TRUST: The Efficacy and Safety of Taletrectinib in TKI-Naïve or Crizotinib-Pretreated ROS1-Positive Non-Small Cell Lung Cancer (NSCLC) Patients

AnHeart Therapeutics

Abstract #8572

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Background

- ROS1 oncogenic fusions are observed in ~1-2% NSCLC patients[1] as well as in cholangiocarcinoma, glioblastoma, ovarian, gastric, and colorectal cancers.
- CNS metastasis occurs in 20-30% ROS1 TKI-naïve and in up to 50% crizotinib-pretreated ROS1-positive NSCLC patients[2].
- Resistance to first-generation ROS1 inhibitors often occurs with secondary mutations such as ROS1 G2032R solvent front mutation[3].
- Taletrectinib, a next-generation, potent, selective ROS1 tyrosine kinase inhibitor, is developed to:
  - overcome resistance to first-generation ROS1 inhibitors,
  - address CNS metastasis,
  - improve efficacy and safety profile in ROS1-positive NSCLC patients,
  - confer less TRKB-related CNS adverse events by selectively inhibiting ROS1 over TRKB[4].
- Here we present the updated results of the TRUST phase 2 study of taletrectinib with the efficacy data retrieved on Feb 23, 2022 (assessed by IRC) and the safety data from multiple trials as of Feb 23, 2022. The preliminary data of the TRUST study were presented at ASCO 2021[5].

Methods

The ongoing TRUST study is a multicenter, open-label, single-arm, phase 2 study of taletrectinib in Chinese ROS1-positive NSCLC patients.

The study consists of two parts:

- Part 1: a lead-in dose titration period in which taletrectinib was orally administered with 400mg QD (N=3) and 600mg QD (N=3) dose regimens;
- Part 2: all patients are orally administered with 600mg QD dose regimen in both the ROS1 TKI-naïve cohort (cohort 1, N=60) and the crizotinib-pretreated cohort (cohort 2, N=40).

Key Efficacy Endpoints:

- Primary endpoints: ORR per RECIST 1.1 assessed by an independent review committee (IRC).
- Secondary endpoints: ORR, DOR, PFS, intracranial (IC)-ORR, IC-DOR, IC-PFS per RECIST 1.1 assessed by IRC and/or investigators.

Key Inclusion Criteria:

- Histologically or cytologically confirmed diagnosis of locally advanced or metastatic NSCLC.
- Age ≥ 18 years old.
- ECOG PS 0-1.
- ROS1 fusions in tumor tissue were determined by molecular assays.
- At least one measurable lesion per RECIST 1.1.

For more details see NCT04395677 at clinicaltrials.gov.

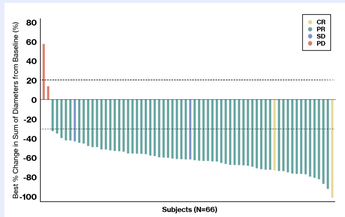
Abbreviations

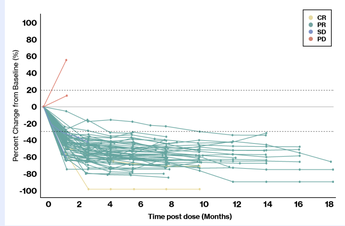
- TKI: tyrosine kinase inhibitor; CNS: central nervous system.
- CR: complete response; cORR: confirmed objective response rate; DCR: disease control rate; DOR: duration of response; IC-ORR: intracranial objective response rate; IC-DCR: intracranial disease control rate; mDOR: median duration of response; mPFS: median progression free survival; NR: not reached; PD: progressive disease; PFS: progression free survival; PR: partial response; SD: stable disease; IRC: independent review committees; RANO-BM: response assessment in neuro-oncology brain metastases criteria; NOS: not otherwise specified.
- TEAE: treatment-emergent adverse event; TRAE: treatment-related adverse event; AST: aspartate aminotransferase; ALT: alanine aminotransferase; WBC: white blood cells.

Demographic and Baseline Characteristics

Category		ROS1 TKI-Naïve N=67 (%)	Crizotinib-Pretreated N=42 (%)	Total N=109 (%)
Sex	Male	28 (41.8)	16 (38.1)	44 (40.4)
	Female	39 (58.2)	26 (61.9)	65 (59.6)
Age (years)	Median (range)	54 (26, 75)	52 (31, 77)	54 (26, 77)
ECOG Performance Status	0	11 (16.4)	17 (40.5)	28 (25.7)
	1	56 (83.6)	25 (59.5)	81 (74.3)
Histological Subtype	Adenocarcinoma	64 (95.5)	38 (90.5)	102 (93.6)
	Squamous carcinoma	0	3 (7.1)	3 (2.8)
	Adenosquamous carcinoma	2 (3.0)	1 (2.4)	3 (2.8)
	NSCLC, NOS	1 (1.5)	0	1 (0.9)
Stages	Locally Advanced	8 (12.0)	2 (4.8)	10 (9.2)
	Metastatic	59 (88.1)	40 (95.2)	99 (90.8)
Prior Anti-cancer Therapy	TKI	0	42 (100.0)	42 (38.5)
	Chemo	15 (22.4)	14 (33.3)	29 (26.6)
	Other	7 (10.4)	7 (16.7)	14 (12.8)
Brain Metastasis (IRC assessed)	Yes	7 (10.4)	13 (31.0)	20 (18.3)
	No	60 (89.6)	29 (69.0)	89 (81.7)

Efficacy in ROS1 TKI-Naïve Patients



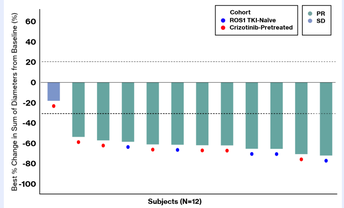


ROS1 TKI-Naïve Patients (N=67)	
cORR (n/N) [95% CI]	92.5% (62/67) [83.4%, 97.5%]
DCR (n/N) [95% CI]	95.5% (64/67) [87.5%, 99.1%]
mDOR, month (min, max)	NR (1.3+, 16.6+)
mPFS, month (min, max)	NR (0+, 18.0+)

- The cORR was 92.5% (62/67), including 2 complete response (CR); DCR was 95.5% (64/67).
- The responses were observed mostly in the first two assessments.
- The mDOR and mPFS were not reached yet. However, in phase 1 + 2 pooled analysis[6], mDOR was 27.6 months with 95% CI of [20.7, NR] and mPFS was 33.2 months with 95% CI of [22.1, NR].

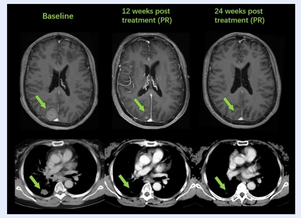
Note: One patient didn't have post-treatment tumor assessment and therefore was not included in the waterfall and spider plots.

Efficacy in Patients with Brain Metastases



ROS1-Positive NSCLC with Measurable Brain Lesions by RANO-BM (N=12)	
IC-ORR (n/N) [95% CI]	91.7% (11/12) [61.5%, 99.8%]
IC-DCR (n/N) [95% CI]	100% (12/12) [73.5%, 100%]

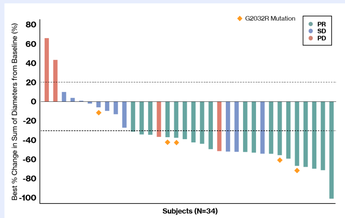
- 12 patients had measurable brain lesions and the IC-ORR and IC-DCR were 91.7% and 100%, respectively.

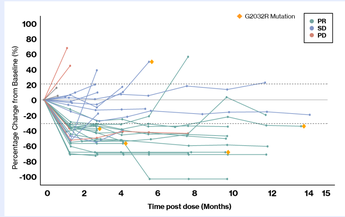


Patient Case:

- A patient with ROS1-positive NSCLC and brain metastasis with measurable brain lesions, no prior ROS1 TKI treatment.
- Near-complete disappearance of target lesions in brain and lung after 12 weeks of taletrectinib 600mg QD.
- Continues to receive treatment with confirmed PR.

Efficacy in Crizotinib-Pretreated Patients





Crizotinib-Pretreated Patients (N=38)	
cORR (n/N) [95% CI]	50.0% (19/38) [33.4%, 66.6%]
DCR (n/N) [95% CI]	78.9% (30/38) [62.7%, 90.4%]
mDOR, month (min, max)	NR (1.4+, 12.3+)
mPFS, month (min, max)	NR (0+, 13.6+)

- The cORR was 50% (19/38), DCR was 78.9% (30/38).
- 5 patients had ROS1 G2032R mutation, 4/5 achieved PR, and 1/5 achieved SD, the cORR was 80%.
- The mDOR and mPFS were not reached yet.

Note: Four patients didn't have post-treatment tumor assessment results and therefore were not included in the waterfall and spider plots.

Safety Profile (Pooled Data)

The Most Common (≥15%) TEAEs (N=190)

Adverse Event (Preferred Term)	TEAE Any Grade (%)	TEAE Grade 3 (%)	TEAE Grade 4 (%)	TRAE (%)
Diarrhea	117 (61.6)	8 (4.2)	0	107 (56.3)
AST increased	106 (55.8)	14 (7.4)	0	102 (53.7)
ALT increased	94 (49.5)	12 (6.3)	0	94 (49.5)
Nausea	90 (47.4)	2 (1.1)	0	82 (43.2)
Vomiting	86 (45.3)	1 (0.5)	0	77 (40.5)
Anemia	52 (27.4)	6 (3.2)	0	41 (21.6)
Dizziness	35 (18.4)	0	0	27 (14.2)
Decreased appetite	33 (17.4)	1 (0.5)	0	30 (15.8)
WBC decreased	29 (15.3)	4 (2.1)	0	28 (14.7)

Note: Data included 190 patients from 5 clinical trials[7] of taletrectinib as of Feb 23, 2022.
No grade 5 event was reported for these common TEAEs listed in the table.

- Taletrectinib was generally well tolerated. Most TEAEs were Grade 1 or 2.
- The most frequently reported TEAEs were low-grade diarrhea and transient AST/ALT elevation without increase in bilirubin.
- Dose modifications due to TEAEs:
  - 14.2% (27/190) patients experienced TEAEs that led to dose reduction
  - 5.3% (10/190) patients experienced TEAEs that led to drug discontinuation
- Low incidence of neurological AEs were observed.
- Some common AEs that are frequently reported in other ROS1 inhibitors, such as vision disorders, edema, headache, dizziness, and muscular disorder including fractures were observed less frequently in taletrectinib studies.

Summary

Taletrectinib is a potential best-in-class next-generation ROS1 inhibitor for treating both ROS1-TKI-naïve and pre-treated NSCLC patients.

- High ORRs observed in 1L and 2L patients.
- Excellent potency against crizotinib resistant mutations, including G2032R solvent front mutation.
- Strong intracranial activity observed in patients. Unpublished preclinical data showed better brain penetration and intracranial activity than competitors, suggesting potentially longer mPFS time for brain metastatic patients.
- Tolerable safety profiles. The selective inhibition of ROS1 over TRKB by taletrectinib may help significantly reduce TRKB-related CNS adverse events.

A separate global phase 2 trial (TRUST-II, NCT04919811) is actively enrolling patients at clinical sites in North America, Europe and Asia. For details see ASCO 2022 Trials in Progress poster (Abstract# TPS8601).

References

1. Lin, et al., J Thoracic Oncology 2017; 12(11):1611.
2. Ou, et al., Lung Cancer 2019; 130:201.
3. Gainor, et al., JCO Precision Oncology 2017; 1:1.
4. Katayama, et al., Nature Communications 2019; 10(1):3604.
5. ASCO 2021 poster (Abstract# 9066).
6. In phase 1 + 2 pooled analysis, data from 11 patients in two phase 1 clinical trials (U101 and J102) were combined with TRUST phase 2 data. U101 was a first-in-human trial in patients with advanced solid tumors in the US. J102 was a phase 1 trial in ROS1-positive NSCLC patients in Japan. The phase 1 trials were assessed by investigators as of Aug 19, 2021.
7. The 5 taletrectinib trials refer to NCT04395677, NCT04919811, NCT02675491, NCT02279433, and NCT04617054 at clinicaltrials.gov.

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