



Efficacy and Safety of Taltrectinib in Patients With ROS1+ NSCLC: Updated Safety Analysis From the Phase 2 TRUST-I and TRUST-II Studies

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Background

- Taltrectinib is a next-generation, CNS-active, selective ROS1 TKI that has shown activity against the G2032R resistance mutation^{1,2}
- Taltrectinib has been approved in the United States, Japan, and China for the treatment of patients with locally advanced or metastatic ROS1+ NSCLC³⁻⁵
- In two Phase 2 studies, TRUST-I (NCT04395677) and TRUST-II (NCT04919811), taltrectinib showed robust efficacy and a manageable safety profile in TKI-naïve and TKI-pretreated patients with advanced ROS1+ NSCLC⁶
- Here we report efficacy data from TRUST-I and TRUST-II, and updated pooled safety results with longer follow-up, including more detailed characterization of TEAEs of clinical interest

Abbreviations

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; IC, intracranial; IQR, interquartile range; IRC, independent review committee; (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.

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Methods

- The study designs of TRUST-I and TRUST-II have been previously reported⁶
- The efficacy population included patients from TRUST-I and TRUST-II with ≥1 measurable lesion(s) at baseline per RECIST v1.1 by IRC who started treatment on taltrectinib 600 mg QD
- The safety population included patients with ROS1+ NSCLC who received ≥1 dose(s) of taltrectinib 600 mg QD from Phase 1 and Phase 2 studies

Results

Patient Demographics and Baseline Characteristics

Baseline Characteristics	TKI-Naïve (N=157)	TKI-Pretreated (N=113)	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)	NA
Brain metastases, ^a n (%)	37 (23.6)	55 (48.7)	NA
Prior crizotinib / entrectinib, n (%)	-	103 (91.2) / 10 (8.8)	NA

^aAssessed by IRC per mRECIST v1.1.

Efficacy Summary

Efficacy	TKI-Naïve (N=157)		TKI-Pretreated (N=113)	
	TRUST-I (n=103) ⁷	TRUST-II (n=54) ⁸	TRUST-I (n=66) ⁷	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. ^aResponses were observed in 8/12 patients with G2032R mutations (ORR 66.7% [95% CI: 34.9-90.1]). ^bDOR reported in responders only. ^cAssessed by IRC per mRECIST v1.1 in patients with ≥1 measurable baseline brain metastasis.

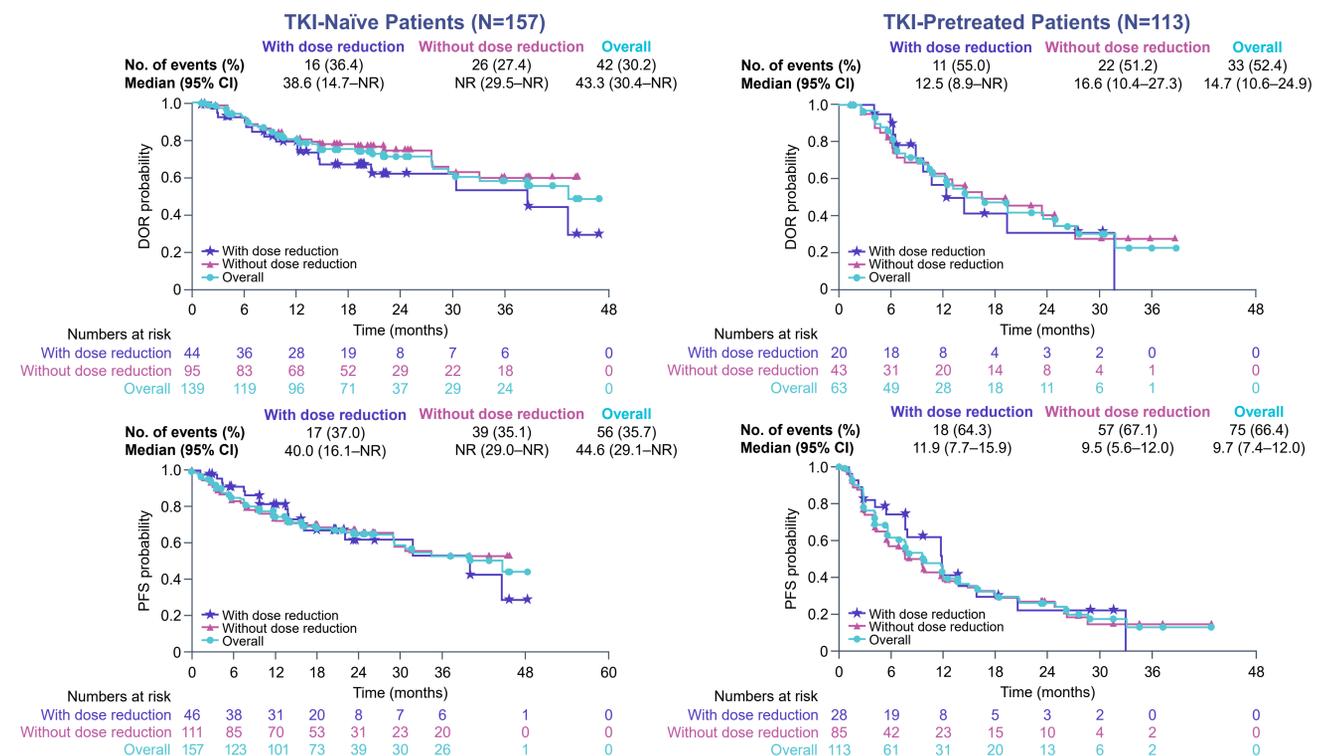
Results (cont'd)

TEAEs of Clinical Interest (N=349)

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) ^a	57 (31, 154) ^a	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. ^aMedian 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.

TRUST-I and TRUST-II: DOR and PFS Were Similar Regardless of Dose Reduction Status⁹



Data cutoff: October 28, 2024.

Conclusions

- Taltrectinib demonstrated robust efficacy in both TKI-naïve and TKI-pretreated patients with advanced ROS1+ NSCLC
- With longer follow-up, taltrectinib maintained a manageable and consistent safety profile, with no new safety signals
- TEAEs of clinical interest, including increased AST/ALT, gastrointestinal events, and CNS events, were largely transient and low grade, and rarely led to treatment discontinuation
- Pooled analyses from the TRUST-I and TRUST-II studies demonstrated that dose reductions did not compromise efficacy