Efficacy of Taletrectinib (AB-106/DS-6051b) in
ROS1+ NSCLC: An Updated Pooled Analysis of U.S. and Japan Phase 1 Studies

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ABSTRACT

Introduction: Taletrectinib (AB-106/DS-6051b) is an oral, potent selective ROS1 and pan-NTRK tyrosine kinase inhibitor (TKI). Preclinically, taletrectinib has activity against ROS1 G2032R solvent-front mutation.

Methods: Patients with ROS1+ NSCLC enrolled into two phase 1 studies conducted in United States (U101, NCT02279433) and Japan (J102, NCT02675491) were analyzed for objective response rate (ORR) by the Response Evaluation Criteria in Solid Tumors version 1.1, progression-free survival, and safety.

Results: A total of 22 patients with ROS1+ NSCLC out of the total 61 patients enrolled were analyzed. Taletrectinib was given at the oral dose of 400 mg, 600 mg, 800 mg, and 1200 mg once daily and 400 mg twice daily as part of the dose-escalation schema. Data cutoff was August 19, 2020. Median follow-up time for all 22 patients was 14.9 months (95% confidence interval [CI]: 4.1–33.8). A total of 18 patients with ROS1+ were assessable for response. The confirmed ORR for ROS1 TKI-naive patients (N = 9) was 66.7% (95% CI: 35.4–87.9) with a disease control rate of 100% (70.1–100). The confirmed ORR for crizotinib pretreated patients (N = 6) was 33.3% (95% CI: 9.7–70.0) with a disease control rate of 88.3% (95% CI: 443.6–97.0). The median progression-free survival for ROS1 TKI-naive patients (N = 11) was 29.1 months (95% CI: 2.6—not reached) and 14.2 months (95% CI: 1.5—not reached) for crizotinib-refractory only patients (N = 8). The most common treatment-related adverse events were alanine transaminase elevations (72.7%), aspartate transaminase elevations (72.7%), nausea (50.0%), and diarrhea (50.0%). Grade 3 or higher adverse events were alanine transaminase elevations (18.2%), aspartate transaminase (9.1%), and diarrhea (4.5%).

Conclusions: Taletrectinib (AB106/DS6051b) has a meaningful clinical activity in patients with advanced ROS1+ NSCLC who are ROS1 TKI-naive or crizotinib-refractory and a manageable safety profile.

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Keywords: Taletrectinib; DS-6051b; AB-106; ROS1+ NSCLC; Crizotinib resistance; Pooled analysis; ROS1 G2032R

Introduction

Currently, two ROS1 tyrosine kinase inhibitors (TKIs), crizotinib and entrectinib, have been approved in United States and Japan. However, resistances to ROS1 TKIs invariably occur with on-target resistance such as the acquired ROS1 G2032R gatekeeper mutation as one of the most common resistance mechanisms. Taletrectinib (AB-106/DS-6051b) is a next-generation ROS1/NTRK TKI that has preclinical activity against ROS1 G2032R mutation.

Materials and Methods

The phase 1 trials in United States (U101) and Japan (J102) have been previously described. In the US phase 1 trial, patients with any brain metastasis was not allowed while the Japan phase 1 trial, patients with asymptomatic brain metastasis was allowed. The U.S. phase 1 study being the first-in-human trial enrolled patients at 50 mg, 100 mg, 200 mg, 400 mg, 800 mg, and 1200 mg once daily and 400 mg twice daily dosing. The Japan phase 1 study enrolled patients at doses of 200 mg, 400 mg, 600 mg, and 800 mg once daily. The maximum tolerated dose was 800 mg once daily determined from the US phase 1 study. The recommended phase 2 dose for Japanese patients was 600 mg once daily from the Japan phase 1 study. Informed consent was obtained from all patients enrolled in both trials.

Results

Patient Characteristics

A total of 22 patients with ROS1+ NSCLC were enrolled in the two phase 1 trials. Three patients had no measurable disease by the Response Evaluation Criteria in Solid Tumors (RECIST) and one patient went off study after 3 weeks without any follow up tumor assessment scans. Thus, a total of 18 patients were assessable for RECIST response (Table 1). Data cutoff date was August 19, 2020. Median follow-up for all 22 patients was 14.9 months (95% confidence interval [CI]: 4.1–33.8).

Among the 11 patients who had received previous ROS1 TKIs, all had received crizotinib. Eight patients received crizotinib only, and the other three patients had received one more ROS1 TKI (2 with lorlatinib, one with ceritinib). No patient has received more than 2 ROS1 TKIs.

Overall Response Rate

The confirmed overall response rate (ORR) among ROS1 TKI-naive patients (N = 9) was 66.7% (95% CI: 35.4–87.9) with a disease control rate (DCR) of 100% (95% CI: 70.1–100) (Fig. 1A and B). The confirmed ORR for crizotinib-refractory only patients (N = 6) was 33.3% (95% CI: 9.7–70.0) with a DCR of 83.3% (95% CI: 43.6–97.0). The confirmed ORR for patients with two previous ROS1 TKI (N = 3) was 33.3% (95% CI: 6.1–79.2) with a DCR of 66.7% (95% CI: 20.8–93.9). When combined, the confirmed ORR of the nine ROS1 TKI-refractory patients was 33.3% (95% CI: 12.1–64.6) with a DCR of 77.8%
Progression-Free Survival and Duration of Response

The median progression-free survival (mPFS) for ROS1 TKI-naive patients (N = 11) was 29.1 months (95% CI: 2.6–not reached [NR], follow up time range from 1.4 to 54.1 months). The mPFS for crizotinib-refractory only ROS1 patients (N = 8) was 14.2 months (95% CI: 1.5–NR, follow up time range from 1.3 to 42.3 months) and was 4.1 months (95% CI: 0.5–7.6, follow up time range from 0.6 to 10.7 months) for patients with two previous ROS1 TKIs (N = 3) (Fig. 2A). The mPFS of the patients with previous ROS1 TKIs (N = 11) was 7.6 months (95% CI: 0.5–18.4) (Fig. 2B). The mPFS of the five patients with brain metastasis was 22.1 months (95% CI: 14.0–NR).

Adverse Events (Treatment-Emergent Adverse Event)

The most common treatment-emergent adverse events were alanine transaminase (ALT) elevation (72.7%), aspartate transaminase (AST) elevation (72.7%), nausea (59.1%), diarrhea (54.5%), vomiting (36.4%), and creatinine elevation (31.8%). The most common greater than or equal to grade 3 treatment-emergent adverse events were ALT elevation (22.7%), AST elevation (13.6%), and diarrhea (4.5%). For treatment-related adverse events, the most common were ALT elevation (72.7%), AST elevation (72.7%), nausea (50.0%), and diarrhea (50.0%). The most common grade 3 or higher treatment-related adverse events were ALT elevation (18.2%), AST elevation (9.1%), and diarrhea (4.5%).

Discussion

In this pooled analysis, taletrectinib demonstrated preliminary potent and durable response in both ROS1 TKI-naive and ROS1 TKI-refractory patients with ROS1+ NSCLC. With the caveat of very limited number of patients and treatment with varying doses of taletrectinib, the mPFS achieved in this initial phase 1 trial by taletrectinib (ORR: 66.7%, mPFS: 29.1 mo, mDoR not reached) as treatment of ROS1 TKI-naive patients is comparable with the efficacy measures achieved by crizotinib (ORR: 72%, mPFS: 19.3 mo, mDoR: 24.7 mo),

Table 1. Characteristics of the 22 Patients With ROS1+ NSCLC From Taletrectinib Pooled Analysis

| Characteristics                      | No. (%) | Total = 22 | No. (%) | Total = 18 (Assessable) |
|--------------------------------------|---------|------------|---------|------------------------|
| Mean age (SD)                        |         | 51.9 (12.7) | 50.8 (13.5) |
| Median age (range)                   | 51.0 (27.70) | 51.0 (27.70) |
| Sex                                  |         |            |         |                        |
| Male                                 | 13 (59.1) | 10 (55.6)  | 9 (41.9) | 8 (44.4)               |
| Female                               | 9 (41.9) | 10 (55.6)  | 8 (44.4) | 8 (44.4)               |
| ECOG PS                              |         |            |         |                        |
| 0                                    | 11 (50) | 10 (55.6)  | 8 (44.4) | 8 (44.4)               |
| 1                                    |         |            |         |                        |
| Race                                 |         |            |         |                        |
| Asian                                | 16 (72.7) | 13 (72.2)  | 5 (27.8) | 5 (27.8)               |
| Non-Asian                            | 6 (27.3) | 5 (27.8)   | 5 (27.8) | 5 (27.8)               |
| Origin                               |         |            |         |                        |
| Japan                                | 15 (68.2) | 12 (66.7)  | 7 (31.8) | 6 (33.3)               |
| U.S.                                 |         |            |         |                        |
| Methods of detectiona                |         |            |         |                        |
| FISH                                 | 14 (59.1) | 13 (72.2)  | 13 (59.1) | 11 (61.1)               |
| RT-PCR                               | 13 (59.1) | 11 (61.1)  | 8 (36.3) | 7 (38.9)               |
| NGS                                  | 8 (36.3) | 7 (38.9)   | 2 (9.1)  | 2 (11.1)               |
| IHC                                  | 2 (9.1)  | 2 (11.1)   | 2 (9.1)  | 2 (11.1)               |
| Brain metastasis                     |         |            |         |                        |
| Yes                                  | 5 (22.7) | 4 (22.2)   | 5 (22.7) | 4 (22.2)               |
| No                                   | 17 (77.3) | 14 (77.8)  | 17 (77.3) | 14 (77.8)              |
| Tumor stage                          |         |            |         |                        |
| IIIB                                 | 1 (5)   | 1 (5.6)    | 1 (5)   | 1 (5.6)                |
| IV                                   | 21 (95) | 17 (94.4)  | 21 (95) | 17 (94.4)              |
| Previous ROS1 TKI                    |         |            |         |                        |
| Yes                                  | 11 (50) | 9 (50)     | 11 (50) | 9 (50)                 |
| No                                   | 11 (50) | 9 (50)     | 11 (50) | 9 (50)                 |
| Previous ROS1 TKIb                   |         |            |         |                        |
| Crizotinib                           | 11 (50.0) | 15 (83.3)  | 11 (50.0) | 15 (83.3)              |
| Ceritinib                            | 1 (4.5)  | 1 (5.6)    | 1 (4.5)  | 1 (5.6)                |
| Lorlatinib                           | 2 (9.1)  | 2 (11.1)   | 2 (9.1)  | 2 (11.1)               |
| Previous regimensc                   |         |            |         |                        |
| <3                                   | 11 (50) | 11 (61.1)  | 11 (50) | 11 (61.1)              |
| ≥3                                   | 11 (50) | 7 (28.9)   | 11 (50) | 7 (28.9)               |
| Taletrectinib dose                   |         |            |         |                        |
| 400 mg once daily                    | 6 (27)  | 5 (27.8)   | 6 (27)  | 5 (27.8)               |
| 600 mg once daily                    | 6 (27)  | 5 (27.8)   | 6 (27)  | 5 (27.8)               |
| 800 mg once daily                    | 8 (36)  | 6 (33.3)   | 8 (36)  | 6 (33.3)               |
| 400 mg twice daily                   | 1 (5)   | 1 (5.6)    | 1 (5)   | 1 (5.6)                |
| 1200 mg once daily                   | 1 (5)   | 1 (5.6)    | 1 (5)   | 1 (5.6)                |

aCan be greater than 100% additive because of overlapping methods of detection.
bData for the 11 patients who had previous ROS1 TKIs.
cInclude both chemotherapy and TKIs.
In addition, the clinical efficacy of taletrectinib in crizotinib-refractory patients with ROS1+ NSCLC (ORR: 33.3%, mPFS: 14.6 mo, mDoR: NR) provided assurance that taletrectinib can also rescue patients with ROS1+ NSCLC who had progressed on crizotinib and justified further investigation of the clinical efficacy of tale-rectinib in crizotinib- or 1 prior ROS TKI-refractory ROS1+ NSCLC patients. Owing to no protocol-mandated repeat biopsy (tumor or liquid biopsy) at progression (tumor or liquid biopsy), we do not have

Figure 1. (A) Waterfall plot of the RECIST-evaluable patients with ROS1+ NSCLC to taletrectinib by number of prior ROS1 TKI therapy. (B) Spider plot of ROS1+ NSCLC patients’ response to taletrectinib by number of prior ROS1 TKI treatment. TKI, tyrosine kinase inhibitor.
the data whether the crizotinib-refractory tumors had developed ROS1 G2032R solvent-front mutation. A large phase 2 trial of taletrectinib at 600 mg once daily in both ROS1 TKI-naive and crizotinib-refractory patients is currently ongoing in the People’s Republic of China (NCT04395677).

Furthermore, the side effects of taletrectinib are well tolerated with the most common side effects of liver enzymes greater than or equal to grade 3 adverse events. Of note, taletrectinib is also a pan-NTRK inhibitor and has demonstrated clinical activity in one patient with well-differentiated thyroid cancer harboring a

**Figure 2.** (A) Progression-free survival of ROS1+ NSCLC by number of prior of ROS1 TKI therapy (N = 0, 1, or 2). (B) Progression-free survival of patients with ROS1+ NSCLC on taletrectinib by ROS1 TKI-naive or ROS1 TKI-refractory status. CI, confidence interval; mPFS, median PFS; NR, not reached; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
TPM3-NRTK1 fusion reported in the US phase 1 trial. Some of the unique side effects of NTRK inhibition are dizziness, dysgeusia, and paresthesia. However, talnetctinib does not have the unique NTRK TKI side effects of dysgeusia, dizziness, and paresthesia generally ascribed to NTRK inhibition while demonstrating central nervous system activity.

Limitations of this analysis included limited numbers of patients in each of the ROS1 TKI subgroup and the different doses of talnetctinib given to the patients as part of the dose-scalation schema. In addition, intracranial responses were not captured nor the on-target and off-target resistance to crizotinib were investigated. The ongoing phase 2 trial of talnetctinib in the People’s Republic of China will provide a more precise measure of the efficacy of talnetctinib in both ROS1 TKI-naive and crizotinib-refractory patients with ROSI+ NSCLC.

Several ROS1 TKIs besides talnetctinib are in clinical development including lorlatinib, which is an ALK/ ROS1 TKI that also has clinical activity in crizotinib-refractory patients with ROSI+ NSCLC (ORR: 35%, mPFS: 8.5 mo, mDoR: 13.8 mo). Other ROS1 TKIs include repotrectinib, SAF-189s [Foritinib] have also demonstrated preclinical activity against the solvent-front G2032R. The clinical activity of these compounds in ROS1 TKI-refractory ROSI+ NSCLC patients setting is highly sorted given this group of patients (represent an unmet medical need).

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