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TRUST-II Global Study: Efficacy and Safety of Taletrectinib After Prior Entrectinib Exposure in Patients With Advanced ROS1+ Non-Small Cell Lung Cancer

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Background

- Taletrectinib is a next-generation, CNS-active, selective, oral ROS1 inhibitor with efficacy against the G2032R resistance mutation[1]
- Taletrectinib is currently approved in the United States, China, and Japan for the treatment of adult patients with locally advanced or metastatic ROS1+ NSCLC[2–4]
- In the global, Phase 2 TRUST-II study (NCT04919811), taletrectinib showed robust overall and IC responses and a favorable safety profile in both TKI-naïve and TKI-pretreated patients with ROS1+ NSCLC[5]
- Here, we report subgroup analyses from TRUST-II in patients who were previously treated with entrectinib, another CNS-active ROS1 TKI

Abbreviations

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BOR, best overall response; c, confirmed; CI, confidence interval; CNS, central nervous system; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, intracranial; IRC, Independent Review Committee; (m)RECIST v1.1, (modified) Response Evaluation Criteria in Solid Tumors version 1.1; NA, not applicable; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; QD, once daily; ROS1, ROS proto-oncogene 1; SD, stable disease; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor; TTR, time to response.

References

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Methods

- TRUST-II (NCT04919811) is a global, multicenter, pivotal, Phase 2 study of taletrectinib in patients with ROS1+ NSCLC, including both TKI-naïve and TKI-pretreated patients, that was initiated in 2021

TRUST-II Study Design

Key eligibility criteria
- Locally advanced or metastatic NSCLC with ROS1 fusion
- Age ≥18 years[a]
- ECOG PS 0–1

Cohort 1 **TKI-naïve[b]**
Cohort 2 **TKI-pretreated[b]**
→ **Taletrectinib** 600 mg QD

Endpoints

Primary
- IRC-assessed cORR per RECIST v1.1

Secondary
- DOR
- IC-ORR[c]
- TTR
- PFS
- OS
- Safety

[a]Or ≥20 years, as required by local regulations. [b]Registrational cohorts are shown. [c]Assessed by IRC per mRECIST v1.1.

- Patients in Cohort 2 received prior treatment with crizotinib or entrectinib; patients may also have received prior chemotherapy with or without immunotherapy
- Here, we report efficacy and safety in the 10 patients from Cohort 2 who received prior entrectinib treatment

Results

Patient Demographics and Baseline Characteristics

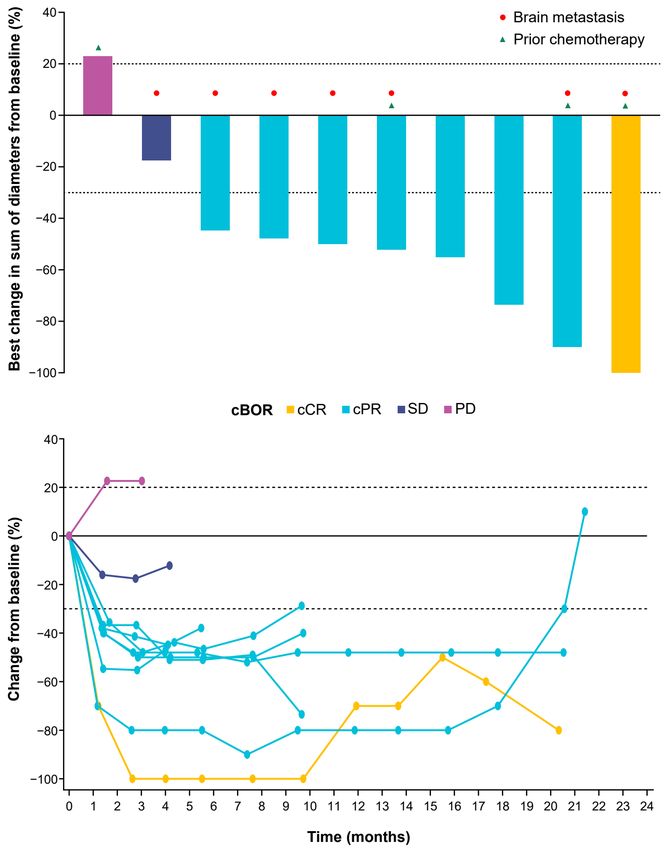
Baseline characteristics	Entrectinib-pretreated (n=10)	All TKI-pretreated (N=50)
Median age, years (range)	54.0 (27–79)	55.5 (27–79)
Female, n (%)	5 (50)	27 (54)
Never smoker, n (%)	6 (60)	30 (60)
Region: Asia / non-Asia, n (%)	3 (30) / 7 (70)	22 (44) / 28 (56)
Stage IV disease, n (%)	10 (100)	49 (98)
ECOG PS 1, n (%)	8 (80)	26 (52)
Prior chemotherapy, n (%)	4 (40)	19 (38)
Brain metastases at baseline,[a] n (%)	7 (70)	28 (56)
Median time on prior entrectinib, months (range)	15.5 (6.3–84.1)	NA
BOR on prior entrectinib, n (%)		
CR	2 (20)	NA
PR	8 (80)	NA

[a]Assessed by IRC per mRECIST v1.1.

- Entrectinib was the most recent anticancer therapy in all patients, received immediately prior to taletrectinib
- All 10 patients experienced disease progression on entrectinib

Results: Efficacy

Tumor Response in Entrectinib-Pretreated Patients



Efficacy[a]	Entrectinib-pretreated (n=10)	All TKI-pretreated (n=47)
cORR, % (95% CI)	80.0 (44.4–97.5)	61.7 (46.4–75.5)
IC efficacy[b]	**(n=4)**	**(n=16)**
IC-ORR, % (95% CI)	50.0 (6.8–93.2)	56.3 (29.9–80.3)

Data cutoff: October 28, 2024. [a]Assessed by IRC per RECIST v1.1 in patients with ≥1 measurable lesion at baseline who received ≥1 dose of taletrectinib. [b]Assessed by IRC per mRECIST v1.1 in patients with ≥1 measurable baseline brain metastasis.

- In entrectinib-pretreated patients, cORR was 80%, including one CR and seven PRs
- Among four patients with measurable brain metastases, the IC-ORR was 50%

Results: Safety

Most Frequent TEAEs (≥20% of Entrectinib-Pretreated Patients)

TEAEs, n (%)	Entrectinib-pretreated (n=10)	All TKI-pretreated (N=50)
Diarrhea	8 (80)	31 (62)
Increased AST	7 (70)	39 (78)
Increased ALT	7 (70)	36 (72)
Vomiting	4 (40)	15 (30)
Nausea	3 (30)	19 (38)
Decreased appetite	3 (30)	6 (12)
Anemia	2 (20)	10 (20)
Constipation	2 (20)	8 (16)
Dizziness	2 (20)	6 (12)
Headache	2 (20)	5 (10)
Dyspnea	2 (20)	5 (10)
Pyrexia	2 (20)	5 (10)
Lymphopenia	2 (20)	2 (4)

Data cutoff: October 28, 2024.

- The most frequent TEAEs in both entrectinib-pretreated and all TKI-pretreated groups were mainly Grade 1 and 2
- AEs of interest commonly associated with entrectinib, such as weight gain, visual disorders, or congestive heart failure, were not observed with taletrectinib in entrectinib-pretreated patients
- Despite a small sample size, the overall safety profile of taletrectinib in entrectinib-pretreated patients was consistent with that observed in the full TKI-pretreated cohort

Conclusions

- Taletrectinib demonstrated high overall and IC response rates in patients with ROS1+ NSCLC who were previously treated with entrectinib, another CNS-active ROS1 TKI
- Among patients previously treated with entrectinib, the safety profile of taletrectinib was consistent with that observed in the full TKI-pretreated cohort
- These data support the use of taletrectinib as a subsequent treatment option for patients with ROS1+ NSCLC after prior entrectinib treatment

Disclosures

The presenting author, Filippo de Braud, declares the following potential conflicts of interest:
Speakers bureau: Ambrosetti, Bayer, Biotechespert, Bristol Myers Squibb, Dephaforum, ESO, Events, Fare Comunicazione, Ignyta, Incyte, Itanet, Merck, Motore Sanità, Nadirex, Pfizer, Prime Oncology, and Roche; Advisory board: Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Dephaforum, Fondazione Menarini, Gentili, Ignyta, Incyte, Lilly, Merck, Novartis, Octimet Oncology, Pfizer, Pharm Research Associates, Pierre Fabre, Roche, Sanofi, Servier, Taiho, and Tiziana Life Sciences; Research grant: Bristol Myers Squibb, Celgene, Darmstadt, Germany, Incyte, Kymab, Merck, Novartis, NMS, the healthcare business of Merck KGaA, Pfizer, Roche, and Tesaro; Principal investigator: Basilea Pharmaceutica, Bristol Myers Squibb, Daiichi Sankyo, Exelixis, Janssen, Ignyta, Kymab, LOXO Oncology, MedImmune, Merck KGaA, MSD, Novartis, Pfizer, Roche, and Tesaro; Consulting: Bristol Myers Squibb, IQVIA, Mattioli 1885, McCann Health, MSD, and Pierre Fabre; Travel expenses: Amgen, Bristol Myers Squibb, Celgene, and Roche.

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