Efficacy and Safety of Lorlatinib in Korean Non–Small-Cell Lung Cancer Patients With *ALK* or *ROS1* Rearrangement Whose Disease Failed to Respond to a Previous Tyrosine Kinase Inhibitor

Jiyun Lee,[1] Jong-Mu Sun,[1] Se-Hoon Lee,[1] Jin Seok Ahn,[1] Keunchil Park,[1] Yoon La Choi,[2] Myung-Ju Ahn[1]

Abstract

The efficacy of lorlatinib, a novel third-generation tyrosine kinase inhibitor (TKI), has not been widely validated in Asian non–small-cell lung cancer (NSCLC) patients. We found an overall response rate of 64% and a disease control rate of 91% for Asian NSCLC patients harboring *ALK*/*ROS1* mutations. Lorlatinib is an important novel strategy for Asian NSCLC patients with disease progression after treatment with first- and second-generation TKIs.

Introduction: Non–small-cell lung cancer (NSCLC) patients harboring *ALK* or *ROS1* rearrangements invariably acquire resistance to the first- and second-generation tyrosine kinase inhibitors (TKIs), most notably *ALK* G1202R and *ROS1* G2032R. Lorlatinib, a novel third-generation TKI, produced remarkable results from the first-in-man phase 1 trial: an overall response rate of 46% and 50% for previously treated *ALK*- and *ROS1*-positive patients, respectively. However, the efficacy of lorlatinib has not been widely validated in Asian patients. **Patients and Methods:** Patients with advanced NSCLC with *ALK* or *ROS1* rearrangements who initiated lorlatinib therapy between November 2016 and July 2018 were retrospectively analyzed. **Results:** Twelve consecutive patients were included. The median age was 55 years (range, 36-76 years). Ten (83%) had *ALK*-positive NSCLC and 2 (17%) had *ROS1*-positive NSCLC. All patients had a history of first- or second-generation *ALK* TKI receipt. Two *ALK*-positive patients and one *ROS1*-positive patient had the G1202R and G2032R mutations, respectively. The overall response rate was 64% and the disease control rate was 91%. Of the 3 *ALK*-positive patients with intracranial target lesions, 1 (33%) had a complete response and 2 (67%) a partial response, producing an intracranial objective response of 100%. The median progression-free survival was 6.5 months (range, 1.0-16.5 months). The most common adverse event was hypercholesterolemia (83%), and no adverse event–related dose reductions or treatment discontinuations were reported. **Conclusion:** This study is the first to report that lorlatinib is an important novel therapeutic option for Asian patients who have advanced NSCLC harboring *ALK*/*ROS1* mutations whose disease progressed during treatment with first- and second-generation TKIs.

Clinical Lung Cancer, Vol. 20, No. 3, 215-21

Keyword: Asian, PF-06463922

Introduction

Chromosomal rearrangements involving the anaplastic lymphoma kinase (*ALK*) or ROS proto-oncogene 1 (*ROS1*) define a distinct molecular subset of non–small-cell lung cancer (NSCLC). The incidence of rearrangements in NSCLC has been reported to be 5% and 1-2%, for *ALK* and *ROS1*, respectively.[1,2] Although not all

[1]Division of Hematology-Oncology, Department of Medicine
[2]Department of Pathology and Translational Genomics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Submitted: Oct 16, 2018; Revised: Dec 11, 2018; Accepted: Dec 25, 2018; Epub: Dec 31, 2018

Address for correspondence: Myung-Ju Ahn, MD, PhD, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea,
Fax: 82-2-3410-1754; e-mail contact: silk.ahn@samsung.com

https://doi.org/10.1016/j.cllc.2018.12.020

clinicopathologic features are shared between *ALK* and *ROS1* rearrangements, both are known to be more common in Asian patients with a never or light smoking history and adenocarcinoma histology.[1-3]

ALK and *ROS1* rearrangements with a significant homology in amino acid sequence within the kinase domain and adenosine triphosphate-binding site[4] have been validated as effective therapeutic targets since their first identification in NSCLC in 2007.[5,6] Crizotinib, ceritinib, alectinib, and brigatinib are widely provided to *ALK*-positive patients, whereas crizotinib and ceritinib are recommended for *ROS1*-positive NSCLC. The Profile 1014 study showed that crizotinib resulted in an overall response rate (ORR) of 74%, with median progression-free survival (PFS) of 10.9 months in treatment-naive patients with stage IV *ALK*-positive NSCLC.[7] As a potent tyrosine kinase inhibitor (TKI) for *ALK*, *ROS1*, and *MET*, crizotinib also showed efficacy for *ROS1* rearrangements. Results from the expanded cohort of the Profile 1001 study showed an ORR of 72% and a median PFS of 19.2 months,[8] although subsequent studies have reported shorter median PFS values of 9.1 to 15.9 months.[9,10]

Frustratingly, the clinical responses to first- and second-generation TKIs are not durable, and patients almost invariably acquire resistance. On-target resistance involving the *ALK*/*ROS1* tyrosine kinase domains has been reported as the mechanism of secondary resistance in 20% to 30% of *ALK*-positive[11,12] and 8% to 50% of *ROS1*-positive patients[13,14] after crizotinib therapy. *ALK* G1202R and *ROS1* G2032R are notable mutations: through steric hindrance to drug binding, they confer high levels of resistance to all currently available first- and second-generation TKIs.[15]

Lorlatinib (PF-06463922) is a novel third-generation TKI against *ALK* and *ROS1* with optimized brain penetration, and the results of its first-in-man phase 1 trial have recently been published: an ORR of 46% and 50% for *ALK*- and *ROS1*-positive patients, respectively.[16] The interim results from the phase 2 trial are even more promising: an ORR of 90% for treatment-naive patients and 69% for previously crizotinib-treated patients.[17] Previous cell line studies have demonstrated that lorlatinib effectively inhibits *ALK*/*ROS1* phosphorylation in crizotinib-resistant *ALK* G1202R and *ROS1* G2032R mutants.[18,19] Lorlatinib, designed specifically for *ALK*/*ROS1* binding, has a better binding capacity than crizotinib, which was originally designed as a MET inhibitor.[19]

However, the above-mentioned clinical studies recruited the patients from the United States, Spain, Australia and France; hence, data on the efficacy and safety of lorlatinib in Asians are very limited.[16] Here, we report the efficacy and safety outcomes of lorlatinib in Korean patients with advanced *ALK*- or *ROS1*-positive NSCLC who experienced treatment failure with previous TKIs.

Patients and Methods

Patients

We identified 12 consecutive patients who had advanced NSCLC with *ALK* or *ROS1* rearrangements, and were treated with lorlatinib via a compassionate program at Samsung Medical Center from November 2016 to July 2018.

ALK positivity was confirmed in formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples using local *ALK* break-apart fluorescence in-situ hybridization (FISH), immunohistochemistry, or next-generation sequencing (NGS). *ROS1*-positivity was confirmed by FISH, with at least 15% of evaluated tumor cells containing split or isolated 3′ signals.[20]

FFPE tumor tissue samples from 2 *ALK*-positive patients and 1 *ROS1*-positive patient underwent NGS to determine the resistance mechanism. The NGS platforms used in this study were the CancerScan panel (LabGenomics, Seongnam, Korea)[21] and the Oncomine Comprehensive Assay (ThermoFisher Scientific, Waltham, MA).

Patients were evaluated for treatment response by either simple chest radiography or chest computed tomography (CT). Chest posterior-anterior radiography was performed every cycle, and chest CT was performed every 2 or 3 cycles of treatment. In addition to regular follow-up, additional imaging was performed at the physicians' discretion. Response categories were assessed using the Response Evaluation Criteria in Solid Tumors version 1.1.[22]

Patients received 100 mg lorlatinib once daily, according to the dose recommended from the phase 1 trial.[16] Cycles were 21 days long, and the treatment was continued until disease progression, uncontrolled toxicity, or patient refusal. This study was approved by the institutional review board of Samsung Medical Center (approval SMC 2018-08-053-001), and the need for informed consent was waived.

Statistical Analysis

Descriptive statistics are reported as proportions and medians. PFS and overall survival were assessed by the Kaplan-Meier method, and patients were censored at the time of analysis, if they were progression-free and/or alive. IBM SPSS Statistics 24 (Armonk, NY, USA) was used for statistical analysis.

The data cutoff date was September 2, 2018.

Results

Patient Characteristics

Twelve patients were enrolled between November 2016 and July 2018, and all patients received at least one dose of lorlatinib. One patient was omitted from efficacy analysis because of extensive pneumonia diagnosed before the initiation of lorlatinib that led to death on the fifth day of drug treatment.

The median age of the patients was 55 years (range, 36-76 years). Most patients were female (67%) and never-smokers (67%). Ten and 2 patients had an ECOG performance status of 1 and 2, respectively. Only one patient had squamous-cell carcinoma; all the other patients (92%) had adenocarcinoma. Brain metastases were present at baseline in 8 patients (67%), 5 of whom had received previous brain radiotherapy (Table 1).

Ten (83%) of the 12 patients had *ALK*-positive NSCLC, and 2 (17%) had *ROS1*-positive NSCLC. *ALK* positivity was confirmed by immunohistochemistry (n = 7) or by both immunohistochemistry and FISH (n = 3). *ROS1* positivity was confirmed by FISH (n = 2). All patients had a history of *ALK* or *ROS1* TKI use (Table 2). Specifically, all 12 patients received first-line crizotinib, with a median treatment duration of 17.3 months (range, 2.3-51.1 months), and the 10 *ALK*-positive patients also received second-line TKI (ceritinib, alectinib, or brigatinib) for a median treatment duration of 9.6 months (range, 2.4-21.5 months). No *ROS1*-positive patients received second-line TKI. The ORR for first-line crizotinib was 100% (10/10) and 100% (2/2) for the *ALK*- and *ROS1*-positive patients, respectively. The ORR for the

Table 1 Patient Characteristics

Characteristic	Value
Patients	12 (100%)
Sex	
Male	4 (33%)
Female	8 (67%)
Age (years), median (range)	55 (35-76)
ECOG PS	
1	10 (83%)
2	2 (17%)
Smoking Status	
Current/former smoker	8 (67%)
Never smoker	4 (33%)
Histology	
Adenocarcinoma	11 (92%)
Squamous-cell carcinoma	1 (8%)
***ALK* and *ROS1* Status**	
ALK positive	10 (83%)
ROS1 positive	2 (17%)
Previous *ALK/ROS1* TKI therapy	
First line	12 (100%)
Crizotinib	12 (100%)
Second line	10 (83%)
Ceritinib	7 (58%)
Alectinib	2 (17%)
Brigatinib	1 (8%)
Brain metastasis	
Present	9 (75%)
Absent	3 (25%)
Previous brain radiotherapy	5 (42%)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; TKI = tyrosine kinase inhibitor.

second-line TKIs was 70% (7/10), and was only applicable to *ALK*-positive patients.

Response and Survival

Of the 9 patients with *ALK*-positive NSCLC who received lorlatinib, excluding one patient who was unavailable for disease evaluation due to severe pneumonia, 6 (67%) of 9 experienced confirmed partial response, and 2 (22%) of 9 had stable disease. One patient demonstrated initial progression but continued lorlatinib at the physician's discretion and maintained stable disease for 6 months. Of the 2 patients with *ROS*-positive NSCLC, one had a confirmed partial response, and the other had confirmed stable disease (Table 2, Figure 1). Response to lorlatinib was demonstrated shortly after drug initiation, with a median time to first response of 1.6 months (range, 1.3-2.1 months). At the data cutoff date (September 2, 2018), 4 (57%) of the 7 responses were ongoing.

The median duration of treatment in all *ALK*- and *ROS1*-positive patients was 5.8 months (range, 1.3-16.5 months), and the median duration of response was 5.0 months (range, 1.0-15.1 months). The median PFS was 6.5 months (range, 1.0-16.5 months), and the median overall survival was not reached.

Of the 9 patients with brain metastases at baseline, 3 *ALK*-positive patients had measurable target lesions. One patient (33%) had a confirmed complete response, and 2 patients (67%) had a confirmed partial response, producing an intracranial objective response of 100% (Figure 2).

Two *ALK*-positive patients who underwent NGS before lorlatinib but postceritinib exposure retained G1202R as a secondary resistance mutation in the *ALK* kinase domain. One *ROS1*-positive patient harbored the *ROS1* G2032R mutation in the specimen obtained after crizotinib exposure. All of these patients experienced partial response to lorlatinib (Figure 3).

Adverse Events

Table 3 summarizes the reported adverse events (AEs) of any grade. Hypercholesterolemia was the most frequent (10/12, 83%) AE. All were grade 1/2 and did not result in dose reductions or treatment discontinuation. Peripheral edema (3/12) was mostly mild and well tolerated. No patients permanently discontinued lorlatinib temporarily or permanently because of treatment-related AEs.

Discussion

Lorlatinib, a third-generation *ALK/ROS1* TKI with superior brain penetration compared to crizotinib and alectinib,[18,23] showed efficacy for patients with advanced *ALK*- or *ROS1*-positive NSCLC and had an acceptable toxicity profile. A recent first-in-man phase 1 study showed an ORR of 42% with a median duration of response of 11.7 months.[16] Our study, which included only Asian subjects, demonstrated a comparable ORR of 64% and a median duration of response of 5.0 months. The duration of response was relatively short, attributable to the limited duration of follow-up. Furthermore, our study included heavily pretreated patients, which is more representative of the advanced NSCLC patients in the clinical setting than the population in the original phase 1 study. These results confirm that lorlatinib is an important novel strategy for patients whose disease progressed after treatment with first- or second-generation *ALK/ROS1* TKIs.

Furthermore, lorlatinib showed an intracranial response of 100% in *ALK*-positive patients: 1 patient had a complete response and 2 patients had a partial response in lesions that progressed shortly after local therapies. This is notable because that more than one-third of patients develop brain metastases despite crizotinib therapy[24] because of its poor penetration of the blood–brain barrier, resulting in a low cerebrospinal fluid (CSF)-to-plasma ratio.[25] Preclinical cell line studies have shown that the superior intracranial response of lorlatinib is directly associated with its increased ability to penetrate the blood–brain barrier.[18] Lorlatinib is reported to reach a CSF-to-plasma ratio of 0.75 in patients,[16] which is higher than that reported in non–tumor-bearing animal models.[23] Unfortunately, we were unable to perform pharmacokinetic analysis of lorlatinib concentration in blood and CSF in our study.

ALK G1202R, rarely reported in postcrizotinib samples, is the most common *ALK* mutation observed after exposure to second-generation *ALK* inhibitors.[15] *ALK* G1202R confers a high level of resistance to all currently available TKIs,[18,19] so it is notable that all the patients in our study who harbored this mutation showed tumor regression with lorlatinib.

Table 2 Outcomes of 12 Patients, Including Those With Extracranial and Cranial Responses to Lorlatinib

Patient No.	Line	Cycle	Best Response to Lorlatinib[a]	PFS	DoR	Site of Progression	Previous TKI Therapy (BR, DoR)	CNS Response[b]	Previous Local Therapy	On-Target Resistance (Time of Rebiopsy)[c]
ALK										
1	6	1	SD	1.8	NA	Ongoing response	Crizotinib (PR, 51.1) Alectinib (SD, 2.6)	—	—	—
2	5	2	PR	3.1	1.0	Ongoing response	Crizotinib (PR, 11.9) Alectinib (PR, 3.7)	—	—	—
3	5	7	PR	9.5	7.6	Ongoing response	Crizotinib (PR, 45.5) Ceritinib (PR, 12.7)	PR	GKS	—
4	4	4	PR	6.5	5.0	Lung, pleura	Crizotinib (PR, 35.4) Ceritinib (PR, 9.6)	—	GKS	*ALK* G1202R (after ceritinib)
5	4	11	PR	15.6	13.7	Ongoing response	Crizotinib (PR, 20.5) Ceritinib (SD, 6.4)	—	—	*ALK* G1202R (after ceritinib)
6	4	12	PR	16.5	15.1	Ongoing response	Crizotinib (PR, 6.3) Ceritinib (SD, 16.1)	PR	WBRT	—
7	5	8	PD[d]	1.0	NA	Lung, pleural effusion	Crizotinib (PR, 17.3) Brigatinib (PR, 21.5)	—	—	—
8	6	6	PR	5.7	4.5	Lung, pleural effusion	Crizotinib (PR, 10.2) Ceritinib (PR 2.4)	CR	—	—
9	9	1	SD	1.3	NA	Pleural/pericardial effusion	Crizotinib (PR, 5.2) Ceritinib (PR, 11.4)	—	GKS	—
10[e]	4	1	NE	0.1	NE	NE	Crizotinib (PR 7.6) Ceritinib (PR 5.2)	—	GKS	—
ROS1										
11	5	2	SD	3.2	NA	Ongoing response	Crizotinib (PR, 2.3)	—	—	—
12	10	5	PR	4.0	2.1	Lung	Crizotinib (PR, 31.6)	—	—	*ROS1* G2032R (after crizotinib)

Abbreviations: BR = best response; CNS = central nervous system; DoR = duration of response (months); GKS = gamma-knife surgery; NA = not applicable; NE = not evaluable; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease; TKI = tyrosine-kinase inhibitor; WBRT = whole-brain radiotherapy.

[a]Best response to lorlatinib was evaluated by using extracranial target lesions.

[b]Three *ALK*-positive patients had data evaluable for intracranial response.

[c]Three patients underwent next-generation sequencing to identify resistance mechanism before lorlatinib administration and were found to harbor on-target mutations.

[d]Patient demonstrated initial progression, continued lorlatinib at physician's discretion, and maintained stable disease for 6 months.

[e]Patient died on fifth day of drug treatment of extensive pneumonia diagnosed before initiation of lorlatinib; patient data were therefore excluded from efficacy analysis.

Figure 1 Best Response for Extracranial Target Lesions by Patient Based on Maximal Percentage of Tumor Reduction. Yellow Bars Indicate *ALK*-Positive and Blue Bars *ROS1*-Positive Patients. Numbers at Bottom of Bars Indicate Duration of Response. Asterisk Indicates Patients With Ongoing Response at Data Cutoff. Patient With Initial Disease Progression had Stable Disease for 6 Months

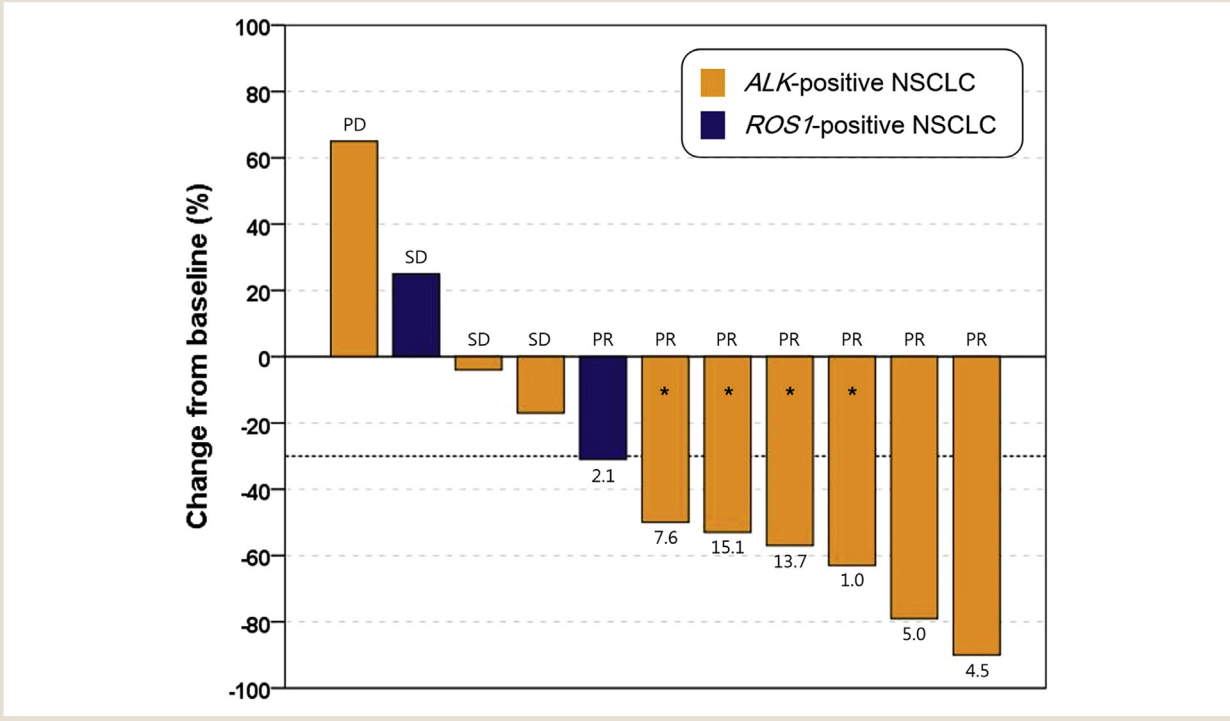
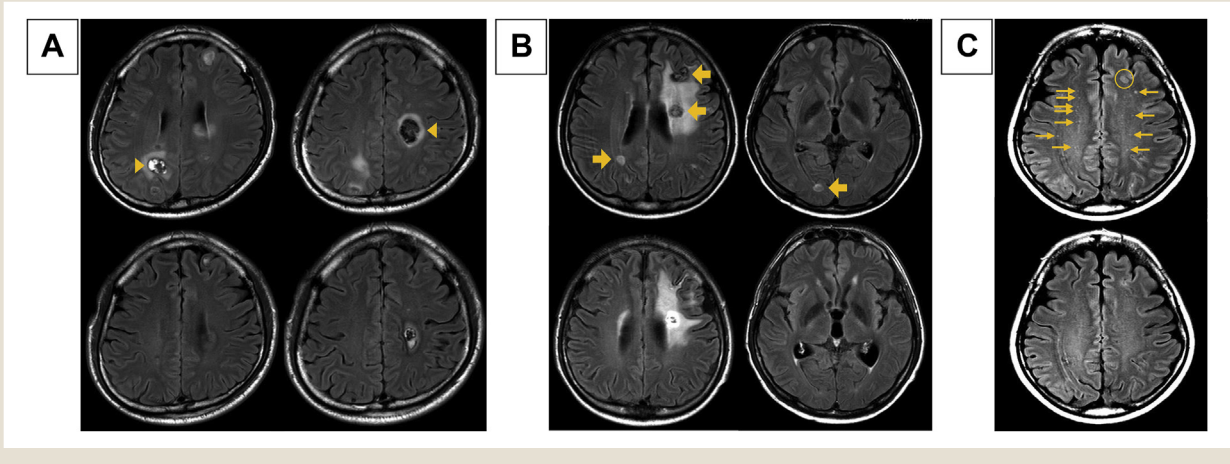
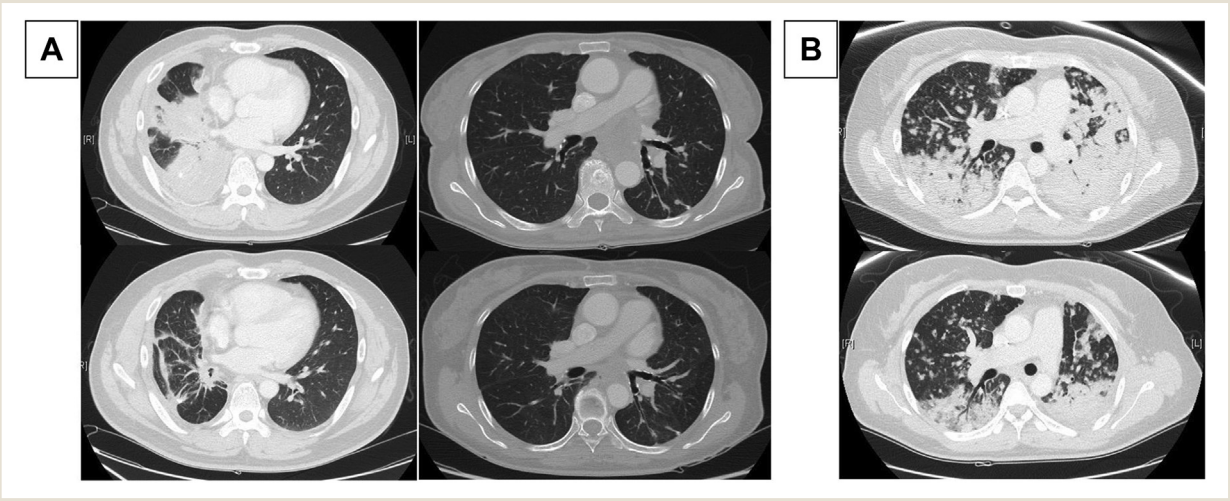


Figure 2 Brain MRI of 3 *ALK*-Positive Patients With Measurable Target Lesions at Baseline (Top) and after 3 or 4 Cycles of Lorlatinib Therapy (Bottom), Demonstrating Intracranial Response. (A) Patient had Progressive Brain Metastatic Lesions (Arrowheads) after Whole-Brain Radiotherapy (Performed 2 Months before Initiation of Lorlatinib) that Regressed With Lorlatinib Therapy. (B) Patient had Gamma-Knife Surgery 1 Month before Initiation of Lorlatinib. However, Lesions Shown (Arrows) Were Not Targeted in Surgery and Regressed With Lorlatinib Therapy. (C) Patient had No Previous Local Therapy. Measurable (Circle) and Nonmeasurable/Scattered (Arrows) Metastatic Lesions Disappeared With Lorlatinib Therapy



Abbreviation: MRI = magnetic resonance imaging.

Figure 3 Patients With (A) *ALK* G1202R and (B) *ROS1* G3202R Mutations. Chest Computed Tomography at Baseline (Top) and After 3 or 4 Cycles of Lorlatinib Therapy (Bottom); Both Demonstrate Partial Response



One patient diagnosed with advanced lung adenocarcinoma and harboring an EML4-ALK fusion was treated with crizotinib for 20.5 months with a partial response and ceritinib for the following 6.4 months with stable disease. However, she progressed with multiple bone metastases, and the rebiopsy demonstrated *ALK* G1202R. She started lorlatinib treatment and had maintained a partial response for more than 15 months at the time of data cutoff.

On-target mutations, ie, mutations in the *ALK*/*ROS1* kinase domain, are reported with varying frequencies in *ROS1*-mutant (8-50%) and *ALK*-mutant NSCLC (20-30%).[13,15,26] *ROS1* G2032R, an analogue of *ALK* G1202R, is the most commonly reported mutation in postcrizotinib samples,[13,27,28] and it is resistant to all currently available TKIs.[19] Despite the improved structural binding of lorlatinib in the *ROS1* kinase domain, *ROS1* G2032R appears to significantly reduce the cellular potency of lorlatinib.[20] One patient from our study who harbored *ROS1* G2032R on a postcrizotinib lung biopsy specimen showed an initial partial response to lorlatinib but rapidly progressed with pulmonary lesions after 3 months of treatment. This was a comparably limited period of response, considering that the median duration of response in our study population was 5.0 months. Initially, lorlatinib seemed promising for its antitumor activity against *ROS1* G2032R in cell line and animal models.[19,29] However, recent evidence suggests that it might be challenging to transform its antitumor efficacy into a clinical benefit, considering the IC_{50} ranging 270 to 500 nmol/L.[20,30,31] Given the limited data on the efficacy of lorlatinib against disease with the *ROS1* G2032R mutation, further studies with larger patient populations are warranted.

The most common AE regarding lorlatinib was hypercholesterolemia, but no patients in our study required treatment with a cholesterol-lowering agent. Toxicities in the lipid profile do not present a concern because they can be readily managed pharmacologically, if needed. None of the treatment-related AEs led to dose reductions or temporary/permanent drug discontinuation. This is compatible with the results from the phase 1 study, which reported no permanent discontinuation due to treatment-related AEs, and no treatment-related deaths.[16]

Although one patient had extensive pneumonia, diagnosed before initiation of lorlatinib that led to death on the fifth day of drug treatment, this event was not attributed to the study drug.

Although our study has significant limitations due to the small number of patients included and the short duration of follow-up, it is the first to report the efficacy and safety outcomes of lorlatinib in Asian patients. Further information on survival outcomes and response according to the presence or absence of the on-target secondary mutations are highly awaited from the randomized

Table 3 Treatment-Related Adverse Events

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Hypercholesterolemia	3	7	—	—
Peripheral edema	3	—	—	—
Hyperglycemia	1	—	—	—
Hyperuricemia	1	—	—	—
Anorexia	1	—	—	—

phase 3 trial of lorlatinib versus crizotinib as first-line therapy in patients with *ALK*-positive NSCLC (ClinicalTrials.gov NCT03052608).

Conclusion

Lorlatinib is an important novel therapeutic option for Asian patients with advanced NSCLC harboring *ALK*/*ROS1* mutations whose disease progressed during treatment with first- and second-generation TKIs. Lorlatinib has a promising future for prolonged responses and robust survival outcomes.

Clinical Practice Points

- Lorlatinib, a novel third-generation TKI, has reported remarkable results from the first-in-man phase 1 trial: an ORR of 46% and 50% for previously treated *ALK*- and *ROS1*-positive patients, respectively. However, this study recruited patients from the United States, Spain, Australia, and France; hence, data on the efficacy and safety of lorlatinib in Asian patients are very limited.
- Our study reports the first data on the efficacy and safety outcomes of lorlatinib in Asian patients harboring *ALK*/*ROS1* mutations whose disease progressed during treatment with first- and second-generation TKIs. The ORR was 64% and the disease control rate was 91%. Of 3 *ALK*-positive patients with intracranial target lesions, 1 (33%) had a complete response and 2 (67%) had a partial response, producing an intracranial objective response of 100%. The median duration of treatment in all *ALK*- and *ROS1*-positive patients was 5.8 months (range, 1.3-16.5 months), and the median duration of response was 5.0 months (range, 1.0-15.1 months). The median PFS was 6.5 months (range, 1.0-16.5 months), and the median overall survival was not reached.
- AEs were generally mild and well tolerated. Hypercholesterolemia was the most frequent (10/12, 83%) AE, and all were grade 1/2. No patients temporarily or permanently discontinued lorlatinib or required dose reduction because of treatment-related AEs.
- Lorlatinib is an important novel therapeutic option for Asian patients with advanced NSCLC harboring *ALK*/*ROS1* mutations. Lorlatinib has a promising future for prolonged responses and robust survival outcomes.

Acknowledgments

Supported in part by grant HI16C1984 from the Korean Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea.

Disclosure

The authors have stated that they have no conflict of interest.

References

1. Chia PL, Mitchell P, Dobrovic A, John T. Prevalence and natural history of *ALK* positive non–small-cell lung cancer and the clinical impact of targeted therapy with *ALK* inhibitors. *Clin Epidemiol* 2014; 6:423-32.
2. Bergethon K, Shaw AT, Ou SH, et al. *ROS1* rearrangements define a unique molecular class of lung cancers. *J Clin Oncol* 2012; 30:863-70.
3. Park S, Ahn BC, Lim SW, et al. Characteristics and outcome of *ROS1*-positive non–small cell lung cancer patients in routine clinical practice. *J Thorac Oncol* 2018; 13:1373-82.
4. Chin LP, Soo RA, Soong R, Ou SH. Targeting *ROS1* with anaplastic lymphoma kinase inhibitors: a promising therapeutic strategy for a newly defined molecular subset of non–small-cell lung cancer. *J Thorac Oncol* 2012; 7:1625-30.
5. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming *EML4-ALK* fusion gene in non–small-cell lung cancer. *Nature* 2007; 448:561-6.
6. Rikova K, Guo A, Zeng Q, et al. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. *Cell* 2007; 131: 1190-203.
7. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in *ALK*-positive lung cancer. *N Engl J Med* 2014; 371:2167-77.
8. Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in *ROS1*-rearranged non–small-cell lung cancer. *N Engl J Med* 2014; 371:1963-71.
9. Mazieres J, Zalcman G, Crino L, et al. Crizotinib therapy for advanced lung adenocarcinoma and a *ROS1* rearrangement: results from the EUROS1 cohort. *J Clin Oncol* 2015; 33:992-9.
10. Wu YL, Yang JC, Kim DW, et al. Phase II study of crizotinib in East Asian patients with *ROS1*-positive advanced non–small-cell lung cancer. *J Clin Oncol* 2018; 36:1405-11.
11. Doebele RC, Pilling AB, Aisner DL, et al. Mechanisms of resistance to crizotinib in patients with *ALK* gene rearranged non–small cell lung cancer. *Clin Cancer Res* 2012; 18:1472-82.
12. Gainor JF, Shaw AT. Emerging paradigms in the development of resistance to tyrosine kinase inhibitors in lung cancer. *J Clin Oncol* 2013; 31: 3987-96.
13. 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. In press.
14. McCoach CE, Le AT, Gowan K, et al. Resistance mechanisms to targeted therapies in $ROS1^{+}$ and ALK^{+} non–small cell lung cancer. *Clin Cancer Res* 2018; 24: 3334-47.
15. Gainor JF, Dardaei L, Yoda S, et al. Molecular mechanisms of resistance to first- and second-generation *ALK* inhibitors in *ALK*-rearranged lung cancer. *Cancer Discov* 2016; 6:1118-33.
16. Shaw AT, Felip E, Bauer TM, et al. Lorlatinib in non–small-cell lung cancer with *ALK* or *ROS1* rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. *Lancet Oncol* 2017; 18:1590-9.
17. Solomon B, Shaw A, Ou S, et al. Phase 2 study of lorlatinib in patients with advanced $ALK^{+}/ROS1^{+}$ non–small-cell lung cancer (abstract OA 05.06). *J Thorac Oncol* 2017; 12:S1756.
18. Zou HY, Friboulet L, Kodack DP, et al. PF-06463922, an *ALK*/*ROS1* inhibitor, overcomes resistance to first and second generation *ALK* inhibitors in preclinical models. *Cancer Cell* 2015; 28:70-81.
19. Zou HY, Li Q, Engstrom LD, et al. PF-06463922 is a potent and selective next-generation *ROS1*/*ALK* inhibitor capable of blocking crizotinib-resistant *ROS1* mutations. *Proc Natl Acad Sci U S A* 2015; 112:3493-8.
20. Lin JJ, Shaw AT. Recent advances in targeting *ROS1* in lung cancer. *J Thorac Oncol* 2017; 12:1611-25.
21. Shin HT, Choi YL, Yun JW, et al. Prevalence and detection of low-allele-fraction variants in clinical cancer samples. *Nat Commun* 2017; 8:1377.
22. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45: 228-47.
23. Johnson TW, Richardson PF, Bailey S, et al. Discovery of (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(m etheno)pyrazolo[4,3-h][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile (PF-06463922), a macrocyclic inhibitor of anaplastic lymphoma kinase (*ALK*) and c-ros oncogene 1 (*ROS1*) with preclinical brain exposure and broad-spectrum potency against *ALK*-resistant mutations. *J Med Chem* 2014; 57:4720-44.
24. Lim SH, Yoh KA, Lee JS, et al. Characteristics and outcomes of ALK^{+} non–small cell lung cancer patients in Korea. *Asia Pac J Clin Oncol* 2017; 13: e239-45.
25. Costa DB, Kobayashi S, Pandya SS, et al. CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. *J Clin Oncol* 2011; 29:e443-5.
26. Lin JJ, Riely GJ, Shaw AT. Targeting *ALK*: precision medicine takes on drug resistance. *Cancer Discov* 2017; 7:137-55.
27. Awad MM, Engelman JA, Shaw AT. Acquired resistance to crizotinib from a mutation in *CD74-ROS1*. *N Engl J Med* 2013; 369:1173.
28. Song A, Kim TM, Kim DW, et al. Molecular changes associated with acquired resistance to crizotinib in *ROS1*-rearranged non–small cell lung cancer. *Clin Cancer Res* 2015; 21:2379-87.
29. Zou HY, Engstrom LR, Li Q, et al. PF-06463922, a novel *ROS1*/*ALK* inhibitor, demonstrates sub-nanomolar potency against oncogenic *ROS1* fusions and capable of blocking the resistant $ROS1^{G2032R}$ mutant in preclinical tumor models. *Mol Cancer Ther* 2013; 12, abstract A277.
30. Facchinetti F, Loriot Y, Kuo MS, et al. Crizotinib-resistant *ROS1* mutations reveal a predictive kinase inhibitor sensitivity model for *ROS1*- and *ALK*-rearranged lung cancers. *Clin Cancer Res* 2016; 22:5983-91.
31. Chong CR, Bahcall M, Capelletti M, et al. Identification of existing drugs that effectively target *NTRK1* and *ROS1* rearrangements in lung cancer. *Clin Cancer Res* 2017; 23:204-13.