Abstract #9066

Preliminary results from TRUST: A phase II clinical study to investigate Taletrectinib in treating patients with ROS1 fusion positive non-small cell lung cancer (NSCLC)

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Background

- TRUST (**T**aletrectinib **R**OS1 L**U**ng **ST**udy, NCT04395677) is an ongoing, multicenter, phase II study of taletrectinib in NSCLC patients with ROS1 fusion in China. Here the preliminary results of TRUST (data cut-off: April 8, 2021) are presented.
- Taletrectinib (AB-106; DS-6051b) is a selective, blood-brain barrier penetrant, next generation ROS1/NTRK inhibitor with potent activities against ROS1 fusion as well as crizotinib resistant ROS1 mutations, primarily G2032R.
- Taletrectinib has demonstrated meaningful clinical activity in patients with advanced ROS1 fusion positive NSCLC who are ROS1 TKI-naïve or crizotinib pre-treated and a manageable safety profile in two completed phase I trials (Sai-Hong Ignatius Ou et al., *JTO Clinical and Research Reports*, 2020).

Methods

Study Design:

- The study consists of two parts: i) 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; and ii) part 2: all patients are orally administered with 600mg QD dose regimen in both the crizotinib naïve cohort (cohort 1, N=60) and the crizotinib pre-treated cohort (cohort 2, N=40).
- Pharmacokinetic samples for determination of drug plasma concentration are collected in all patients (18 patients with extensive sampling and the remaining patients with sparse sampling).
- Adverse events (AEs) are reported and graded using CTC-AE 5.0.

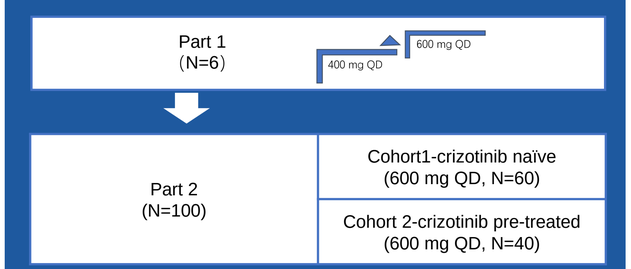
Endpoints:

- 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.

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 and confirmed by central lab.
- At least one measurable lesion per RECIST 1.1.

Figure 1. Study design



Baseline characteristics

- Between July 2020 and April 2021, 40 patients were treated with taletrectinib.
- Patient baseline characteristics are summarized in Table 1.

Table 1. Patient baseline characteristics

Characteristics	N=40
Age, Median (range), years	53.5 (32-77)
Sex, n(%)	
Male	17 (42.5%)
Female	23 (57.5%)
ECOG performance status, n(%)	
0	9 (22.5%)
1	31 (77.5%)
Staging	
IIIb/c	6 (15%)
IVa	10 (25%)
IVb	24 (60%)
Histology	
Adenocarcinoma	36 (90%)
Squamous carcinoma	3 (7.5%)
Adenosquamous carcinoma	1 (2.5%)
Brain metastases	
Present	6 (15%)
Absent	34 (85%)
Prior treatment	
No prior treatment	10 (25%)
Chemotherapy only	11 (27.5%)
Crizotinib only	7 (17.5%)
Both chemotherapy and crizotinib	12 (30%)

- 6 patients were enrolled in part 1 with 5 crizotinib naïve and 1 crizotinib pre-treated.
- 34 patients were enrolled in part 2 with 16 crizotinib naïve and 18 crizotinib pre-treated;
- ROS1 fusions were confirmed by central lab in all 21 crizotinib naïve patients and in 11 of 19 of crizotinib pre-treated patients.

Efficacy

- In evaluable patients with confirmed ROS1 fusion and assessed by investigators:
  - ORR in crizotinib naïve patients (n=15) with exact 95% confidence interval (CI) was 93%(14/15: 68.1%, 99.8%), DCR was 93% (14/15: 68.1%, 99.8%) (Figure 2).
  - ORR in crizotinib pre-treated patients (n=5) was 60% (3/5: 14.7%, 94.7%), DCR was 100% (5/5: 47.8%, 100%) (Figure 3).
- ROS1 G2032R were identified in 3 patients who had prior crizotinib treatment. All 3 patients experienced tumor regressions.

Figure 2. ORR in crizotinib naïve patients

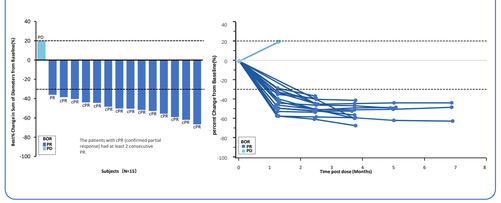
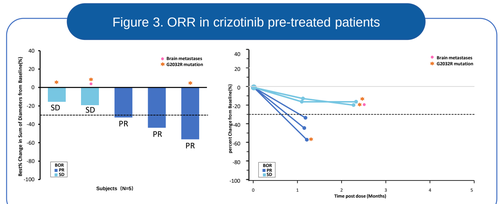


Figure 3. ORR in crizotinib pre-treated patients

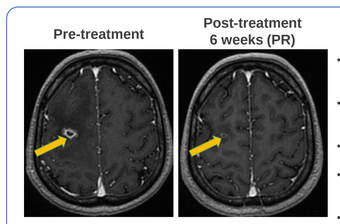


Taletrectinib for treating a NSCLC patient with brain metastasis

Table 2. Brain/plasma ratio in preclinical study

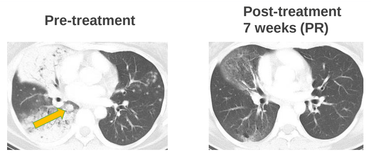
Time points (h)	Taletrectinib	Repotrectinib
4	0.40±0.10	0.07±0.01
10	0.90±0.19	0.53±0.15
24	3.11±1.20	0

- Taletrectinib and repotrectinib were administered to rats (N=9 in each group) at 30 mg/Kg. Plasma were collected at 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 hours and tissues (quadricep femoris muscle and brain without choroid plexus) collected at 4, 10 and 24 hours. Drug concentrations in plasma and brain tissues were measured for brain/plasma ratio calculation.
- Taletrectinb demonstrated a higher brain/plasma ratio at all time points and remained in brain longer than repotrectinib.



- 49-year-old male subject with ROS1 fusion positive NSCLC
- Failure with chemotherapy and crizotinib treatment
- Received taletrectinib at 600 mg QD
- Achieved intracranial PR by investigator evaluation at week 6
- Remains on treatment

Taletrectinib overcomes ROS1 G2032R resistant mutation



- 38-year-old female subject with CD74-ROS1 fusion positive NSCLC
- 2 prior systematic regimens: chemotherapy and crizotinib
- Acquired ROS1 G2032R resistant mutation post-crizotinib therapy
- Received taletrectinib at 600 mg QD
- Achieved PR by investigator evaluation at week 7
- Remains on treatment

Safety

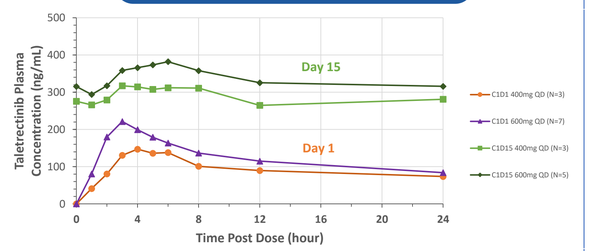
Table 3. TRAEs in taletrectinib treated patients (N=40)

TRAE, n(%)	All Grade	≥ Grade 3
Any TRAE	34 (85.0%)	5 (12.5%)
Diarrhea	22 (55.0%)	0
Nausea	14 (35.0%)	0
Vomiting	14 (35.0%)	0
Aspartate aminotransferase increase	23 (57.5%)	4 (10%)
Alanine aminotransferase increase	22 (55%)	3 (7.5%)
Anemia	7 (17.5%)	0
Neutrophil count decrease	6 (15.0%)	1 (2.5%)

The adverse events (AEs) listed here were those that occurred at any grade in at least 15% of patients. 85.0% (34/40) of patients had treatment-related adverse events (TRAEs), including diarrhea, nausea, vomiting, AST increase, ALT increase, anemia and neutrophil count decrease. 12.5% (5/40) patients had treatment-related adverse events of grade ≥ 3, including AST increase (10%), ALT increase (7.5%) and neutrophil count decrease (2.5%). All AST increase and ALT increase were reversible.

PK profile

Figure 4. Taletrectinib plasma concentration - time profiles



- T_{max} was ~ 3 to 4 hours after oral administration of taletrectinib.
- Exposure increase of taletrectinib was dose dependent.
- Steady state for taletrectinib was reached on Day 8 following multiple doses with accumulation ratios of 2 to 4.

Conclusions

- Taletrectinib has demonstrated favorable efficacy with preliminary ORR of 93% and 60% in crizotinib naïve and crizotinib pre-treated ROS1 positive NSCLC patients, respectively.
- Taletrectinib has shown potential intracranial treatment effect and ability to overcome G2032R resistant mutation in crizotinib pre-treated patients.
- Taletrectinib has shown a manageable safety profile with reversible ALT/AST increases.
- The exposure increase of taletrectinib was dose dependent and steady state was reached on Day 8 following oral administration of taletrectinib 400-600 mg QD.

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