0.3)	0

Data cutoff: October 28, 2024.

[a]The safety population included patients with ROS1+ NSCLC who received ≥1 dose(s) of taletrectinib 600 mg QD from Phase 2 trials (TRUST-I and TRUST-II) and a Phase 1 trial (J102).

[b]Median time to onset for Grade ≥3 increased AST/ALT was 43 days (IQR: 22, 86) and median time to resolution was 13 days (IQR: 8, 19.5). These results are based on laboratory data.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range; NSCLC, non-small cell lung cancer; QD, once daily; ROS1, ROS proto-oncogene 1; TEAE, treatment-emergent adverse event.

TEAEs Associated With TRK Inhibition (N=349)[a]

TEAEs, n (%)	Any Grade	Grade 1	Grade 2	Grade ≥3	Dose Interruption	Dose Reduction	Treatment Discontinuation
Dizziness	75 (21.5)	65 (18.6)	9 (2.6)	1 (0.3)	2 (0.6)	1 (0.3)	0
Dysgeusia	51 (14.6)	44 (12.6)	7 (2.0)	0	1 (0.3)	1 (0.3)	0
Weight gain	46 (13.2)	21 (6.0)	21 (6.0)	4 (1.1)	0	0	0
Paresthesia[b]	42 (12.0)	38 (10.9)	3 (0.9)	1 (0.3)	2 (0.6)	2 (0.6)	0
Sleep disturbance[c]	21 (6.0)	20 (5.7)	1 (0.3)	0	0	0	0
Mood disorders[d]	10 (2.9)	6 (1.7)	4 (1.1)	0	0	1 (0.3)	0
Cognitive impairment[e]	6 (1.7)	5 (1.4)	0	1 (0.3)	0	0	0
Dysarthria	2 (0.6)	1 (0.3)	0	1 (0.3)	0	0	1 (0.3)
Ataxia	0	0	0	0	0	0	0

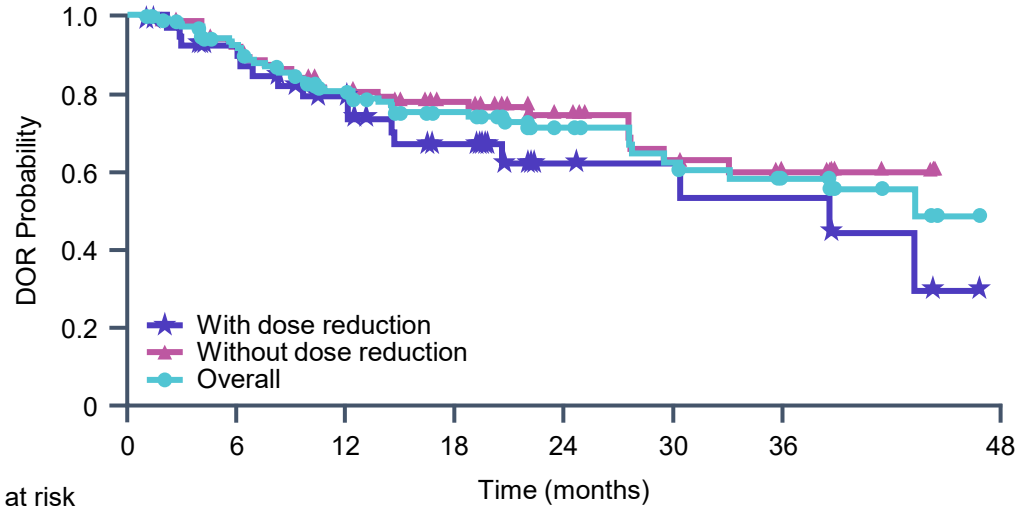
Data cutoff: October 28, 2024.

[a]The inclusion of treatment-related AEs in the table is based on AEs commonly attributed to TRK inhibition by other ROS1/TRK inhibitors. Withdrawal pain has been associated with TRK inhibition. Clinical and nonclinical data do not suggest a risk of physical dependence and subsequent withdrawal symptoms with cessation of taletrectinib. [b]Grouped term for paresthesia, hyperesthesia, hypoesthesia, dysesthesia, and anesthesia. [c]Grouped term for somnolence, insomnia, and sleep disorder. [d]Grouped term for depression and anxiety. [e]Grouped term for cognitive disorder, dementia, disturbance in attention, mental impairment, confusional state, delirium, memory impairment, and amnesia.

AE, adverse event; ROS1, ROS proto-oncogene 1; TEAE, treatment-emergent adverse event; TRK, tropomyosin receptor kinase.

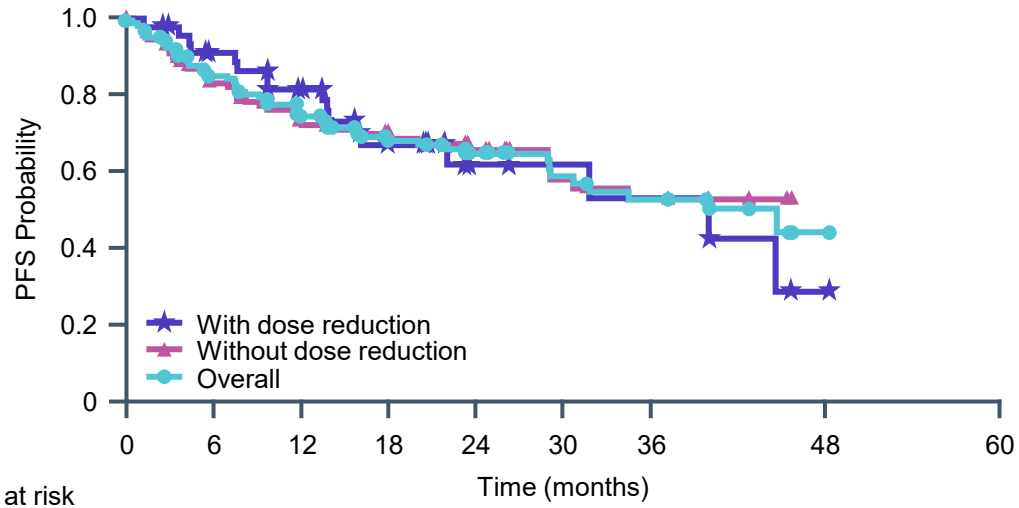
DOR and PFS Across the Efficacy Population Were Similar Regardless of Dose Reduction Status in TKI-Naïve Patients (N=157)[a]

	With dose reduction	Without dose reduction	Overall
No. of events (%)	16 (36.4)	26 (27.4)	42 (30.2)
Median (95% CI)	38.6 (14.7–NR)	NR (29.5–NR)	43.3 (30.4–NR)



Numbers at risk								
With dose reduction	44	36	28	19	8	7	6	0
Without dose reduction	95	83	68	52	29	22	18	0
Overall	139	119	96	71	37	29	24	0

	With dose reduction	Without dose reduction	Overall
No. of events (%)	17 (37.0)	39 (35.1)	56 (35.7)
Median (95% CI)	40.0 (16.1–NR)	NR (29.0–NR)	44.6 (29.1–NR)



Numbers at risk									
With dose reduction	46	38	31	20	8	7	6	1	0
Without dose reduction	111	85	70	53	31	23	20	0	0
Overall	157	123	101	73	39	30	26	1	0

Data cutoff: October 28, 2024.

[a]The efficacy population included patients from TRUST-I and TRUST-II with ≥1 measurable lesion at baseline per RECIST v1.1 by IRC who started treatment on taletrectinib 600 mg QD.

CI, confidence interval; DOR, duration of response; IRC, independent review committee; NR, not reached; PFS, progression-free survival; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TKI, tyrosine kinase inhibitor.

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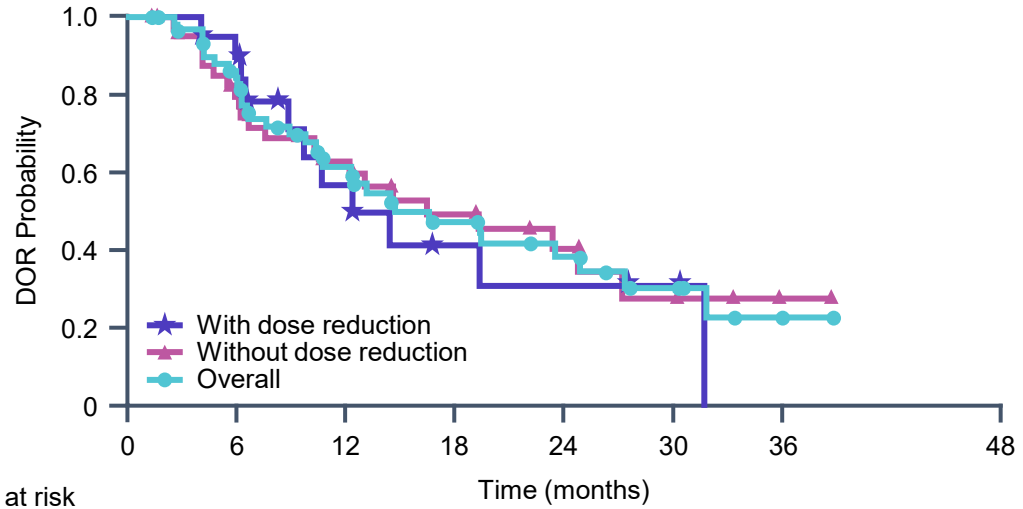
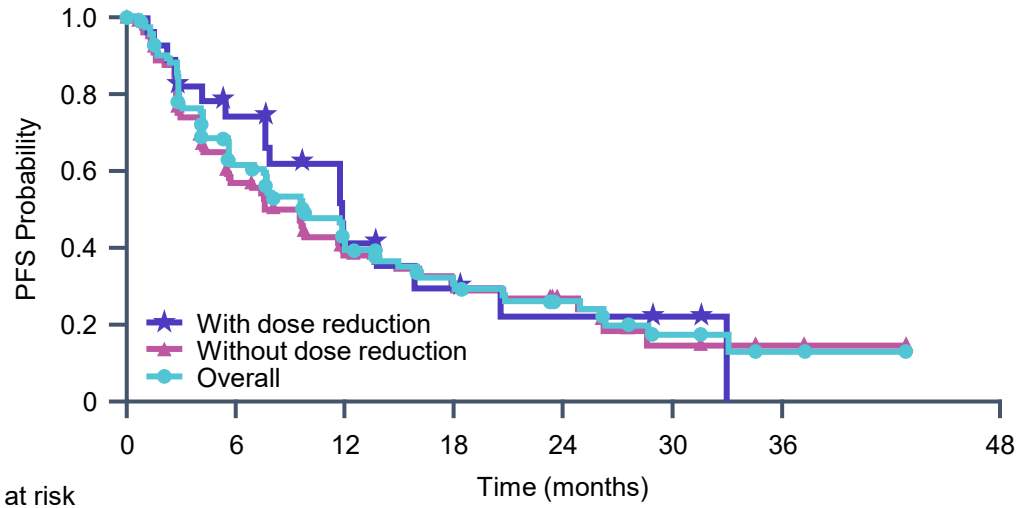
DOR and PFS Across the Efficacy Population Were Similar Regardless of Dose Reduction Status in TKI-Pretreated Patients (N=113)[a]

	With dose reduction	Without dose reduction	Overall
No. of events (%)	11 (55.0)	22 (51.2)	33 (52.4)
Median (95% CI)	12.5 (8.9–NR)	16.6 (10.4–27.3)	14.7 (10.6–24.9)



Numbers at risk								
With dose reduction	20	18	8	4	3	2	0	0
Without dose reduction	43	31	20	14	8	4	1	0
Overall	63	49	28	18	11	6	1	0

	With dose reduction	Without dose reduction	Overall
No. of events (%)	18 (64.3)	57 (67.1)	75 (66.4)
Median (95% CI)	11.9 (7.7–15.9)	9.5 (5.6–12.0)	9.7 (7.4–12.0)



Numbers at risk								
With dose reduction	28	19	8	5	3	2	0	0
Without dose reduction	85	42	23	15	10	4	2	0
Overall	113	61	31	20	13	6	2	0

Data cutoff: October 28, 2024.

[a]The efficacy population included patients from TRUST-I and TRUST-II with ≥1 measurable lesion at baseline per RECIST v1.1 by IRC who started treatment on taletrectinib 600 mg QD.

CI, confidence interval; DOR, duration of response; IRC, independent review committee; NR, not reached; PFS, progression-free survival; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TKI, tyrosine kinase inhibitor.

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