BRIEF REPORT

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

Sai-Hong Ignatius Ou, MD, PhD,[a,*] Yutaka Fujiwara, MD, PhD,[b,c] Alice T. Shaw, MD, PhD,[d,e] Noboru Yamamoto, MD, PhD,[b,c] Kazuhiko Nakagawa, MD, PhD,[f] Frank Fan, MD,[g] Yuki Hao, MSc,[g] Yanfei Gao, MSc,[g] Pasi A. Jänne, MD,[h] Takashi Seto, MD[i]

[a]*Division of Hematology-Oncology, Department of Medicine, Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, Orange, California*
[b]*Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan*
[c]*Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan*
[d]*Translational Clinical Oncology, Novartis Institutes for BioMedical Research, Cambridge, Massachusetts*
[e]*Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, Massachusetts*
[f]*Department of Medical Oncology, Kindai University Faculty of Medicine, Osaka-Sayama-shi, Osaka, Japan*
[g]*AnHeart Therapeutics (Hangzhou) Company Ltd., Hangzhou, Zhejiang Province, People's Republic of China*
[h]*Dana-Faber Cancer Institute, Harvard Medical School, Boston, Massachusetts*
[i]*Department of Thoracic Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan*

Received 12 October 2020; accepted 12 October 2020
Available online - 21 October 2020

***Corresponding author.**

***Disclosure**: Dr. Ou has received honorarium from AstraZeneca, Takeda Pharmaceuticals/ARIAD Pharmaceuticals, Roche/Genentech, Pfizer, Jassen/JNJ, X-covery Inc, and Daiichi Sankyo; was a scientific advisory board member of Turning Point Therapeutics; and has stock ownership in Turning Point Therapeutics and currently a scientific advisory board member of Elevation Oncology and has stock ownership in Elevation Oncology. Dr. Fujiwara has received honorarium from AstraZeneca, Chugai Pharmaceuticals, Merck Sharp & Dohme, and Novartis and has research grants from Astra Zeneca, Bristol-Myers Squibb, Daiichi Sankyo, Eisai, Eli Lilly, Incyte, Merck Serono, Merck Sharp & Dohme, and Novartis. Dr. Shaw is an employee of Novartis and has stock ownership; has served as a compensated consultant or received honoraria from Pfizer, Novartis, Genentech/Roche, Ariad/Takeda Pharmaceuticals, Ignyta, Loxo Oncology, Bayer, Chugai Pharmaceuticals, Blueprint Medicines, KSQ Therapeutics, Daiichi Sankyo, EMD Serono, Taiho Pharmaceutical, TP Therapeutics, Servier, Syros, Foundation Medicine, Guardant, Natera, Achilles, and Archer; has received institutional research funding from Pfizer, Novartis, Roche/Genentech, Ariad, Ignyta, and TP Therapeutics; and has received travel support from Pfizer and Genentech. Dr. Yamamoto has received honorarium from Bristol-Myers Squibb, Pfizer, AstraZeneca, Eli Lilly, Ono Pharmaceuticals, Chugai Pharmaceuticals, and Sysmex; has received research grant from Astellas, Chugai Pharmaceuticals, Eisai, Taiho, Bristol-Myers Squibb, Pfizer, Novartis, Eli Lilly, AbbVie, Daiichi Sankyo, Bayer, Boehringer Ingelheim, Kyowa-Hakko Kirin, Takeda Pharmaceuticals, Ono Pharmaceuticals, Janssen Pharma, Merck Sharp & Dohme, Merck, GlaxoSmithKline, Sumitomo Dainippon, and Chiome Bioscience; and is a member of the scientific advisory board of Eisai, Takeda Pharmaceuticals, Otsuka, Boehringer Ingelheim, Cimic, and Chugai Pharmaceuticals. Ms. Hao is an employee of AnHeart Therapeutics. Dr. Fan is an employee of AnHeart Therapeutics and has stock ownership. Ms. Gao is an employee of AnHeart Therapeutics. Dr. Nakagawa has received research funding from A2 Healthcare, AbbVie, Astellas Pharma, Bristol-Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Eli Lilly, CRSU, Gritstone Oncology, ICON Japan, inVentiv Health, Linical, Merck Sharp & Dohme, Novartis, Ono Pharmaceutical, Parexel International, Quintiles, Taiho Pharmaceutical, and Takeda Pharmaceutical; has received fees from Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Nichi-Iko Pharmaceutical, Nippon Boehringer Ingelheim, Novartis, Ono Pharmaceutical, Pfizer, SymBio Pharmaceuticals, and Taiho Pharmaceutical; and has also acted as a consultant for Astellas Pharma and Ono Pharmaceutical. Dr. Jänne has received honorarium from Araxes Bioscience, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly/Loxo Oncology, Pfizer, Roche/Genentech/Ignyta, Sanofi, Takeda, SFJ Pharmaceuticals, and Voronoi; has received research grant from AstraZeneca, Astellas Pharmaceutics, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Takeda Pharmaceuticals, and Revolution Medicine; is a member of the scientific advisory board of Mirati; has stock ownership in Gatekeeper Pharmaceutics; and has received royalties from Labcorp for detection of EGFR mutations. Dr. Seto has received honorarium from AstraZeneca, Astellas, Bristol-Myers Squibb, Chugai Pharmaceuticals, Daiichi Sankyo, Takeda, Pfizer, Eli Lilly, MSD, Novartis, Boehringer Ingelheim, Kyowa-Hakko Kirin, Ono Pharmaceutical, Taiho Pharmaceutical, and Thermal Fisher Scientific; has received research grants from AbbVie, Bayer Yakuhin, Kissei Pharmaceutical, Loxo Oncology, and Merck Sereno; and is an employee of Precision Medicine Asia Ltd. Co. Dr. Hao declares no conflict of interest.*

Address for correspondence: Sai-Hong Ignatius Ou, MD, PhD, Division of Hematology-Oncology, Department of Medicine, Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, 200 South Manchester Ave., Suite 400, Orange, CA 92868. E-mail: siou@hs.uci.edu

Cite this article as: Ou S-HI, et al. Efficacy of Taletrectinib (AB-106/DS-6051b) in *ROS1*+ NSCLC: An Updated Pooled Analysis of U.S. and Japan Phase 1 Studies. JTO Clin Res Rep 2:100108

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2020.100108

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.

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.[1,2] 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.[3,4] Taletrectinib (AB-106/DS-6051b) is a next-generation ROS1/NTRK TKI that has preclinical activity against *ROS1* G2032R mutation.[5]

Materials and Methods

The phase 1 trials in United States (U101) and Japan (J102) have been previously described.[6,7] In the US phase 1 trial, patients with any brain metastasis was not allowed while the Japan phase 1 trial, patients with asympotmatic 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.[6] The recommended phase 2 dose for Japanese patients was 600 mg once daily from the Japan phase 1 study.[7] 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. 1*A* 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%

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)
Female	9 (41.9)	8 (44.4)
ECOG PS		
0	11 (50)	10 (55.6)
1	11 (50)	8 (44.4)
Race		
Asian	16 (72.7)	13 (72.2)
Non-Asian	6 (27.3)	5 (27.8)
Origin		
Japan	15 (68.2)	12 (66.7)
U.S.	7 (31.8)	6 (33.3)
Methods of detection[a]		
FISH	14 (59.1)	13 (72.2)
RT-PCR	13 (59.1)	11 (61.1)
NGS	8 (36.3)	7 (38.9)
IHC	2 (9.1)	2 (11.1)
Brain metastasis		
Yes	5 (22.7)	4 (22.2)
No	17 (77.3)	14 (77.8)
Tumor stage		
IIIB	1 (5)	I (5.6)
IV	21 (95)	17 (94.4)
Previous ROS1 TKI		
Yes	11 (50)	9 (50)
No	11 (50)	9 (50)
Previous ROS1 TKI[b]		
Crizotinib	11 (50.0)	15 (83.3)
Ceritinib	1 (4.5)	1 (5.6)
Lorlatinib	2 (9.1)	2 (11.1)
Previous regimens[c]		
<3	11 (50)	11 (61.1)
≥3	11 (50)	7 (28.9)
Taletrectinib dose		
400 mg once daily	6 (27)	5 (27.8)
600 mg once daily	6 (27)	5 (27.8)
800 mg once daily	8 (36)	6 (33.3)
400 mg twice daily	1 (5)	1 (5.6)
1200 mg once daily	1 (5)	1 (5.6)

[a]Can be greater than 100% additive because of overlapping methods of detection.
[b]Data for the 11 patients who had previous ROS1 TKIs.
[c]Include both chemotherapy and TKIs.
ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NA, not applicable; NGS, next-generation sequencing; RT-PCR, reverse-transcriptase polymerase chain reaction.

(95% CI: 45.3–93.7) (Fig. 1*A* and B). The intracranial response rates were not captured, but in the four assessable patients with brain metastasis, the ORR was 75% (95% CI: 30.1–95.4) with a DCR of 100% (95% CI: 51.0–100).

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. 2*A*). The mPFS of the patients with previous ROS1 TKIs (N = 11) was 7.6 months (95% CI: 0.5–18.4) (Fig. 2*B*). The mPFS of the five patients with brain metastasis was 22.1 months (95% CI: 14.0–NR).

The median duration of response (mDoR) was not reached for both ROS1 TKI-naive (95% CI: 12.5–NR) and ROS1 TKI-refractory patients (95% CI: 5.6–NR). The median duration of stable disease was 23.5 months (95% CI: 2.6–NR) for ROS1 TKI-naive patients and 14.0 months for ROS1 TKI-refractory patients (95% CI: 2.1–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),[8] entrectinib (ORR: 77%, mPFS: 19.0 mo, mDoR: 24.6 mo),[9] ceritinib (ORR: 67%, mPFS: 19.3 mo, mDoR: 21 mo),[10] and lorlatinib (ORR: 62%, mPFS: 21.0 mo, mDoR: 25.3 mo).[11]

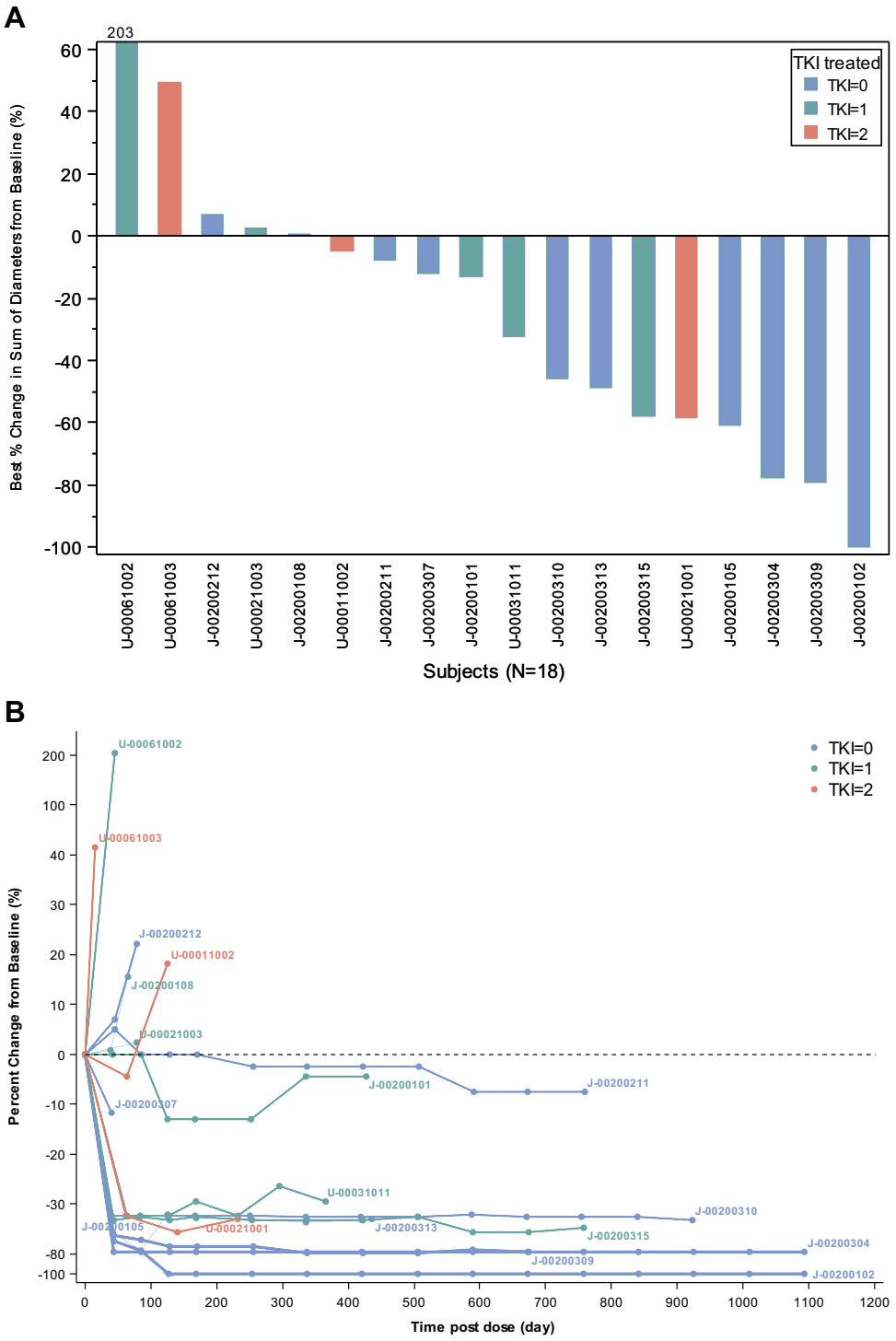

Figure 1. (*A*) Waterfall plot of the RECIST-evaluable patients with *ROS1*+ NSCLC to taletrectinib by number of prior ROS1 TKI therapy. (*B*) Spider plot of *ROS1*+ NSCLC patients' response to taletrectinib by number of prior ROS1 TKI treatment. TKI, tyrosine kinase inhibitor.

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 taletrectinib 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

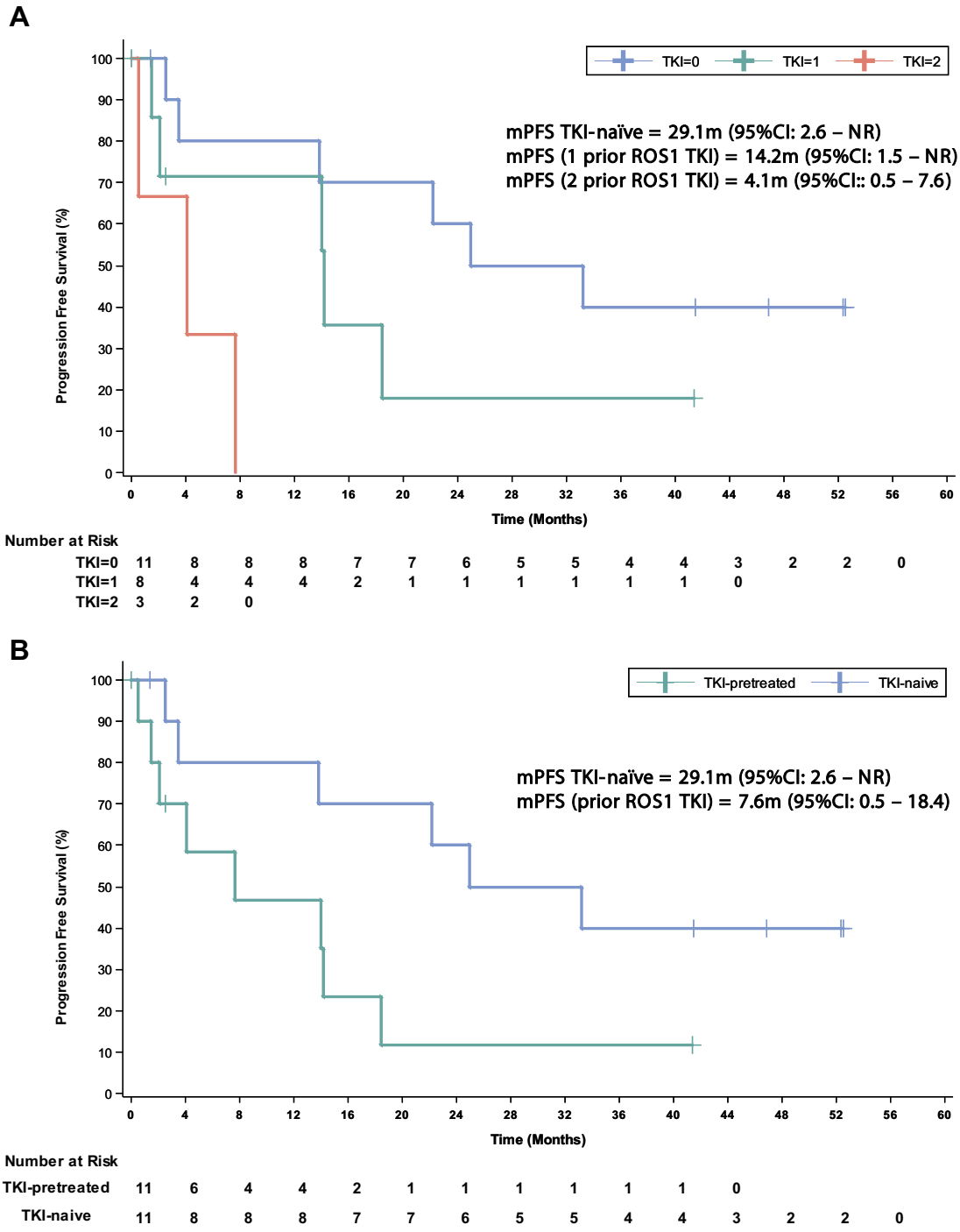

Figure 2. (*A*) Progression-free survival of *ROS1*+ NSCLC by number of prior of ROS1 TKI therapy (N = 0, 1, or 2). (*B*) Progression-free survival of patients with *ROS1*+ NSCLC on taletrectinib by ROS1 TKI-naive or ROS1 TKI-refractory status. CI, confidence interval; mPFS, median PFS; NR, not reached; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

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[5,6] and has demonstrated clinical activity in one patient with well-differentiated thyroid cancer harboring a

TPM3-NRTK1 fusion reported in the US phase 1 trial.[6] Some of the unique side effects of NTRK inhibition are dizziness, dysgeusia, and paresthesia.[12] However, taletrectinib 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.[7]

Limitations of this analysis included limited numbers of patients in each of the ROS1 TKI subgroup and the different doses of taletrectinib 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 taletrectinib in the People's Republic of China will provide a more precise measure of the efficacy of taletrectinib in both ROS1 TKI-naive and crizotinib-refractory patients with *ROS1*+ NSCLC.

Several ROS1 TKIs besides taletrectinib are in clinical developemnt including lorlatinib, which is an ALK/ ROS1 TKI that also has clinical activity in crizotinib-refractory patients with *ROS1*+ 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.[13,14] The clinical activity of these compounds in ROS1 TKI-refractory *ROS1*+ NSCLC patients setting is highly sorted given this group of patients (represent an unmet medical need).

References

1. Kazandjian D, Blumenthal GM, Luo L, et al. Benefit-risk summary of crizotinib for the treatment of patients with ROS1 alteration-positive, metastatic non-small cell lung cancer. *Oncologist*. 2016;21:974–980.
2. Drilon A, Siena S, Dziadziuszko R, et al. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1–2 trials [published correction appears in *Lancet Oncol*. 2020;21:e70] [published correction appears in *Lancet Oncol*. 2020;21:e341]. *Lancet Oncol*. 2020;21:261–270.
3. Gainor JF, Tseng D, Yoda S, et al. Patterns of metastatic spread and mechanisms of resistance to crizotinib in ROS1-positive non-small-cell lung cancer. *JCO Precis Oncol*. 2017;1:1–13.
4. Dagogo-Jack I, Rooney M, Nagy RJ, et al. Molecular analysis of plasma from patients with ROS1-positive NSCLC. *J Thorac Oncol*. 2019;14:816–824.
5. Katayama R, Gong B, Togashi N, et al. The new-generation selective ROS1/NTRK inhibitor DS-6051b overcomes crizotinib resistant ROS1-G2032R mutation in preclinical models. *Nat Commun*. 2019;10:3604.
6. Papadopoulos KP, Borazanci E, Shaw AT, et al. US phase 1 first-in-human study of taletrectinib (DS-6051b/AB-106), a ROS1/TRK inhibitor, in patients with advanced solid tumors. *Clin Cancer Res*. 2020;26:4785–4794.
7. Fujiwara Y, Takeda M, Yamamoto N, et al. Safety and pharmacokinetics of DS-6051b in Japanese patients with non-small cell lung cancer harboring ROS1 fusions: a phase I study. *Oncotarget*. 2018;9:23729–23737.
8. Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014;371:1963–1971.
9. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1–2 trials [published correction appears in *Lancet Oncol*. 2020;21:e70] [published correction appears in *Lancet Oncol*. 2020;21:e341] [published correction appears in *Lancet Oncol*. 2020;21:e372]. *Lancet Oncol*. 2020;21:271–282.
10. Lim SM, Kim HR, Lee JS, et al. Open-label, multicenter, phase II study of ceritinib in patients with non-small-cell lung cancer harboring ROS1 rearrangement. *J Clin Oncol*. 2017;35:2613–2618.
11. Shaw AT, Solomon BJ, Chiari R, et al. Lorlatinib in advanced ROS1-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1–2 trial. *Lancet Oncol*. 2019;20:1691–1701.
12. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. *Nat Rev Clin Oncol*. 2018;15:731–747.
13. Yun MR, Kim DH, Kim SY, et al. Repotrectinib exhibits potent antitumor activity in treatment-naïve and solvent-front-mutant ROS1-rearranged non-small cell lung cancer. *Clin Cancer Res*. 2020;26:3287–3295.
14. Xia ZJ, Ji YC, Sun DQ, et al. SAF-189s, a potent new-generation ROS1 inhibitor, is active against crizotinib-resistant ROS1 mutant-driven tumors [e-pub ahead of print]. *Acta Pharmacol Sin*. https://doi.org/10.1038/s41401-020-00513-3, accessed September 12, 2020.