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ORIGINAL REPORT

Open-Label, Multicenter, Phase II Study of Ceritinib in Patients With Non–Small-Cell Lung Cancer Harboring *ROS1* Rearrangement

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ABSTRACT

Purpose

ROS1 rearrangement is a distinct molecular subset of non–small-cell lung cancer (NSCLC). We investigated the efficacy and safety of ceritinib in patients with *ROS1*-rearranged NSCLC.

Patients and Methods

We enrolled 32 patients with advanced NSCLC who tested positive for *ROS1* rearrangement by fluorescent in situ hybridization. Ceritinib 750 mg was administered once daily. The primary end point was objective response rate. The secondary end points were disease control rate; duration of response; progression-free survival; overall survival; toxicity; and concordance among fluorescent in situ hybridization, immunohistochemistry, and next-generation sequencing.

Results

Between June 7, 2013, and February 1, 2016, 404 patients underwent *ROS1* prescreening, and 32 patients with *ROS1* rearrangement were enrolled. All patients except two were crizotinib-naïve. At the time of data cutoff, the median follow-up was 14.0 months, and 18 patients (56%) had discontinued treatment. Of the 32 patients enrolled, 28 were evaluable for response by independent radiologic review. Objective response rate was 62% (95% CI, 45% to 77%), with one complete response and 19 partial responses; duration of response was 21.0 months (95% CI, 17 to 25 months); and disease control rate was 81% (95% CI, 65% to 91%). The median progression-free survival was 9.3 months (95% CI, 0 to 22 months) for all patients and 19.3 months (95% CI, 1 to 37 months) for crizotinib-naïve patients. The median overall survival was 24 months (95% CI, 5 to 43 months). Of the eight patients with brain metastases, intracranial disease control was reported in five (63%; 95% CI, 31% to 86%). The most common adverse events (majority, grade 1 or 2) for all treated patients were diarrhea (78%), nausea (59%), and anorexia (56%).

Conclusion

Ceritinib demonstrated potent clinical activity in patients with *ROS1*-rearranged NSCLC who were heavily treated previously with multiple lines of chemotherapy.

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INTRODUCTION

ROS1 rearrangement is a therapeutically tractable oncogenic driver that occurs in 1% to 2% of patients with non–small-cell lung cancer (NSCLC).[1-3] ROS1 is a receptor tyrosine kinase with constitutive kinase activity, and the kinase domain is retained on the ROS1 fusion protein.[4] The prevalence of *ROS1* rearrangement reaches up to 3.2% in never-smokers and 5% in patients with *EGFR* and *ALK* wild type.[5] *ROS1*-rearranged tumors are highly sensitive to ROS1 inhibition, which makes such aberrations an important therapeutic target.[4] Given the high homology in the kinase domains of ROS1 and ALK, ALK inhibitors have been shown to be efficacious in *ROS1*-positive cell lines and tumors.[6,7] A phase I trial of crizotinib (ClinicalTrials.gov identifier NCT00585195) that originally enrolled patients with *ALK*-positive NSCLC was amended to include patients with *ROS1*-positive NSCLC, and treatment with crizotinib elicited an overall response rate (ORR) of 72% and a median progression-free survival (PFS) of 19.2 months.[8] However, despite the initial response to crizotinib, most patients

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eventually develop acquired resistance. Mechanisms of acquired resistance have been reported to result from both *ROS1*-dependent and *ROS1*-independent mechanisms.[9,10] In addition, limited blood-brain barrier penetration of crizotinib can result in a high incidence of brain recurrence.[11] Therefore, treatment options beyond crizotinib are needed, and clinical development of other ROS1 inhibitors should be accelerated to improve treatment outcome of patients with *ROS1*-positive NSCLC.

Ceritinib (LDK378) is a more potent and selective oral tyrosine kinase inhibitor of *ALK* and has shown promising clinical activity in both crizotinib-naïve and crizotinib-treated patients.[12] In a confirmatory phase III trial (ASCEND-5 [LDK378 in Adult Patients With ALK-Activated NSCLC Previously Treated With Chemotherapy and Crizotinib]), ceritinib demonstrated superior efficacy compared with standard second-line chemotherapy in patients with crizotinib-resistant *ALK* rearrangement, which established ceritinib as a preferred treatment option in this patient population. Ceritinib also showed clinically meaningful benefits in patients with brain metastases.[13] Preclinical studies have shown that ceritinib can also inhibit ROS1 and has nanomolar-range half maximal inhibitory concentration (IC_{50}) values in Ba/F3 cell lines engineered to express *ROS1* rearrangement (IC_{50} = 180 nM) and in HCC78 (IC_{50} = 50 nM).[5,14] In addition, ceritinib crossed the blood-brain barrier with a brain-to-blood exposure ratio of approximately 15%.[14] These results raise the possibility that ceritinib plays a role as an alternative to crizotinib in patients with *ROS1*-rearranged NSCLC and may be effective for intracranial lesions. However, clinical activity of ceritinib in patients with *ROS1*-rearranged NSCLC has not been investigated. On the basis of these rationales, we investigated the antitumor activity and safety profile of ceritinib in patients with *ROS1*-rearranged NSCLC.

PATIENTS AND METHODS

Study Design and Participants

In this multicenter, open-label, phase II study, patients were prescreened and recruited from 10 academic hospitals across the Republic of Korea (Appendix Tables A1 and A2, online only). Eligibility criteria were *ROS1*-rearranged NSCLC, age 20 years or older, locally advanced or metastatic NSCLC that had progressed despite standard therapy, an Eastern Cooperative Oncology Group performance status of 0 to 2, and adequate organ function and laboratory results. Patients were required to have at least one measurable lesion at baseline according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Key exclusion criteria are listed in the Appendix (online only). This trial was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice and was approved by the institutional review board of each study center. All patients provided written informed consent.

Procedure

Patients received oral ceritinib at the recommended dose of 750 mg/day after 2-hour fasting in continuous 28-day treatment cycles. Patients continued with ceritinib until objective evidence of disease progression or intolerance. Dose adjustments were permitted for those who had any grade 3 or worse adverse event, and dose reductions were allowed for a maximum of three (150 mg/day per reduction). Re-escalation after dose reduction was not permitted. If toxicity that resulted in a dose delay of $>$ 21 days occurred, treatment was discontinued permanently. All adverse events during study participation were recorded and graded according to the Common Terminology Criteria for Adverse Events (version 4).

ROS1 rearrangement was prescreened in patients with *EGFR* and *ALK* wild type. ROS1 fluorescent in situ hybridization (FISH [Vysis LSI Dual Color, Break Apart Rearrangement Probe; Abbott Molecular, Abbott Park, IL]) and immunohistochemistry (IHC [rabbit monoclonal, clone D4D6; Cell Signaling Technology, Danvers, MA]) were performed. Patients were required to have ROS1 positivity by FISH to be enrolled in the trial. ROS1 positivity was defined as $>$ 15% of tumor cells that displayed split or isolated signals that contained a kinase domain as previously described.[1] IHC positivity was defined as an H score of $>$ 100 or extent of $>$ 75% or the presence of 2+ or 3+ intensity (Appendix Fig A1, online only).[15] Next-generation sequencing (NGS) of tumor tissue was performed at Foundation Medicine using a comprehensive genomic profiling assay as previously reported.[16] Details are provided in the Appendix.

Outcomes

The primary end point of this trial was ORR. An overall response was defined as a complete response (CR) or partial response (PR) by RECIST 1.1. Secondary end points were disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and toxicity. All efficacy outcomes were based on results from a central independent review committee (IRC) and were confirmed. Exploratory end points were detection of known or unknown *ROS1* fusion partners by NGS, correlative study between FISH and IHC, and PFS until second progressive disease. Details are provided in the Appendix.

Statistical Analysis

This trial used a Simon's two-stage minimax design, with 80% power to accept the hypothesis and 10% significance to reject the hypothesis (α-error = 0.10, power = 0.80, one-sided). The expected sample size is 28 to test the null hypothesis of P = .40 versus the alternative hypothesis of P = .60. For a total of 28 patients, 16 need to be recruited during the first stage and 12 during the second stage. If six or fewer responses are observed during the first stage, then the trial is stopped early. If 14 or fewer responses are observed by the end of the trial, then no further investigation of the drug is warranted. With an allowance for a follow-up loss rate of 10%, the total sample size is 32 patients.

All patients who received at least one dose of ceritinib were included in the intention-to-treat analyses for efficacy and safety. Data were summarized using descriptive statistics (continuous data) or contingency tables (categorical data) for demographic and baseline characteristics, response measurements, and safety measurements. All survival analyses were estimated using Kaplan-Meier method and associated 95% CIs. All statistical analyses were performed with SPSS version 20.0 software (IBM Corporation, Chicago, IL).

RESULTS

ROS1 rearrangement status was prescreened in 404 patients, and 34 patients (8.4%) were positive for ROS1 by FISH. We enrolled 32 patients between June 7, 2013, and February 1, 2016 (Appendix Fig A2, online only). Of these, two patients (6%) were treated with crizotinib, and the rest were crizotinib-naïve. The median age was 62 years, and 24 patients (75%) were female. The majority of patients (84%) were never-smokers, and all had adenocarcinoma histology. The median number of previous treatments before study enrollment was three (range, two to seven), and 17 patients (53%) had received three or more lines of chemotherapy. The median time from diagnosis to initiation of ceritinib was 18.3 months (range, 2 to 96 months; Table 1). Eight patients (25%) had asymptomatic or controlled brain metastases.

Table 1. Baseline Characteristics

Characteristic	No. (%)
No. of patients	32
Age, years, median (range)	62 (35-79)
Female sex	24 (75)
WHO/ECOG performance status	
0	14 (44)
1	14 (44)
≥ 2	4 (13)
Smoking history	
Never-smoker	27 (84)
Former or current smoker	5 (16)
Tumor histology	
Adenocarcinoma	32 (100)
No. of previous treatment, median (range)	3 (2-7)
Months from diagnosis to initiation of ceritinib, median (range)	18.3 (2-96)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

The median duration of follow-up at the data cutoff (October 30, 2016) was 14.0 months (interquartile range [IQR], 9.0 to 19.0). Among the 14 patients enrolled in the first stage, seven objective responses were observed, and the trial continued to the second stage. Of the 32 patients enrolled, 28 were evaluable for response by the IRC. Four patients (including two treated with crizotinib) were not evaluable as a result of early progression or death (n = 3) or withdrawal as a result of adverse events (n = 1) before the first on-treatment evaluation. The ORR of all patients was 62% (95% CI, 45% to 77%; 20 of 32 patients). The ORR of crizotinib-naïve patients was 67% (95% CI, 48% to 81%; 20 of 30 patients). DCR was 81% (95% CI, 65% to 91%; 26 of 32 patients) among all patients and 87% (95% CI, 70% to 95%) among crizotinib-naïve patients (Table 2). A decrease in tumor burden from baseline was observed in 24 (75%) of 28 patients (Fig 1). For all patients, the median PFS was 9.3 months (95% CI, 0 to 22 months), and the median PFS for crizotinib-naïve patients was 19.3 months (95% CI, 1 to 37 months; Fig 2). For crizotinib-naïve patients, the median DoR was 21.0 months (95% CI, 17 to 25 months; Fig 3). The most common site of progression was lung (66%; 12 of 18 patients), and two (11%) of 18 patients were known to have CNS events. At the time of data cutoff, 14 patients (43%) were still in follow-up for progression and still on treatment. The median OS was 24 months (95% CI, 5 to 43 months), with a 6-month OS rate of 84% (95% CI, 68% to 93%) and 12-month OS rate of 56% (95% CI, 39% to 72%). The investigator-assessed activity analyses are listed in Appendix Table A3 (online only).

Table 2. Independent Review Committee–Assessed Activity

Best Response	All Patients, No. (%)	Crizotinib-Naïve Patients, No. (%)
No. of patients	32	30
CR	1 (3)	1 (3)
PR	19 (59)	19 (63)
SD	6 (19)	6 (20)
PD	2 (6)	2 (7)
Not evaluable*	4 (12)	2 (7)
ORR, % (95% CI)	62 (45 to 77)	67 (48 to 81)
DCR (CR + PR + SD), % (95% CI)	81 (65 to 91)	87 (70 to 95)

Abbreviations: CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
*As a result of early death (n = 3) or withdrawal (n = 1) before first response evaluation.

To evaluate intracranial response, we performed comprehensive analyses to assess patients with brain metastases on the basis of IRC. At study entry, eight patients had brain metastases (one crizotinib-treated, seven crizotinib-naïve), and of these, two had measurable intracranial lesions on the basis of RECIST 1.1. Three patients, including the crizotinib-treated patient, were excluded from the analysis as a result of no available baseline (n = 2) or postbaseline (n = 1) image for review. Two patients with measurable intracranial lesions showed tumor shrinkage of −66% (PR) and −2.3% (stable disease). The patient who achieved PR had not received radiotherapy to the brain previously. PR was achieved after 4 weeks on ceritinib, and the response lasted 26 weeks. Among three patients with nonmeasurable intracranial lesions, one showed CR, and two showed non-CR, nonprogressive disease. The patient who achieved CR had received radiotherapy to the brain 2 months before the start of ceritinib. CR was achieved after 8 weeks of ceritinib, and the response was ongoing at the date of cutoff (> 70 weeks). Overall, intracranial ORR was 25% (95% CI, 7% to 59%; two of eight patients), and disease control was achieved in 63% (95% CI 31% to 86%; five of eight patients; Appendix Table A4, online only). The intracranial efficacy results are in line with whole-body responses (Appendix Table A5, online only).

The mean daily dose intensity of ceritinib up to the time of progression was 648.8 mg, and the mean daily dose intensity of ceritinib, including patients who continue beyond progression, was 640 mg. Median duration of exposure to ceritinib for all patients was 27.0 weeks (IQR, 13.1 to 40.9 weeks). For six patients who continued ceritinib beyond disease progression, the median duration of postprogression exposure was 7.8 weeks (IQR, 2.5 to 13.2 weeks). Overall, 22 (68%) of 32 patients had at least one dose reduction, and 23 (72%) had at least one dose interruption. Fifteen (47%) of 32 patients had one dose reduction, six (19%) had two dose reductions, and one (3%) had three or more dose reductions. The median time to first dose reduction was 8.7 weeks.

All 32 patients experienced at least one adverse event irrespective of study drug association (Table 3). Serious adverse events (of any grade) occurred in 16 patients (50%), and serious adverse events suspected to be related to the drug were reported in seven (22%; Appendix Tables A6 and A7, online only). Grade 3 or higher toxicity occurred in 12 patients (37%; 95% CI, 23% to 55%). The most common grade 1 to 2 nonlaboratory adverse events were diarrhea (78%), nausea (59%), and anorexia (56%). These events were manageable through concomitant medications and dose reductions. The most common grade 3 to 4 nonlaboratory adverse event was fatigue (16%), which was reversible through dose interruptions. The most common grade 1 to 2 laboratory adverse events were increased blood creatinine (41%), alanine aminotransferase (31%), and aspartate aminotransferase (28%) levels.

Only one patient (3%) discontinued treatment as a result of adverse events (general weakness and anorexia, grade 3) related to the study drug. Three on-treatment deaths occurred as a result of grade 5 dyspnea, which occurred as a result of aggravation of an underlying pulmonary thromboembolism; grade 5 pneumonia, which resulted from an aspiration event in a patient with brain

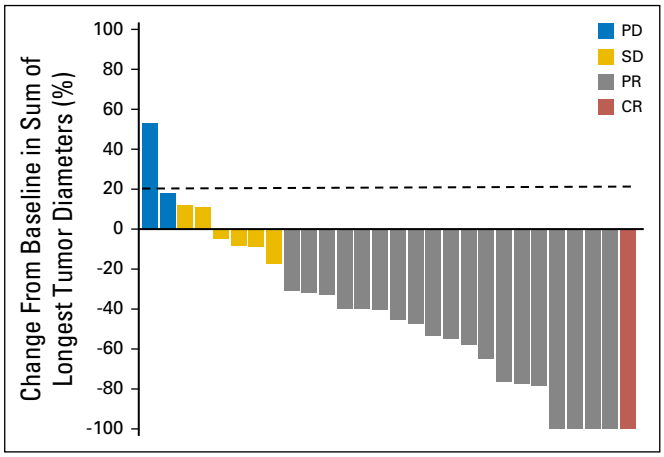

Fig 1. Best percentage change from baseline in tumor volume in patients with at least one postbaseline measurement. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

metastases; and grade 5 pneumonia, which progressed rapidly in a patient who was administered only one dose of ceritinib. All three on-treatment deaths were deemed not related to the study drug.

Among the 32 patients with positive FISH results, IHC was performed in 29 with available tissue. Among these 29 patients, 25 were IHC positive and four were IHC negative (concordance rate, 86.2%). We performed NGS in 15 available patient tissue samples. NGS revealed ROS1 positivity in only 11 patients, and four patients were negative for *ROS1* rearrangement. *CD74-ROS1* (n = 2), *EZR-ROS1* (n = 7), and *SLC34A2-ROS1* (n = 2) rearrangements were identified, and their correlation with clinical outcome is listed in Appendix Table A8 (online only). All patients with *ROS1* rearrangements based on NGS achieved disease control (which excluded one patient without evaluation). Among the four patients with negative NGS, one had negative IHC results and progressed within 1 month of ceritinib treatment, which suggests that FISH was falsely positive. Two patients with negative NGS, however, showed clinical response to ceritinib, which suggests that NGS results may have been false-negative because of a limited quantity of tumor material.

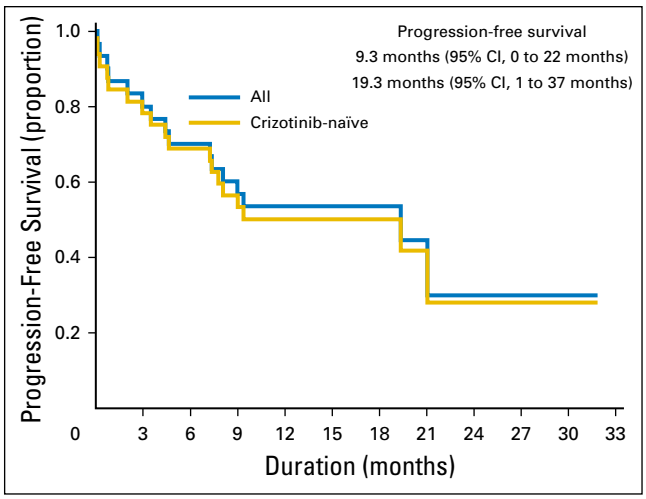

Fig 2. Kaplan-Meier curve of progression-free survival in all patients and crizotinib-naïve patients.

DISCUSSION

Ceritinib shows robust, clinically meaningful efficacy end points of ORR, DoR, and PFS in patients with *ROS1*-positive NSCLC previously treated with multiple lines of chemotherapy. In addition, ceritinib showed intracranial responses in patients with brain metastases. The safety profile in this patient population is considered manageable and consistent with the established safety profile of ceritinib.

At the beginning of this trial, two patients previously treated with crizotinib were enrolled. Both these patients were unavailable for the objective response evaluation because one withdrew from the study as a result of general weakness and anorexia grade 3 2 weeks after the start of ceritinib, and the other patient died suddenly as a result of suspected leptomeningeal metastasis. These two patients did not show signs of clinical improvement after the initiation of ceritinib, and the protocol was amended to only enroll crizotinib-naïve patients who had received at least one platinum doublet. Previous studies reported acquired *ROS1* mutations, such as G2032R or D2033N, after crizotinib treatment,[10] but we did not identify *ROS1* mutations in two patients with postceritinib tumor samples. Although acquired *ROS1* mutations after crizotinib treatment could be overcome by cabozantinib and lorlatinib,[17-19] no current data show that ceritinib could overcome crizotinib resistance in patients with *ROS1*-rearranged NSCLC, and its clinical activity remains to clarified.

The National Comprehensive Cancer Network 2017 guideline[19a] recommends testing for *ROS1* rearrangement. We enrolled patients on the basis of FISH criteria and tested IHC at the same time to compare the concordance between the two methods. The incidence of *ROS1* rearrangement by FISH was higher (8.4%) than previously reported because we prescreened mostly never-smokers who were negative for *EGFR* mutation and *EML4-ALK* rearrangement.[1] This prescreening strategy has been known to increase the rate of identifying *ROS1* rearrangement by 5% to 7%.[5,20] Although IHC and FISH can be used as prescreening methods, confirmation with NGS may help to eliminate false-positive results. Anchored multiplex polymerase chain reaction, a targeted NGS that can detect multiple gene rearrangements in lung cancer, has been developed, but the best method for *ROS1* testing remains to be defined.[21]

Previously, the standard treatment of *ROS1*-positive metastatic NSCLC was cytotoxic chemotherapies, similar to the standard treatment of patients without actionable mutations. Crizotinib received US Food and Drug Administration approval for *ROS1*-positive metastatic NSCLC on March 11, 2016, on the basis of a single-arm, multicenter study (N = 50).[8] The median age of patients in the study was 53 years, and the Eastern Cooperative Oncology Group performance status was 0 or 1 (98%). Fourteen percent received no prior systemic therapy for metastatic disease. Results showed an ORR of 72%, which included three CRs and 33 PRs, and a median DoR of 17.6 months. Although the ORR and PFS data are comparable with the current study results,

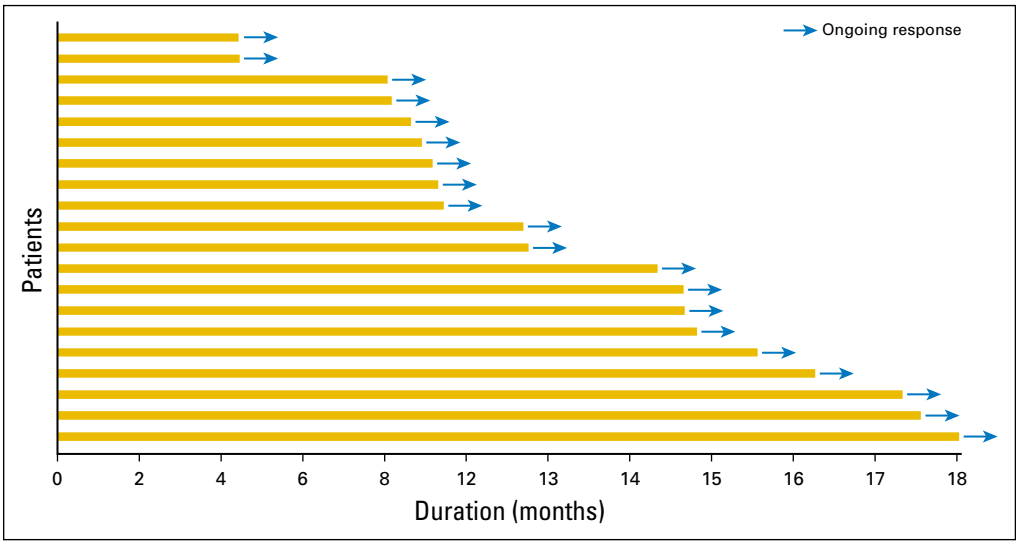

Fig 3. Duration of response in patients who achieved objective responses.

no information was reported on intracranial activities in patients with brain metastases.

Brain metastases are difficult to tackle in patients with advanced NSCLC and represent the most common site of disease progression.[22] Although the number of patients with brain metastases at baseline was small (n = 8), the intracranial DCR in the current study is comparable with pooled data from the ASCEND-1 and ASCEND-2 trials.[13] Nonetheless, the data should be interpreted cautiously because the effect of local radiotherapy to brain should also be considered. A confirmatory clinical trial is necessary to prospectively assess intracranial activity of ceritinib in patients with *ROS1*-rearranged NSCLC.

Table 3. Adverse Events That Occurred at Grades 1 to 2 in 10% or More Patients or at Grades 3 to 5

Adverse Event	Grade, No. (%)			
	1 to 2	3	4	5
Diarrhea	25 (78)	0	0	0
Nausea	19 (59)	1 (3)	0	0
Anorexia	18 (56)	1 (3)	0	0
Vomiting	17 (53)	0	0	0
Cough	15 (47)	0	0	0
Abdominal pain	13 (41)	0	0	0
Musculoskeletal pain	13 (41)	0	0	0
Fatigue	7 (22)	5 (16)	0	0
Dyspnea	7 (22)	0	0	1 (3)
Fever	6 (19)	0	0	0
Pruritus	5 (16)	0	0	0
Dyspepsia	4 (13)	0	0	0
Pneumonia	4 (13)	2 (6)	0	2 (6)
Dizziness	4 (13)	0	0	0
Infection	0	1 (3)	0	0
Dry mouth	0	1 (3)	0	0
Abdominal discomfort	0	1 (3)	0	0
Pleural effusion	0	1 (3)	0	0
Superior vena cava syndrome	0	1 (3)	0	0
Acute hepatitis	0	0	1 (3)	0
Laboratory abnormalities				
Blood creatinine increased	13 (41)	0	0	0
Alanine aminotransferase increased	10 (31)	2 (6)	1 (3)	0
Aspartate aminotransferase increased	9 (28)	3 (9)	1 (3)	0
Blood alkaline phosphatase increased	8 (25)	1 (3)	0	0
Hyperglycemia	4 (13)	3 (9)	1 (3)	0
Anemia	0	2 (6)	0	0
γ-Glutamyl transferase increased	0	1 (3)	0	0
Hyperuricemia	0	0	1 (3)	0

Incidence and type of adverse events were comparable with previously reported safety results.[12,23] As expected, GI adverse events were the most frequent events. The rates of grade 3 or 4 nausea and vomiting were lower as a result of active treatment with antiemetic therapy. Although direct comparison of adverse events between ceritinib and crizotinib studies is not possible, common events such as all-grade diarrhea (78% *v* 44%) and nausea (62% *v* 40%) are significantly lower with crizotinib. The percentage of patients who required dose adjustment (68%) or interruption (72%) was similar to that of ASCEND-3 trial in which 72.6% of patients required dose adjustment or interruption. No case of pneumonitis or QTc prolongation was found in the current study, and all grade 5 adverse events were considered to be unrelated to treatment. In addition, the discontinuation rate of ceritinib as a result of adverse events was low (3%). Of note, an increased creatinine level was more frequent (41%), but all events were grade 1 to 2. Proactive and early intervention of GI adverse events may be necessary to avoid subsequent dehydration.

Because this study was conducted in a single country, we should be cautious about generalizing the data. The median age of the patients was 62 years, which is older than reported in previous studies.[1,5,8,24] Furthermore, the median time from diagnosis to ceritinib administration was 18.3 months, which suggests that patients with indolent disease or favorable prognosis may have been enrolled.

In conclusion, ceritinib is active in patients with *ROS1*-rearranged NSCLC who are crizotinib-naïve. This study shows durable responses and prolonged PFS, with intracranial responses in patients with asymptomatic or neurologically stable brain metastases at study entry. Toxicities are manageable with dose adjustment or interruption and supportive care. Taken together, these data expand the role of ceritinib in patients with *ROS1*-rearranged NSCLC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Manuscript writing: All authors
Final approval of manuscript: All authors
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Appendix

Methods

Study design and participants. Patients with untreated or locally treated asymptomatic and stable (> 4 weeks) CNS disease were eligible. The initial protocol allowed patients who were treated with crizotinib but was later amended to exclude crizotinib-treated patients.

Procedure. At baseline, computed tomography scans of the chest and abdomen were done in all patients. Tumor response was assessed every 8 weeks, and computed tomography scans were examined by both an investigator and an independent review committee. In patients with brain or bone metastasis, brain magnetic resonance imaging or whole-body bone scan was done every 8 weeks. Patient assessments, including laboratory findings, Eastern Cooperative Oncology Group performance status, and overall general condition, were collected at baseline and day 1, day 15 of cycle 1, and day 1 of each cycle thereafter until the end of treatment.

Outcomes. Disease control rate was defined as the percentage of complete or partial responses or stable disease. Duration of response was defined as the time of first documented partial or complete response to the date of first disease progression or death as a result of any cause. Progression-free survival was defined as the time from start of treatment to the date of radiologically documented disease progression or death as a result of any cause. Overall survival was defined as the time from start of treatment to date of death as a result of any cause.

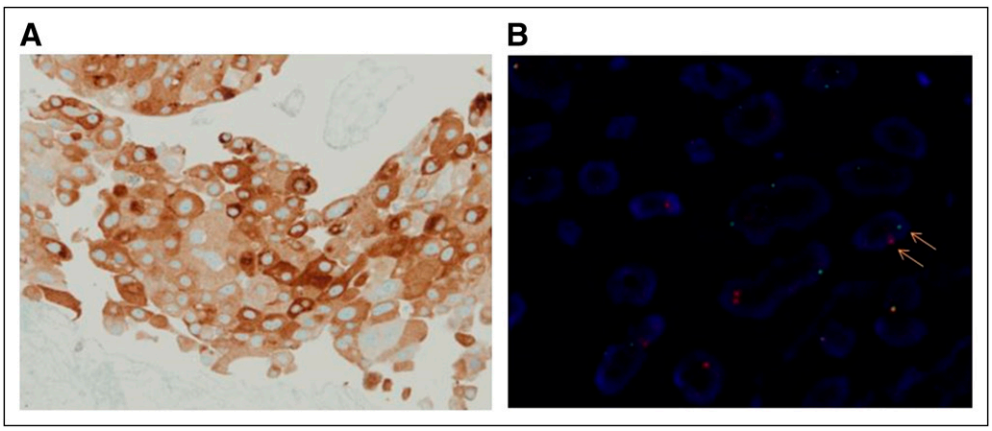

Fig A1. Representative pictures of an *ROS1*-rearranged tumor by (A) immunohistochemistry that shows strong and diffuse cytoplasmic staining and (B) fluorescent in situ hybridization that shows split signals.

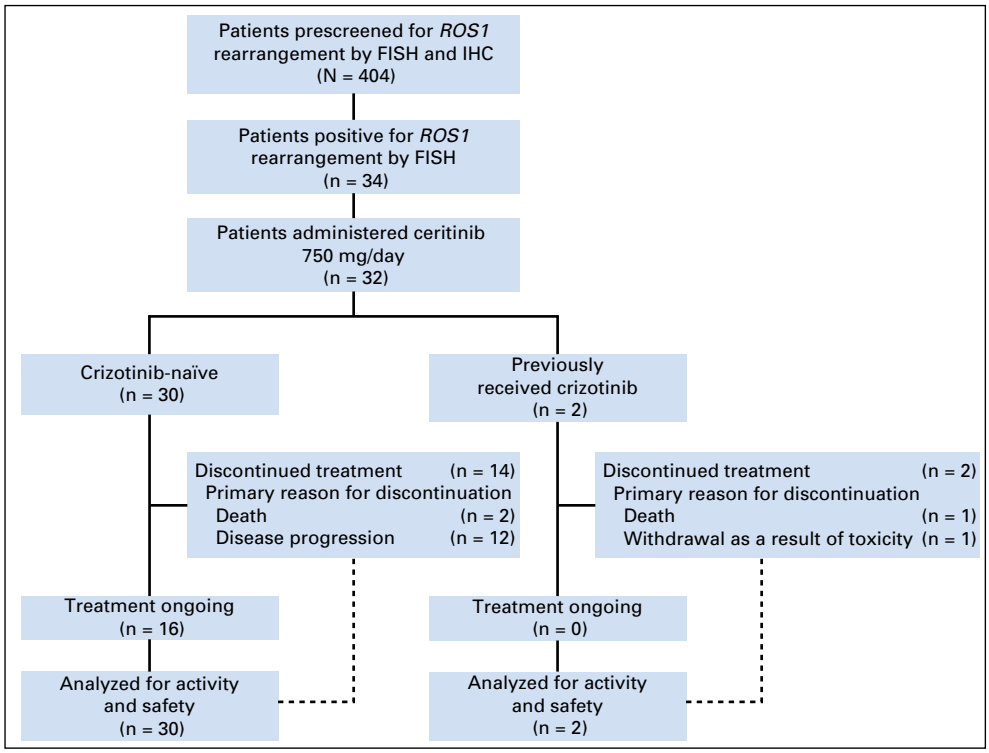

Fig A2. Trial profile. FISH, fluorescent in situ hybridization; IHC, immunohistochemistry.

Table A1. Study Centers in Order of Number of Patients Enrolled in the Study

Site	Principal Investigator	Patients Who Entered Treatment
Yonsei Cancer Center	Byoung Chul Cho	17
Samsung Medical Center	Myung-Ju Ahn	10
Seoul National University Bundang Hospital	Jong-Seok Lee	3
Chungbuk University	Ki Hyeong Lee	1
Kangbuk Samsung Hospital	Yun-Gyoo Lee	1

Table A2. Study Centers Where Prescreening for *ROS1* Rearrangement Was Performed Without Enrollment of Patients

Site	Principal Investigator	No. Prescreened
University of Ulsan College of Medicine	Young Joo Min	24
Gil Medical Center	Eun Kyung Cho	16
Inje University Haeundae Paik Hospital	Sung Sook Lee	11
VHS Medical Center	Bong-Seog Kim	8
Inje University School of Medicine	Moon Young Choi	2

Table A3. Investigator-Assessed Activity

Best Response	All Patients, No. (%)	Crizotinib-Naïve Patients, No. (%)
No. of patients	32	30
CR	1 (3)	1 (3)
PR	18 (56)	18 (60)
SD	7 (22)	7 (23)
PD	2 (6)	2 (7)
Not evaluable*	4 (12)	2 (7)
ORR, % (95% CI)	59 (42 to 74)	63 (45 to 78)
DCR (CR + PR + SD), % (95% CI)	81 (65 to 91)	87 (70 to 95)

Abbreviations: CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
*As a result of early deaths (n = 3) or withdrawal (n = 1) before first response evaluation.

Table A4. Intracranial Response

Best Response	Patients With Brain Metastases at Baseline (n = 8)
CR	1 (13)
PR	1 (13)
SD*/non-CR/non-PD†	3 (37)
PD	0
Not evaluable	3 (37)
Overall intracranial response rate, % (95% CI)	25 (7 to 59)
Intracranial DCR (CR + PR + SD*/non-CR/non-PD†), % (95% CI)	63 (31 to 86)

Abbreviations: CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; SD, stable disease.
*SD for measurable brain metastases.
†Non-CR/non-PD for nonmeasurable brain metastases.

Table A5. Whole-Body and Intracranial Responses in Patients With Brain Metastases at Study Entry

Patient	Previous Systemic Chemotherapy for Advanced Disease	Treatment of Brain Metastasis Before Ceritinib	Progression of Previously Radiated Lesions	Intracranial Response	Whole-Body Response	PFS, months
3	Pemetrexed + cisplatin and pemetrexed maintenance	Gamma knife surgery	Yes	SD (−2.3%)	SD	7.3
4	Pemetrexed + cisplatin and pemetrexed maintenance Docetaxel Bevacizumab + gemcitabine Crizotinib	Stereotactic radiotherapy	Yes	NA	NA	7.7
10	Gemcitabine + carboplatin Pemetrexed	Gamma knife surgery	Yes	Non-CR, non-PD	SD	2.9
18	Pemetrexed + cisplatin and pemetrexed maintenance Gefitinib Docetaxel Gemcitabine + carboplatin	Gamma knife surgery	Yes	PR (−66%)	PR	7.2
19	Pemetrexed + cisplatin	None	—	CR (−100%)	PR	≥ 16.4
21	Pemetrexed + cisplatin and pemetrexed maintenance Gefitinib	Whole-brain radiotherapy	Yes	NA	NA	0.2
28	Pemetrexed + cisplatin and pemetrexed maintenance Nivolumab Docetaxel Vinorelbine	None	—	NA	SD	4.6
29	Pemetrexed + cisplatin	None	—	Non-CR, non-PD	PR	4.7

Abbreviations: CR, complete response; NA, not available; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Table A6. Serious Adverse Events (regardless of study drug relationship)

Serious Adverse Event	No. (%)
Abdominal pain	1 (3)
Alanine aminotransferase increased	1 (3)
Appendicitis	1 (3)
Aspartate aminotransferase increased	1 (3)
Back pain	2 (6)
Dyspnea	2 (6)
Fatigue	1 (3)
Fever	1 (3)
Flu-like symptoms	1 (3)
Hyperglycemia	2 (6)
Lung infection (pneumonia)	1 (3)
Pneumonia	4 (12)
Ruled out leptomeningeal seedings	1 (3)
Superior vena cava syndrome	1 (3)
Upper respiratory infection	1 (3)
Urinary tract infection	1 (3)

Table A7. Serious Adverse Events Suspected to Be Related to the Study Drug

Serious Adverse Event	No. (%)
Abdominal pain	1 (3)
Alanine aminotransferase increased	1 (3)
Aspartate aminotransferase increased	1 (3)
Fatigue	1 (3)
Hypercalcemia	1 (3)
Hyperglycemia	1 (3)
Pneumonia	1 (3)
Upper respiratory infection	1 (3)

Table A8. Next-Generation Sequencing Results of Fifteen Patients With Available Tissue

Patient	FISH	IHC	ROS1 Fusion Variant	Best Overall Response	PFS, months
1	Positive	Positive	*CD74-ROS1*	PR	≥ 31.8
3	Positive	Positive	Negative	SD	7.3
10	Positive	Positive	*SLC34A2-ROS1*	SD	2.9
12	Positive	Positive	Negative	PR	≥ 20.7
13	Positive	Negative	Negative	PR	≥ 20.6
14	Positive	Negative	Negative	PD	0.78
15	Positive	Positive	*EZR-ROS1*	CR	8.61
17	Positive	Positive	*EZR-ROS1*	PR	≥ 17.3
19	Positive	Positive	*EZR-ROS1*	PR	≥ 16.4
20	Positive	Positive	*EZR-ROS1*	PR	≥ 16.2
21	Positive	Positive	*EZR-ROS1*	NA	0.25
23	Positive	Positive	*CD74-ROS1*	PR	≥ 14.2
27	Positive	Positive	*EZR-ROS1*	PR	13.6
29	Positive	Positive	*SLC34A2-ROS1*	PR	4.4
32	Positive	Positive	*EZR-ROS1*	PR	8.9

Abbreviations: CR, complete response; FISH, fluorescent in situ hybridization; IHC, immunohistochemistry; NA, not available; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.