53P

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

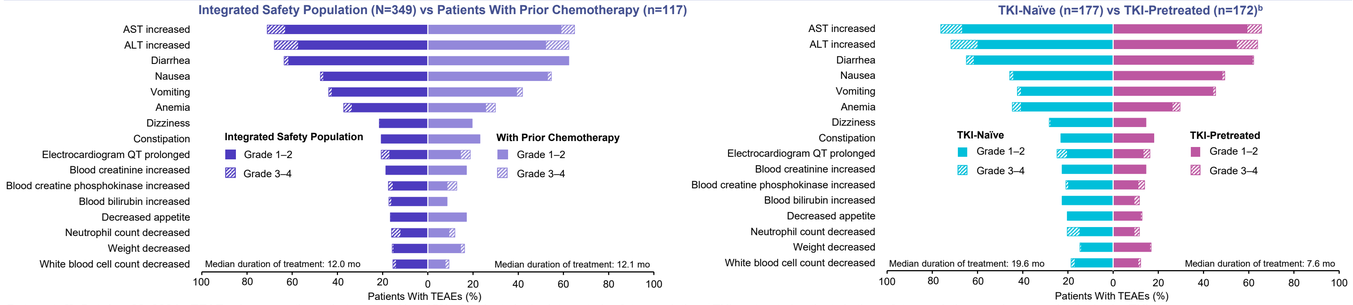
- Some ROS1 TKIs also inhibit TRK proteins, which can lead to neurologic toxicities that may impact patient quality of life[9]
- Taletrectinib was associated with low rates of neurologic treatment-related AEs, which were mostly Grade 1 and led to few dose reductions and no treatment discontinuations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