ORIGINAL ARTICLE

Final Overall Survival and Other Efficacy and Safety Results From ASCEND-3: Phase II Study of Ceritinib in ALKi-Naive Patients With *ALK*-Rearranged NSCLC

Makoto Nishio, MD, PhD,[a,*] Enriqueta Felip, MD, PhD,[b] Sergey Orlov, MD,[c] Keunchil Park, MD, PhD,[d] Chong-Jen Yu, MD, PhD,[e] Chun-Ming Tsai, MD,[f] Manuel Cobo, MD, PhD,[g] Mark McKeage, PhD, FRACP,[h] Wu-Chou Su, MD,[i] Tony Mok, MD,[j] Giorgio V. Scagliotti, MD, PhD,[k] David R. Spigel, MD,[l] Kalyanee Viraswami-Appanna, PhD,[m] Zhe Chen, MSc,[m] Vanessa Q. Passos, MD,[m] Alice T. Shaw, MD[n]

[a]*Thoracic Medical Oncology Department, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan*
[b]*Department of Medical Oncology, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain*

*Corresponding author.

Disclosure: Dr. Viraswami-Appanna and Dr. Passos are employees of and own stocks in Novartis. Dr. Chen was an employee of Novartis at the time of analysis and initiation of the manuscript and owned stock in Novartis. Dr. Nishio has received research funding from Novartis, Ono Pharmaceutical, MSD, Chugai Pharmaceutical, BMS, Taiho Pharmaceutical, Eli Lilly, Pfizer, Astellas Pharma, and AZ, and has acted as an advisor and a consultant for MSD, Novartis, Pfizer, BMS, Ono Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, Taiho Pharmaceutical, Astellas, and AZ. Dr. Felip has acted as an advisor and a consultant for AbbVie, AZ, BerGenBio, Blue Print Medicines, BI, BMS, Celgene, Eli Lilly, Guardant Health, Janssen, Medscape, Merck KGaA, MSD, Novartis, Pfizer, Prime Oncology, Roche, Samsung, Takeda, and Touchtime; received research funding from Fundacion Merck Salud and Grant for Oncology Innovation EMD Serono; and has been compensated for a leadership role at Grifols. Dr. Orlov has acted as an advisor and a consultant for BMS, BI, MSD, Novartis, and Roche. Dr. Park has acted as an advisor and a consultant for Amgen, Astellas, AZ, BluePrint Medicines, BI, BMS, Clovis, Eli Lilly, Hanmi, KHK, Loxo, Merck KGaA, MSD, Novartis, Ono Pharmaceutical, and Roche; participated in a speakers' bureau for AZ and BI; and received research funding from AZ and MSD. Dr. Yu has acted as an advisor and a consultant for AZ, BI, Novartis, GSK, MSD, Ono Pharmaceutical, and Roche. Dr. Tsai has acted as an advisorand a consultant for Novartis, Pfizer, Roche, Eli Lilly, MSD, BMS, and AZ and has received honoraria from Novartis, Pfizer, Roche, Eli Lilly, MSD, BMS, and AZ. Dr. McKeage has acted as an advisor and a consultant for Novartis and Pfizer and has received research funding from Pfizer. Dr. Mok is a current employee at The Chinese University of Hong Kong; has been compensated for a leadership role at AZ PLC and Hutchison Chi-Med; owns stocks of Hutchison Chi-Med and Sanomics; has received honoraria from ACEA Pharma, Alpha Biopharma Co., Amgen, Amoy Diagnostics Co., AZ, Bayer, BI, Blueprint Medicines, BMS, Celgene, CStone Pharmaceuticals, Eli Lilly, Fishawack Facilitate, Hengrui Therapeutics, Ignyta, Incyte Corporation, InMed Medical Communication, IQVIA, Janssen, Loxo Oncology, Merck Serono, MSD, MoreHealth, Novartis, OncoGenex Pharmaceuticals, OrigiMed, PeerVoice, Pfizer, Prime Oncology, Roche and Genentech, Sanofi-Aventis R&D, SFJ Pharmaceutical, Takeda Pharmaceuticals HK, Vertex Pharmaceuticals, and Yuhan Corporation; has acted as an advisor and a consultant for ACEA Pharma, Alpha Biopharma Co., Amgen, Amoy Diagnostics Co., AZ, Bayer, BI, Blueprint Medicines, BMS, Celgene, Cirina, CStone Pharmaceuticals, Eli Lilly, Fishawack Facilitate, geneDecode Co., Hengrui Therapeutics, Ignyta, Incyte Corporation, InMed Medical Communication, IQVIA, Janssen, Loxo Oncology, Merck Serono, MSD, MoreHealth, Novartis, OncoGenex Pharmaceuticals, OrigiMed, PeerVoice, Pfizer, Prime Oncology, Roche and Genentech, Sanofi-Aventis R&D, SFJ Pharmaceutical, Takeda Pharmaceuticals HK, Vertex Pharmaceuticals, and Yuhan Corporation; has participated in a speakers' bureau for ACEA Pharma, Alpha Biopharma Co., Amgen, Amoy Diagnostics Co., AstraZeneca, BI, BMS, Eli Lilly, InMed Medical Communication, MSD, Novartis, Pfizer, Prime Oncology, Roche and Genentech, Taiho, and Takeda Oncology; and has received research funding from AZ, BMS, Clovis Oncology, MSD, Novartis, Pfizer, Roche, SFJ, and XCovery. Dr. Scagliotti has acted as a consultant for MSD and Eli Lilly and has received honoraria from Eli Lilly, AZ, Roche, and AbbVie. Dr. Spigel has been compensated for a leadership role at the Centennial Medical Center; has acted as an advisor and a consultant for Genentech and Roche, Novartis, Celgene, BMS, AZ, Pfizer, BI, AbbVie, Foundation Medicine, GSK, Lilly, Merck, Moderna Therapeutics, Nektar, Takeda, Amgen, TRM Oncology, Precision Oncology, Evelo Therapeutics, Illumina, and PharmaMar; has received research funding from Genentech and Roche, Novartis, Celgene, BMS, Lilly, AZ, Pfizer, BI, University of Texas Southwestern Medical Center-Simmons Cancer Center, Merck, AbbVie, GSK, G1 Therapeutics, Neon Therapeutics, Takeda, Foundation Medicine, Nektar, Celldex, Clovis Oncology, Daiichi Sankyo, EMD Serono, Acerta Pharma, Oncogenex, Astellas Pharma, Grail, Transgene, Aeglea Biotherapeutics, Tesaro, Ipsen, ARMO BioSciences, Amgen, and Millennium; and has received travel support from AZ, BI, Celgene, Lilly, EMD Serono, BMS, Genentech, Genzyme, Intuitive Surgical, Merck, Pfizer, Purdue Pharma, Spectrum Pharmaceuticals, and Sysmex. Dr. Shaw has served as a compensated consultant or received honoraria from Achilles, ARIAD, Bayer, Blueprint Medicines, Chugai, Daiichi Sankyo, EMD Serono, Foundation Medicine, Genentech/Roche, Guardant, Ignyta, KSQ Therapeutics, Loxo, Natera, Novartis, Pfizer, Servier, Taiho Pharmaceutical, Takeda, and TP Therapeutics; has received research funding from Daiichi Sankyo, Ignyta, Novartis, Pfizer, Roche and Genentech, and TP Therapeutics; and has received travel support from Pfizer and Genentech and Roche. The remaining authors have nothing to disclose.

ClinicalTrials.gov identifier: NCT01685138

Presented at the American Society for Clinical Oncology Annual Meeting, May 20, 2015 (abstract # 8060), the European Society for Medical Oncology (ESMO) Asia Congress, December 19, 2015 (abstract # 419O), ESMO Congress, October 9, 2016 (abstract # 1208O), and ESMO Congress, October 23, 2018 (abstract # LBA57).

Address for correspondence: Makoto Nishio, MD, PhD, Thoracic Medical Oncology Department, Cancer Institute Hospital of Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan. E-mail: mnishio@jfcr.or.jp

ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2019.11.006

[c]Department of Thoracic Oncology, Pavlov First Saint Petersburg State Medical University, St. Petersburg, Russia
[d]Division of Hematology and Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[e]Department of Internal Medicine, National Taiwan University, Taipei, Taiwan
[f]Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan
[g]Medical Oncology Department, Hospital Regional Universitario Málaga, Instituto de Investigaciones Biomédicas, Málaga, Spain
[h]Division of Pharmacology and Clinical Pharmacology, Auckland City Hospital and University of Auckland, Auckland, New Zealand
[i]Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan
[j]Department of Clinical Oncology, The Chinese University of Hong Kong, Shatin, The People's Republic of China
[k]Department of Oncology, University of Torino, Orbassano, Torino, Italy
[l]Medical Oncology, Sarah Cannon Research Institute, Nashville, Tennessee
[m]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey
[n]Department of Medicine and Pathology, Massachusetts General Hospital, Boston, Massachusetts

Received 24 October 2019; revised 13 November 2019; accepted 15 November 2019
Available online - 25 November 2019

ABSTRACT

Introduction: The phase II, single-arm ASCEND-3 study assessed the efficacy and safety of ceritinib in anaplastic lymphoma kinase (*ALK*) inhibitor (ALKi)–naive patients with *ALK*-rearranged NSCLC who had received at least three previous lines of chemotherapy. Here, we report the final efficacy and safety results.

Methods: Eligible patients (including those with asymptomatic or neurologically stable brain metastases) received oral ceritinib (750 mg/day, fasted). The primary end point was investigator-assessed overall response rate (ORR). Secondary end points were Blinded Independent Review Committee–assessed ORR; investigator- and Blinded Independent Review Committee–assessed overall intracranial response rate, duration of response, time to response, disease control rate, and progression-free survival (PFS); overall survival (OS); and safety. Exploratory end points included patient-reported outcomes.

Results: Of the 124 patients enrolled, 122 (98.4%) had received previous antineoplastic medications (31 patients [25.0%] received at least three regimens), and 49 (39.5%) had baseline brain metastases. The median follow-up time (data cutoff: January 22, 2018) was 52.1 (range, 48.4–60.1) months. The investigator-assessed ORR was 67.7% (95% confidence interval [CI]: 58.8–75.9), and the median PFS was 16.6 months (95% CI: 11.0–23.2). The median OS was 51.3 months (95% CI: 42.7–55.3). Most common adverse events (all grades, $\geq$60% of patients, all-causality) were diarrhea (85.5%), nausea (78.2%), and vomiting (71.8%). Overall, 18 patients (14.5%) had an adverse event leading to treatment discontinuation. Health-related quality of life was maintained during ceritinib treatment.

Conclusions: Ceritinib exhibited prolonged and clinically meaningful OS, PFS, and duration of response in chemotherapy-pretreated (at least three lines), ALKi-naive patients with *ALK*+ NSCLC. The safety profile was consistent with that reported in previous studies.

Keywords: Ceritinib; ALK; NSCLC; Phase II

Introduction

Anaplastic lymphoma kinase (*ALK*) has been identified as a key oncogenic driver.[1] Chromosomal rearrangements of *ALK* occur in approximately 3% to 7% of patients with NSCLC.[2,3]

Ceritinib (Zykadia; Novartis, East Hanover, NJ), a selective, next-generation *ALK* inhibitor (ALKi), has been approved for the treatment of patients with metastatic *ALK*-rearranged NSCLC.[4,5]

In the phase I ASCEND-1 study,[6] ceritinib at a dose of 750 mg (fasted) exhibited clinically meaningful whole-body efficacy in heavily pretreated patients with *ALK*-rearranged NSCLC with and without baseline brain metastases (BMs), including both ALKi-naive patients (83 of 246) and patients previously treated with an ALKi (163 of 246). The investigator-assessed overall response rate (ORR) and median progression-free survival (PFS) of ALKi-naive patients were 72.3% and 18.4 months, respectively.[6] Furthermore, data from phase III, randomized ASCEND-4 trial exhibited a statistically significant and clinically meaningful improvement in median PFS and ORR by Blinded Independent Review Committee (BIRC) with ceritinib versus chemotherapy (median PFS, 16.6 versus 8.1 months; ORR, 72.5% versus 26.7%, respectively) in treatment-naive patients with *ALK*-rearranged metastatic NSCLC (including those with and without BMs).[7]

ASCEND-3 was a phase II, single-arm study (NCT01685138) that assessed the efficacy and safety of ceritinib (750 mg/day) in ALKi-naive patients with *ALK*-

rearranged NSCLC who received at least three lines of previous chemotherapy. Results from the ASCEND-3 study, as of the data cutoff of November 15, 2015, with a median follow-up time of 25.9 (range, 22.2–33.8) months exhibited robust ORR and prolonged PFS; the investigator-assessed ORR was 67.7% (95% confidence interval [CI]: 58.8–75.9), and median PFS was 16.6 months (95% CI: 11.0–22.1). However, the median overall survival (OS) was not reached at the time of cutoff, with a 24-month OS rate of 67.5% (95% CI: 58.0–75.2). Ceritinib was active in patients with measurable BM at the baseline, with an overall intracranial response rate (OIRR) of 20.0% (two of 10 patients; 95% CI: 2.5–55.6) by investigator and 61.5% (eight of 13 patients; 95% CI: 31.6–86.1) by BIRC. Adverse events (AEs) were consistent with the known safety profile of ceritinib, and quality of life (QOL) was maintained with improvements in the lung symptom burden. Here, we report the final safety and efficacy results, including OS.

Materials and Methods

Patients

Patients (age, $\geq$18 years) with locally advanced or metastatic *ALK*-rearranged NSCLC who had not received previous ALKi treatment but could have received at least three lines of chemotherapy were eligible. *ALK* status was confirmed centrally at a Novartis-designated laboratory using the break-apart fluorescence in situ hybridization assay. Other key inclusion criteria included a WHO performance status (PS) of less than or equal to two and at least one measurable lesion, as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients must have progressed during or after the last chemotherapy regimen received before receiving ceritinib.

Patients with asymptomatic or neurologically stable BM at the baseline were eligible. Previous radiotherapy to the brain must have been completed at least 2 weeks before ceritinib treatment was started. Before starting ceritinib, patients must have recovered from all toxicities related to previous anticancer therapies to less than or equal to grade 2 AEs on the basis of Common Terminology Criteria for Adverse Events version 4.03.

Study Design

This single-arm, open-label, multicenter, phase II study with a Simon 2-stage design assessed ceritinib (750 mg/day, fasted) administered orally on a continuous, 28-day cycle. Treatment continued until the following ensued: (1) disease progression (progressive disease; radiologically documented according to RECIST version 1.1, as assessed by the investigator); (2) unacceptable toxicity; (3) treatment discontinuation at patient or investigator discretion; (4) initiation of new anticancer therapy; and/or (5) death. Patients with investigator-assessed, RECIST-defined progressive disease could continue ceritinib treatment at the physician's discretion if there was evidence of continued clinical benefit.

The primary objective of the study was to evaluate the antitumor activity of ceritinib, as measured by investigator-assessed ORR per RECIST version 1.1. Secondary objectives included the evaluation of response-related end points such as ORR by BIRC; duration of response (DOR), time to response (TTR), disease control rate (DCR), PFS, and OIRR assessed by investigator and BIRC; OS; and safety. The exploratory objective was to assess patient-reported outcomes (PROs).

Before study initiation, the protocol was reviewed and approved by the local human investigations committee at each participating site. All patients provided written informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Council for Harmonisation.

Study Assessments

Efficacy analysis. Tumor assessments were performed at baseline and every 8 weeks ($\pm$1 week) from the start of ceritinib treatment using contrast-enhanced computerized tomography or magnetic resonance imaging. Scans of the chest, upper abdomen, and brain were performed for all patients at the baseline. A consistent imaging modality was required throughout the study.

Whole-body (extracranial plus intracranial) and intracranial responses were assessed by investigator review and BIRC according to RECIST version 1.1. Intracranial responses were calculated in patients with measurable BMs at the baseline (after screening, brain scans were only performed at subsequent assessments in patients with brain lesions at the baseline and in patients with suspected brain lesions during study treatment) and were selected as target lesions by the investigator and BIRC. All target lesions in the brain were confirmed to ensure that patients with previous radiotherapy and without progression were not included in the analyses.

Safety analysis. Safety was monitored at the baseline and at every subsequent visit. Physical condition, electrocardiogram, WHO PS, and laboratory parameters were assessed. AEs were recorded and graded according to Common Terminology Criteria for Adverse Events version 4.03.

PRO analysis. PROs were assessed using the Lung Cancer Symptom Scale (LCSS) and the European Organization for Research and Treatment of Cancer (EORTC), the Core

Quality of Life Questionnaire (QLQ-C30 version 3.0), and the complementary lung cancer–specific questionnaire (QLQ-LC13 version 1.0). In addition, function, symptom impact, and overall health status were evaluated.

Statistical Analysis

Analysis sets. The full analysis set (FAS) and the safety set consisted of all patients who received at least one dose of ceritinib. In this study, the FAS and safety set were identical. Unless otherwise specified, the FAS was used for all analyses.

Efficacy analysis. The ORR, OIRR, and DCR were assessed by investigator and BIRC and were estimated along with 95% CIs. DOR, PFS, and OS were analyzed using the Kaplan-Meier method. TTR was summarized using descriptive statistics. Per RECIST version 1.1, the confirmation of response at 4 weeks or more after the initial documentation was required for the determination of the best overall response.

A response rate of 35% or fewer was considered as an insufficient level of activity for the proposed patient population. A total of 105 patients were required to test a null hypothesis of an ORR of 35% or fewer versus an alternative hypothesis of an ORR of greater than 50% using a one-sided test with an α of 0.05 on the basis of the Simon optimal 2-stage design. Among 105 patients, if 45 or more responses were observed (estimated ORR, 42.9%), the null hypothesis would be rejected. The point estimate along with its 95% CI was provided for ORR.

PRO analysis. The raw summary scores of EORTC QLQ-C30/LC13 and LCSS were generated by adding up item responses to the questions that comprised each domain. For LCSS, the average of all nine items was used for the total score. In addition, a subscore was calculated using the mean of all six major symptoms for the average symptom burden index, the single health-related QOL item, and/or individual items to report specific areas of change. Descriptive statistics were used to summarize scored scales at each scheduled assessment time point. In addition, change from the baseline in the domain scores at the time of each assessment was summarized. Patients with an evaluable baseline score and at least one evaluable postbaseline score during the treatment period were included in the change from baseline analyses.

Results

Patients

In total, 124 patients were enrolled between January 2013 and January 2014 across 41 centers globally (16 countries). All patients received one or more doses of ceritinib (750 mg/day, fasted). The median follow-up time was 52.1 (range, 48.4–60.1) months.

Table 1. Patient Demographics and Disease Characteristics at the Baseline (Full Analysis Set)

Characteristic	N = 124
Age, median (range), y	56.0 (27.0–82.0)
Age category, n (%)	
<65 y	94 (75.8)
Sex, n (%)	
Female	74 (59.7)
Race, n (%)	
White	48 (38.7)
Black	1 (0.8)
Asian	74 (59.7)
Other	1 (0.8)
WHO performance status, n (%)	
0	46 (37.1)
1	69 (55.6)
2	9 (7.3)
Tumor histologic or cytologic diagnosis, n (%)	
Adenocarcinoma	120 (96.8)
Others	4 (3.2)
Stage at the time of study entry, n (%)	
IV[a]	124 (100.0)
Median number of metastatic sites of disease (range)	4.0 (1.0–8.0)
Key sites of metastasis, n (%)	
Lung	118 (95.2)
Lymph nodes	78 (62.9)
Bone	55 (44.4)
Pleura	50 (40.3)
Brain	49 (39.5)
Liver	33 (26.6)
Time since most recent relapse or progression, median (range), m	1.7 (0.1–8.1)
Previous antineoplastic therapies[b], n (%)	
Any	123 (99.2)
Operation	38 (30.6)
Radiotherapy	60 (48.4)
Previous radiotherapy to the brain	27 (21.8)
Chemotherapy setting[c]	
Adjuvant	16 (12.9)
Neoadjuvant	8 (6.5)
Prevention	1 (0.8)
Palliative	86 (69.4)
Therapeutic	31 (25.0)
Other	7 (5.6)
Other therapy setting[c]	38 (30.6)
Number of previous antineoplastic regimens, n (%)	
0	2 (1.6)
1	54 (43.5)
2	37 (29.8)
3	24 (19.4)
>3	7 (5.6)

[a]Includes stages IVa (N = 4) and IVb (N = 20).
[b]Any previous antineoplastic therapy includes medication, radiotherapy, or operation.
[c]A patient may have multiple settings.

Baseline demographics and disease characteristics are presented in Table 1. Most patients were Asian (59.7%) or white (38.7%), with a WHO PS of one or fewer (92.7%). In

Table 2. Best Overall Whole-Body Response in All Patients (Full Analysis Set)

Parameter	N = 124 By Investigator	N = 124 By BIRC
ORR (CR + PR), n (%) (95% CI)	84 (67.7) (58.8, 75.9)	79 (63.7) (54.6, 72.2)
Best overall response, n (%)		
CR	2 (1.6)	2 (1.6)
PR	82 (66.1)	77 (62.1)
SD	27 (21.8)	20 (16.1)
PD	5 (4.0)	9 (7.3)
NCR/NPD[a]	1 (0.8)	8 (6.5)
Unknown	7 (5.6)	8 (6.5)
DCR (CR + PR + SD + NCR/NPD), n (%) (95% CI)	112 (90.3) (83.7, 94.9)	107 (86.3) (79.0, 91.8)
	M[b] = 84	M[b] = 79
Median DOR, mo (95% CI)	24.0 (14.8, 37.5)	27.3 (16.6, 44.3)
Median PFS, mo (95% CI)	16.6 (11.0, 23.2)	19.4 (10.9, 29.3)
	M[b] = 84	M[b] = 79
Median time to first response (range), mo	1.8 (1.6-18.4)	1.8 (1.5-9.0)

[a]NCR/NPD refers to the best overall responses that are neither CR nor PD per RECIST 1.1 criteria for patients with nonmeasurable disease only at baseline.
[b]Total number of patients with confirmed CR or PR.
BIRC, Blinded Independent Review Committee; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; NCR, noncomplete response; NPD, nonprogressive disease; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

total, 49 patients (39.5%) presented with BMs at study entry. Previous antineoplastic medications were received by 122 of 124 patients (98.4%), with 31 patients (25.0%) having received three or more previous antineoplastic regimens.

At the time of data cutoff (January 22, 2018), 32 patients (25.8%) had completed ceritinib treatment in this study and were transferred to a separate roll-over study (25 patients) or commercial supply (seven patients) to ensure continued ceritinib treatment (Supplementary Table 1). All other patients had discontinued ceritinib treatment. The primary reason for discontinuation was disease progression occurring in 53 patients (42.7%), followed by AEs in 18 patients (14.5%) and death in 10 patients (8.1%). Antineoplastic therapies since the discontinuation of ceritinib are summarized in Supplementary Table 2.

Efficacy

The best overall whole-body responses are reported in Table 2. The ORR and DCR by investigator review were 67.7% (95% CI: 58.8–75.9) and 90.3% (95% CI: 83.7–94.9), respectively. Among patients with the best overall complete response or partial response, the median time to first response by investigator was 1.8 (range, 1.6–18.4) months. Among 114 patients with a measurable disease at the baseline and at least one postbaseline assessment, 108 (94.7%) had decreased tumor burden from the baseline, as assessed by the investigator (Fig. 1). Median PFS was 16.6 months (95% CI: 11.0–23.2) by investigator and 19.4 months (95% CI: 10.9–29.3) by BIRC (Fig. 2). Median OS was 51.3 months (95% CI: 42.7–55.3); the estimated 54-month OS rate was 48.1% (95% CI: 36.2–58.9) (Fig. 3).

Efficacy in patients with BMs at baseline. In patients with BMs at the baseline (49 of 124), the investigator-assessed ORR was 57.1% (95% CI: 42.2–71.2), DCR was 87.8% (95% CI: 75.2–95.4), and median PFS was 10.8 months (95% CI: 7.3–16.6). In patients without baseline BMs (75 of 124), the investigator-assessed ORR was 74.7% (95% CI: 63.3–84.0), DCR was 92.0% (95% CI: 83.4–97.0), and median PFS was 19.6 months (95% CI: 14.5–36.7). Results on the basis of BIRC assessment were consistent with those on the basis of investigator assessment. Median OS was 36.2 months (95% CI: 17.7 to not evaluable) in patients with BMs at the baseline (49 of 124) and 55.3 months (95% CI: 50.1–55.3) in patients without baseline BMs (75 of 124); the estimated 18-month OS rate was 65.5% (95% CI: 49.9–77.2) and 78.4% (95% CI: 67.2–86.2), respectively.

Intracranial responses in patients with measurable BM at baseline. Ten patients had measurable investigator-assessed brain lesions at the baseline. In these patients, the OIRR and intracranial disease control rate (IDCR) were 20.0% (two of 10 patients; 95% CI: 2.5–55.6) and 80.0% (eight of 20 patients; 95% CI: 44.4–97.5), respectively. By BIRC, 13 patients had measurable brain lesions at the baseline, for whom OIRR and IDCR were 61.5% (eight of 13 patients; 95% CI: 31.6–86.1) and 76.9% (10 of 13 patients; 95% CI: 46.2–95.0), respectively.

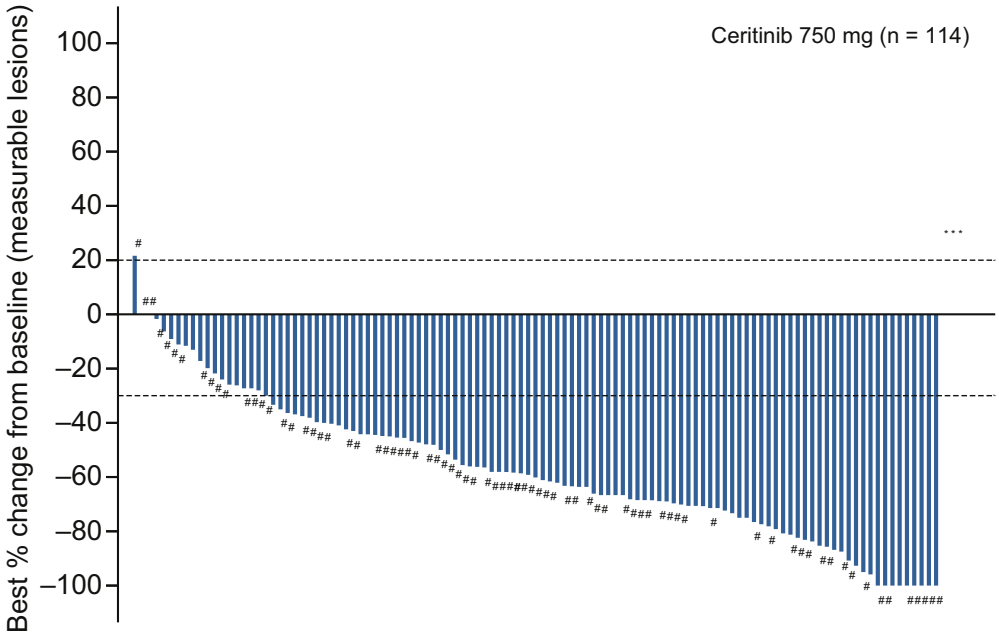

Figure 1. Waterfall plot of best percentage change from the baseline in the sum of diameters per investigator assessment (FAS). Best percentage change from BL > 0: 1 (0.88%). Best percentage change from BL < 0: 108 (94.74%). Best percentage change from BL = 0: 2 (1.75%). *Percent change in target lesion available but contradicted by overall lesion response equals PD (contradicting assessment represents the only valid postbaseline assessment): 3 (2.63%). n (number of patients with measurable disease at baseline and at least one valid postbaseline assessment) was used for the calculation of percentages. A postbaseline assessment with unknown response for target lesion or unknown overall lesion response was considered invalid. # PFS event. BL, baseline; FAS, full analysis set; PD, progressive disease; PFS, progression-free survival.

Safety

The median duration of ceritinib exposure was 23.2 (range, 0.1–55.2) months, with a median relative dose intensity of 77.5% (range, 32.6%–100.0%). All patients experienced one or more AEs irrespective of the relationship to study drug (Supplementary Table 3). AEs requiring dose adjustment or interruption were reported in 105 patients (84.7%). At least one dose reduction was required in 90 patients (72.6%); the median time to the first dose reduction was 1.9 (range, 0.2–46.0) months. AEs leading to treatment discontinuation were reported in 18 patients (14.5%), with no particular AE predominating. Overall, 19 on-treatment deaths (15.3%) were reported, of which 16 (12.9%) were considered to be because of the study indication (NSCLC) and one (0.8%) death each because of acute pulmonary edema, pneumonia aspiration, and atypical pneumonia.

The most common AEs (≥50% of patients, all grades, regardless of study drug relationship) were diarrhea (85.5%), nausea (78.2%), vomiting (71.8%), decreased appetite (55.6%), and increased alanine aminotransferase (ALT) (52.4%) (Table 3). Grade 3 or 4 AEs (all-causality) were reported in 87.9% of patients, with 65.3% of patients experiencing grade 3 or 4 AEs that were suspected to be study drug related. The most common (≥10% of patients) drug-related grade 3 or 4 AEs were elevated ALT (20.2%) and gamma-glutamyl transferase (16.1%). Gastrointestinal (GI) AEs were the most frequently reported all-causality AEs. The most frequently reported GI AEs were of grade 1 or 2, with grade 3 or 4 diarrhea, nausea, vomiting, and decreased appetite reported in 3.2%, 8.1%, 6.5%, and 3.2% of patients, respectively.

Patient-Reported Outcomes

Compliance was high, with at least 98.0% of patients completing the QLQ-C30, QLQ-LC13, and LCSS questionnaire during ceritinib treatment.

Patients exhibited improvement in lung cancer–related symptoms (i.e., cough, pain, and shortness of breath) as assessed by the LCSS questionnaire, with a mean change from the baseline in the overall LCSS score ranging from −14.83 to −3.39 during treatment cycles 2 to 53 (lower scores indicate improvement in symptoms; Supplementary Fig. 1). Scores for lung cancer symptoms as measured using QLQ-LC13 were generally maintained on treatment (Supplementary Fig. 2), confirming LCSS findings. A similar pattern was observed for the other domains of EORTC QLQ-C30/LC13 and LCSS; for example, for the QLQ-C30 global health status, a mean change from the baseline in the overall QLQ-C30 score ranging from 0.53 to 12.84 during treatment cycles 3 to 53 (Supplementary Fig. 3) was observed. Overall, PROs and health status generally were maintained or slightly improved in patients receiving ceritinib.

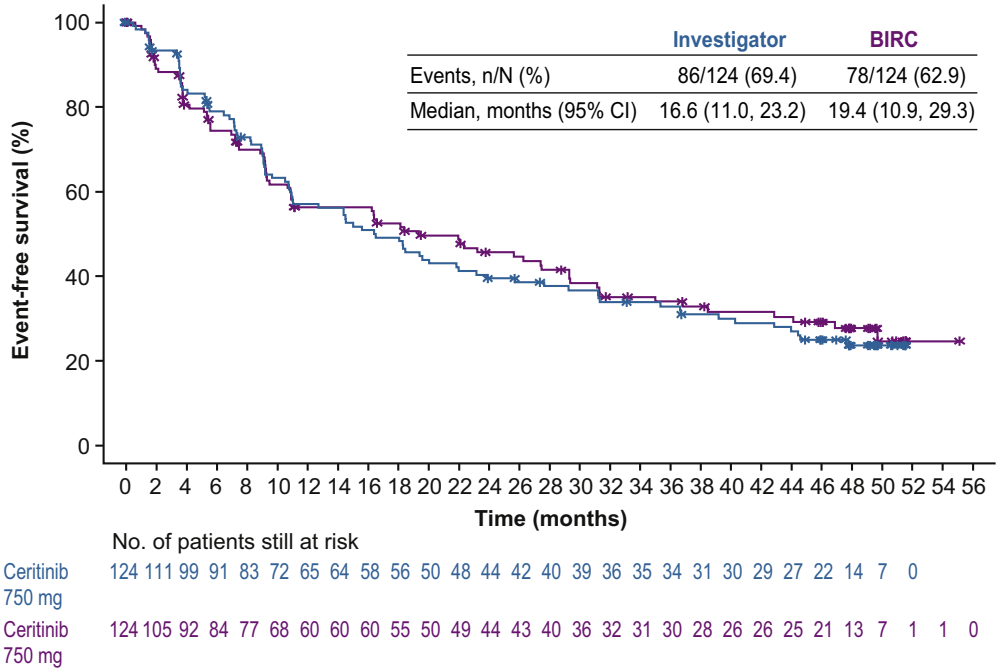

Figure 2. Kaplan-Meier plot of PFS per investigator and BIRC assessment (FAS). *Censoring times. BIRC, Blinded Independent Review Committee; CI, confidence interval; FAS, full analysis set; PFS, progression-free survival.

Discussion

In this study, ceritinib (750 mg/day, fasted) exhibited clinically meaningful antitumor activity, as reflected by the high whole-body response rate in heavily pretreated patients with *ALK*-rearranged NSCLC who were ALKi-naive. Despite 98.4% of patients receiving at least one antineoplastic medication before study initiation and a high proportion of patients having baseline BMs (39.5%), these results are consistent with previous findings in ALKi-naive and treatment-naive patients with *ALK*-rearranged NSCLC who received ceritinib.[6,7] In addition, a prolonged OS was observed with a median OS

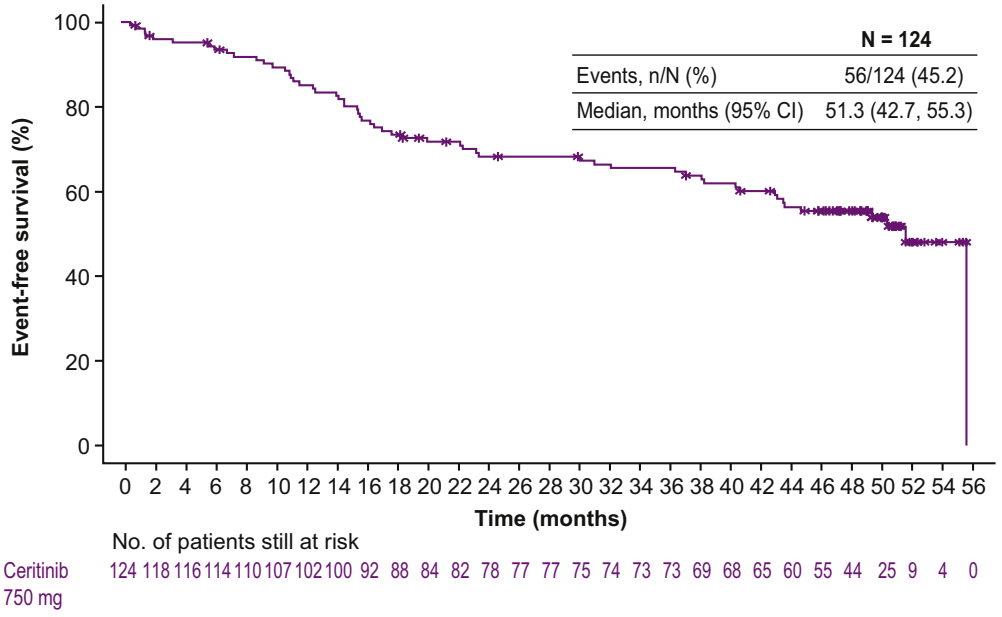

Figure 3. Kaplan-Meier plot of OS (FAS). *Censoring times. CI, confidence interval; FAS, full analysis set; OS, overall survival.

Table 3. Most Common AEs (≥25% of Patients, All Grades, All-Causality) (Safety Set)

	N = 124	
AEs by Preferred Term	All Grades n (%)	Grade 3/4 n (%)
Total	124 (100.0)	109 (87.9)
Diarrhea	106 (85.5)	4 (3.2)
Nausea	97 (78.2)	10 (8.1)
Vomiting	89 (71.8)	8 (6.5)
Decreased appetite	69 (55.6)	4 (3.2)
Increased alanine aminotransferase	65 (52.4)	30 (24.2)
Increased aspartate aminotransferase	58 (46.8)	15 (12.1)
Abdominal pain	51 (41.1)	1 (0.8)
Fatigue	48 (38.7)	11 (8.9)
Decreased weight	47 (37.9)	2 (1.6)
Increased gamma-glutamyl transferase	36 (29.0)	24 (19.4)
Constipation	35 (28.2)	0
Increased blood creatinine	33 (26.6)	1 (0.8)
Back pain	32 (25.8)	3 (2.4)
Dyspnea	31 (25.0)	4 (3.2)
Headache	31 (25.0)	1 (0.8)

AEs, adverse events.

of 51.3 months (95% CI: 42.7–55.3) and an estimated 54-month OS rate of 48.1% (95% CI: 36.2–58.9).

Similar to the findings of the ASCEND-4 study, ceritinib exhibited strong efficacy in patients with baseline BMs despite a large proportion of patients (78.2%) having not received radiotherapy to the brain before enrollment in the current study. The lack of previous treatment in patients with baseline BM in these studies differs from other ALKi studies that required baseline BM to be stable and pretreated,[8-10] and may account for the difference observed in the median PFS between patients with and without baseline BM.

Ceritinib (750 mg/day, fasted) achieved intracranial responses in patients with measurable investigator-assessed brain lesions at the baseline, with an IDCR of 80.0% (95% CI: 44.4–97.5). These results are comparable with those reported in the ASCEND-1 and ASCEND-4 studies.[6,7] In addition to the relatively small sample size, the difference in responses observed between investigator- and BIRC-assessed brain lesions could be explained by the fact that the central and local assessors selected different patients with target brain lesions.

The safety profile of ceritinib was consistent with that previously reported,[6,7] with no new or unexpected AEs identified. GI AEs (diarrhea, nausea, and vomiting) were the most frequently reported all-causality drug-related AEs, with most being grade 1 or 2. Promising data have recently been reported, suggesting that ceritinib at a dosage of 450 mg/day taken with food has a similar exposure to that of ceritinib at a dose of 750 mg taken under fasting conditions and significantly reduces GI toxicity.[11,12] In the current study, elevated ALT and gamma-glutamyl transferase were the most frequently reported grade 3 or 4 AEs (all-causality). Interstitial lung disease, a known complication of ALKi treatment,[8] was reported in one patient (0.8%; grade 2). Pericarditis, suspected to be drug related, was reported in four patients; however, malignant involvement of the pericardium is known to occur in patients with advanced cancer (up to 21% of cases), with lung cancer being the most common cause of malignant pericarditis (34%–76%).[13-15] Very few patients (14.5%) treated with ceritinib discontinued treatment because of an AE. Most ceritinib-related AEs were managed with dose interruptions and/or reductions.

In addition to the antitumor activity exhibited by ceritinib, global health-related QOL was generally maintained during ceritinib treatment, with improvements in lung cancer symptoms such as cough, pain, and shortness of breath.

In conclusion, ceritinib treatment exhibited prolonged and clinically meaningful OS, PFS, and DOR in chemotherapy-pretreated (≤3 lines), ALKi-naive patients with *ALK*-rearranged NSCLC irrespective of BMs at the baseline. In addition, the safety profile was consistent with that reported in previous studies. These results further support the positive benefit-risk profile of ceritinib in ALKi-naive patients with *ALK*-rearranged NSCLC.

Acknowledgments

This study was funded by Novartis Pharmaceuticals Corporation. The authors thank the participating patients, their families, all study coinvestigators, and research coordinators. In addition, the authors thank Vanessa Giannone, Novartis Healthcare Pvt. Ltd. (East Hanover, United States), for her contribution to this study. Medical writing support was provided by Shilpa Garg, Novartis Healthcare Pvt. Ltd. (Hyderabad, India).

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.11.006.

References

1. Rikova K, Guo A, Zeng Q, et al. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. *Cell*. 2007;131:1190–1203.
2. Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol*. 2009;27:4247–4253.

3. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature*. 2007;448:561–566.
4. US Food and Drug Administration. FDA approves ceritinib. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-broadens-ceritinib-indication-previously-untreated-alk-positive-metastatic-NSCLC. Accessed September 26, 2019.
5. Novartis. Novartis lung cancer drug Zykadia® gains EU approval. https://www.novartis.com/news/media-releases/novartis-receives-eu-approval-first-line-use-zykadia-alk-positive-advanced-non-small-cell-lung-cancer-NSCLC. Accessed September 26, 2019.
6. Kim DW, Mehra R, Tan DSW, et al. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. *Lancet Oncol*. 2016;17:452–463.
7. Soria JC, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. *Lancet*. 2017;389:917–929.
8. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Eng J Med*. 2013;368:2385–2394.
9. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. 2014;371:2167–2177.
10. Gettinger SN, Bazhenova LA, Langer CJ, et al. Activity and safety of brigatinib in ALK-rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial. *Lancet Oncol*. 2017;17:1683–1696.
11. Cho BC, Kim DW, Bearz A, et al. ASCEND-8: a randomized phase 1 study of ceritinib, 450 mg or 600 mg, taken with a low-fat meal versus 750 mg in fasted state in patients with anaplastic lymphoma kinase (ALK)-rearranged metastatic non-small cell lung cancer (NSCLC). *J Thorac Oncol*. 2017;12:1357–1367.
12. Cho BC, Obermannova R, Bearz A, et al. Efficacy and safety of ceritinib (450 mg/d or 600 mg/d) with food versus 750-mg/d fasted in patients with ALK receptor tyrosine kinase (ALK)-positive NSCLC: primary efficacy results from the ASCEND-8 study. *J Thorac Oncol*. 2019;14:1255–1265.
13. Bischiniotis TS, Lafaras CT, Platogiannis DN, Moldovan L, Barbetakis NG, Katseas GP. Intrapericardial cisplatin administration after pericardiocentesis in patients with lung adenocarcinoma and malignant cardiac tamponade. *Hellenic J Cardiol*. 2005;46:324–329.
14. El Haddad D, Iliescu C, Yusuf SW, et al. Outcomes of cancer patients undergoing percutaneous pericardiocentesis for pericardial effusion. *J Am Coll Cardiol*. 2015;66:1119–1128.
15. Jeong TD, Jang S, Park CJ, et al. Prognostic relevance of pericardial effusion in patients with malignant diseases. *Korean J Hematol*. 2012;47:237–238.