ORIGINAL ARTICLE

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

Byoung Chul Cho, MD, PhD,[a,*] Radka Obermannova, MD, PhD,[b] Alessandra Bearz, MD,[c] Mark McKeage, MBChB, PhD, FRACP,[d] Dong-Wang Kim, MD, PhD,[e] Ullas Batra, MD, DM, ECMO,[f] Gloria Borra, MD,[g] Sergey Orlov, MD, PhD,[h] Sang-We Kim, MD,[i] Sarayut L. Geater, MD,[j] Pieter E. Postmus, MD, PhD,[k] Scott A. Laurie, MD, FRCPC,[l] Keunchil Park, MD, PhD,[m] Cheng-Ta Yang, MD,[n] Andrea Ardizzoni, MD,[o] Anna C. Bettini, MD,[p] Gilberto de Castro Jr., MD, PhD,[q] Flavia Kiertsman, DDS, MS,[r] Zhe Chen, PhD,[r] Yvonne Y. Lau, PhD,[r] Kalyanee Viraswami-Appanna, PhD,[r] Vanessa Q. Passos, MD, PhD,[r] Rafal Dziadziuszko, MD, PhD[s]

[a]*Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea*
[b]*Masaryk Memorial Cancer Institute, Brno-střed-Staré Brno, Czech Republic*
[c]*Centro di Riferimento Oncologico-IRCCS, Aviano, Italy*
[d]*University of Auckland, Auckland, New Zealand*
[e]*Seoul National University Hospital, Seoul, Republic of Korea*
[f]*Rajiv Gandhi Cancer Institute, Rohini, New Delhi, India*
[g]*Az. Osp. Univ.Maggiore della Carità, Italy*
[h]*State Pavlov Medical University, St. Petersburg, Russia*
[i]*Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea*
[j]*Songklanagarind Hospital, Prince of Songkla University, Songkhla, Thailand*
[k]*The Clatterbridge Centre NHS Foundation Trust, Liverpool, United Kingdom*
[l]*Ottawa Hospital Cancer Centre, Ottawa, Ontario, Canada*
[m]*Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*
[n]*Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan*
[o]*S.Orsola-Malpighi University Hospital, Bologna, Italy*
[p]*A.S.S.T. Papa Giovanni XXIII, Bergamo, Italy*
[q]*Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil*
[r]*Novartis Pharmaceuticals Corporation, East Hanover, New Jersey*
[s]*Rafal Dziadziuszko, Medical University of Gdansk, Gdansk, Poland*

Received 21 December 2018; revised 25 February 2019; accepted 1 March 2019
Available online - 6 March 2019

*Corresponding author.

Disclosure: Dr. D.-W. Kim has received nonfinancial support from Novartis. Dr. Geater has received grants from Novartis; and has received personal fees from Astra Zeneca, Boehringer Ingelheim, and Roche. Dr. Postmus has received personal fees from Novartis, Bristol-Myers Squibb, Astra Zeneca, Abbvie, Roche, Boehringer Ingelheim, Merck Sharp & Dohme, G1 Therapeutics, and Janssen. Dr. Park has received personal fees from Novartis. Dr. Ardizzoni has received grants from Bristol-Myers Squibb and Celgene; and personal fees from Pfizer, Eli Lilly, Roche, and Merck Sharp & Dohme. Dr. de Castro has received personal fees from Novartis and Pfizer. Drs. Kiertsman, Chen, Lau, Viraswami-Appanna, and Passos are employees with and have stock in Novartis Pharmaceuticals Corporation. Dr. Dziadziuszko has received personal fees from Novartis, Roche, Pfizer, Tesaro, Astra Zeneca, Bristol-Myers Squibb, Ignyta, and Novacure. The remaining authors declare no conflict of interest.

Address for correspondence: Byoung Chul Cho, MD, PhD, Division of Medical Oncology, Yonsei Cancer Center, Department of Internal Medicine, Yonsei University College of Medicine, 50 Yonsei-ro, Sinchondong, Seodaemun-gu, Seoul, Republic of Korea. E-mail: CBC1971@yuhs.ac

ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2019.03.002

ABSTRACT

Introduction: In an earlier report of the ASCEND-8 study (open-label, phase I, three-arm study, treatment-naive patients and pre-treated patients with advanced/metastatic NSCLC), it was shown that ceritinib 450 mg with food had comparable exposure and better gastrointestinal tolerability than 750-mg fasted.

Methods: Here, we report efficacy and updated safety data from primary efficacy analysis of the ASCEND-8 study. Key secondary endpoints were overall response rate and duration of response, assessed by blinded independent review committee (BIRC) using Response Evaluation Criteria in Solid Tumors 1.1.

Results: In total, 306 patients were randomized to ceritinib 450-mg fed (n = 108) or 600-mg fed (n = 87) or 750-mg fasted (n = 111), of which 304 patients were included in safety analysis and 198 treatment-naive patients (ALK receptor tyrosine kinase [*ALK*]–positive by immunohistochemistry) were included in the efficacy analysis (450-mg fed [n = 73], 600-mg fed [n = 51], and 750-mg fasted [n = 74]). The BIRC-assessed overall response rate was 78.1% (95% confidence interval [CI]: 66.9–86.9), 72.5% (95% CI: 58.3–84.1), and 75.7% (95% CI: 64.3–84.9), respectively; and the median duration of response (months) by BIRC was not estimable (NE) (95% CI: 11.2–NE), 20.7 (95% CI: 15.8–NE), and 15.4 (95% CI: 8.3–NE), respectively. Based on the safety analysis (n = 304), the 450-mg fed arm showed the highest median relative dose intensity (100% versus 78.5% versus 83.7%), lowest proportion of patients with dose reductions (24.1% versus 65.1% versus 60.9%), and lowest proportion of patients with gastrointestinal toxicities (75.9% versus 82.6% versus 91.8%).

Conclusion: Ceritinib at a dose of 450 mg with food compared to 750-mg fasted showed consistent efficacy and less gastrointestinal toxicity.

Keywords: Ceritinib; ALK receptor tyrosine kinase; NSCLC; Food effect

Introduction

ALK receptor tyrosine kinase (*ALK*) rearrangement occurs in approximately 3% to 7% of patients with NSCLC, and the clinical data have shown the success of therapeutic approaches targeting the ALK protein in this patient population.[1–4] Ceritinib is a next-generation ALK inhibitor, initially approved at the recommended dose of 750 mg/d fasted for the treatment of patients with *ALK*-positive NSCLC who are treatment-naive or have progressed on crizotinib.[5–7] Results of the two randomized phase III studies comparing ceritinib 750-mg/d fasted with chemotherapy in patients with advanced *ALK*-positive NSCLC showed that the progression-free survival (PFS) and overall response rate (ORR) were improved significantly with ceritinib versus chemotherapy in both first-line (ASCEND-4) and second-line (ASCEND-5) settings.[3,8] The safety data from these two phase III studies have shown a high frequency of overall gastrointestinal adverse events (AEs) with nausea, diarrhea, and vomiting being the most common events in patients treated with ceritinib.[3,8]

Based on the known safety profile of ceritinib 750-mg/d fasted[3], the increased systemic exposure of ceritinib with food[9], and the improved gastrointestinal tolerability of other tyrosine kinase inhibitors (TKIs) when administered with food[10,11], the ongoing, multicenter, randomized open-label ASCEND-8 study aimed to evaluate ceritinib 450 mg or 600 mg with a low-fat meal (food) versus 750-mg fasted in patients with *ALK*-positive NSCLC. The primary pharmacokinetic results from the ASCEND-8 study have shown that the 450-mg fed arm had no meaningful difference in steady-state exposure and a more favorable gastrointestinal safety profile compared to the 750-mg fasted arm in a heterogeneous group of patients with *ALK*-positive NSCLC who were either treatment-naïve or previously treated with different lines of therapy.[12] Based on the pharmacokinetics, safety, and efficacy results of the ASCEND-8 study, the recommended starting dose of ceritinib has been changed to 450 mg once daily with food in the United States, European Union, and other countries worldwide.[13,14] The approval of the new starting dose was based on the interim efficacy analysis generated on an earlier cutoff date (July 26, 2017), for which the data has not been published. Here, we report the primary efficacy analysis results based on treatment-naive patients who are *ALK*-positive, confirmed by immunohistochemistry (IHC), and updated safety for all treated patients based on a March 27, 2018, data cutoff, which presents a longer follow-up time compared to the interim efficacy analysis and more comprehensive efficacy results.

Patients and Methods

Study Population

At study entry, eligible patients (aged 18 years or older) had stage IIIB or IV NSCLC harboring an *ALK* rearrangement. For patients previously treated with systemic anticancer therapy, *ALK*-positivity was determined locally using the US Food and Drug Administration–approved Vysis ALK Break Apart Fluorescence In Situ Hybridization (FISH) Probe Kit

(Abbott Molecular Inc., Des Plaines, Illinois) or centrally by Ventana IHC (Tucson, Arizona). All treatment-naive patients included in the efficacy analysis had *ALK*-positivity confirmed centrally by IHC. Eligible patients were either treatment-naive (except for neoadjuvant/adjuvant systemic therapy, excluding regimens containing an ALK inhibitor [if relapse had occurred more than 12 months from the end of therapy]) or were previously treated with at least one systemic anticancer therapy (including crizotinib); had a WHO performance score of 0 to 2; treatment-naive patients with *ALK*-positive by IHC must have at least one measurable lesion, as per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1; and could have asymptomatic or neurologically stable central nervous system metastases.

Study Design

The study methods for the randomized, multicenter, open-label, parallel design, phase I, ASCEND-8 study were published previously.[12] Patients were recruited from 87 centers across 24 countries. Eligible patients were randomly assigned in a 1:1:1 ratio to receive ceritinib 450 mg with food (450-mg fed arm), ceritinib 600 mg with food (600-mg fed arm), or ceritinib 750 mg in a fasted state (750-mg fasted arm). Ceritinib was administered immediately (within 30 minutes) following a low-fat meal (food) defined as approximately 100 to 500 calories and 1.5 to 15 g of fat was used in this study given the modest difference in pharmacokinetics between the light snack, low-fat meal, and high-fat meal after a single dose of ceritinib.[9] Randomization was stratified by two stratification factors: brain metastases at screening (present or absent) and prior treatment (not applicable for efficacy analysis; prior crizotinib use [ALK-positive by FISH], crizotinib-naive but could have previously been treated with other systemic anticancer therapy [ALK-positive by FISH], and treatment-naive patients [ALK-positive by IHC]). The enrollment to the 600-mg fed arm had been halted on July 14, 2017, based on the available results from primary pharmacokinetics which showed that the 600-mg fed arm presented a higher exposure and a less favorable safety profile when compared to the other two treatment arms.[12]

The primary objective, pharmacokinetics, was already addressed previously.[12] Key secondary endpoints were blinded independent review committee (BIRC)–assessed ORR (per RECIST 1.1) and duration of response (DOR). Other secondary efficacy endpoints were the following: investigator assessed (per RECIST1.1) ORR and DOR; time to response (TTR), disease control rate (DCR), PFS based on investigator and BIRC assessment; and overall survival. Other secondary endpoints included the assessment of safety. Exposure-response analysis corresponding to an exploratory objective based on data pooled from the three treatment arms was performed to explore the relationship between ceritinib evaluable average trough concentration (average C_{trough}) and best overall response. Average C_{trough} was defined as the geometric mean of all evaluable C_{trough} values for each patient, considering the distribution of plasma concentrations is generally log normal. Patients were grouped by quartiles of average C_{trough} and the proportion of patients with complete response (CR) or partial response (PR) was presented by quartile range.

Treatment with ceritinib was continued until unacceptable toxicity, disease progression, and withdrawal of consent or at the discretion of the investigator. Patients were allowed to receive treatment with ceritinib following disease progression, including cases of isolated brain progression if, in the opinion of the investigator, continued treatment provided clinical benefit.

Before study initiation, the study protocol was reviewed and approved by the independent ethics committee and/or institutional review board for each center according to local regulations. The study was conducted in accordance with the ethical principles laid down in the Declaration of Helsinki and the guidelines for Good Clinical Practice. All patients provided written informed consent before screening. The study protocol, including the statistical analysis plan, is available in the supplementary material.

Assessments

At baseline, computed tomography of chest, abdomen, and computed tomography or magnetic resonance imaging of brain was performed in all patients. Assessments of tumor response were performed starting at cycle 3 (1 cycle = 21 days) and then every 2 cycles thereafter (i.e., every 6 weeks) through cycle 9. Subsequently, the frequency of tumor assessments may be reduced as clinically indicated, at the discretion of the investigator, but no less than once every 4 cycles until end of treatment. Tumor assessments in patients who discontinued treatment for reasons other than death, loss to follow-up, pregnancy, or disease progression were performed at least every 12 weeks following the end of treatment, until RECIST 1.1–defined progressive disease (as confirmed by BIRC for treatment-naive patients with *ALK*-positive NSCLC by IHC; and as determined by investigator for other patients), withdrawal of consent for further tumor assessments, or death. AEs were coded using the Medical Dictionary for Regulatory Activities version 21.0 and graded according to the Common Terminology Criteria for Adverse Events version 4.03. Dose reductions (150 mg/d per dose reduction) were allowed in all the arms, maximum of two dose reductions in the 450-mg fed arm and

maximum of three dose reductions in the 600-mg fed and 750-mg fasted arms. In the event of dose reduction, the patient continued to receive ceritinib according to the originally assigned prandial condition (i.e., with food or in the fasted state). The patient was to be discontinued from treatment with ceritinib if further reduction was necessary. In case the dose of ceritinib was reduced due to toxicity, re-escalation was not allowed.

Statistical Analysis

In this primary efficacy analysis, the following three analysis sets were considered: full analysis set (all patients to whom study treatment has been assigned by randomization), safety set (all patients who received at least one dose of ceritinib), and pharmacokinetic analysis set (all patients who received at least one dose of ceritinib and have at least one evaluable pharmacokinetic sample). The key secondary endpoints and other secondary efficacy endpoints were analyzed based on the subset of patients in full analysis set who were treatment-naive with *ALK*-positive by IHC (hereafter, referred to as treatment-naive patients with *ALK*-positive by IHC). No formal statistical power calculations were performed to determine the sample size due to the primary objective of the study (pharmacokinetics). ORR and DCR were estimated and the associated exact binomial 95% confidence intervals (CIs) were reported. DOR, PFS, TTR, and overall survival were analyzed using the Kaplan–Meier method to estimate the median value with the corresponding 95% CI calculated using the Brookmeyer and Crowley method.[15] All statistical analyses were performed using SAS version 9.4.

Results

Patient Disposition

Between April 20, 2015, and November 21, 2017, 306 patients (full analysis set) were randomized to ceritinib 450-mg/d fed arm (n = 108) or 600-mg/d fed arm (n = 87) or 750-mg/d fasted arm (n = 111). The efficacy was assessed in 198 treatment-naive patients who were *ALK*-positive by IHC with 73, 51, and 74 patients in the 450-mg fed, 600-mg fed, and 750-mg fasted arms, respectively. The median duration of study follow-up was 19.6 months (range, 4.2 months to 35.5 months) in all randomized patients and 14.3 months (range, 4.2 months to 30.2 months) in treatment-naive patients who were *ALK*-positive by IHC.

At the time of data cutoff, among the treatment-naive patients who were *ALK*-positive by IHC, 31.5% in the 450-mg fed arm, 41.2% in the 600-mg fed arm, and 29.7% in the 750-mg fasted arm had discontinued the treatment (Supplementary Fig. 1). The primary reason for discontinuation was disease progression, occurring in 19.2%, 21.6%, and 18.9% of patients in the 450-mg fed, 600-mg fed, and 750-mg fasted arms, respectively.

Patient Demographics and Disease Characteristics

Among the treatment-naive patients who were *ALK*-positive by IHC, baseline patient characteristics were well balanced between the 450-mg fed arm and the 750-mg fasted arm (Table 1). The proportion of female patients was lower in the 600-mg fed arm. The majority of the patients (in all the arms) had adenocarcinoma histology, and all patients had at least one metastatic site at study entry (Table 1). Brain metastases at baseline were present in 32.9%, 29.4%, and 28.4% of patients in the 450-mg fed, 600-mg fed, and 750-mg fasted arms, respectively.

Efficacy

The ORR per BIRC was 78.1% (95% CI: 66.9–86.9) in the 450-mg fed arm, 72.5% (95% CI: 58.3–84.1) in the600-mg fed arm, and 75.7% (95% CI: 64.3–84.9) in the 750-mg fasted arm (Table 2). Among the responders with confirmed CR or PR, the median DOR by BIRC was not estimable (NE) (95% CI: 11.2–NE), 20.7 months (95% CI: 15.8–NE), and 15.4 months (95% CI: 8.3–NE) in the 450-mg fed, 600-mg fed, and 750-mg fasted arms, respectively (Table 2, Fig. 1*A*). The estimated event-free rate at 18 months was 52.9% (95% CI: 30.9–70.8) in the 450-mg fed arm, 61.1% (95% CI: 36.7–78.5) in the 600-mg fed arm, and 36.7% (95% CI: 14.5–59.4) in the 750-mg fasted arm. The ORR and DOR based on the investigator assessment were generally consistent with the results obtained based on BIRC assessment (Table 2). The exploratory analysis showed no significant exposure-response relationship with best overall response (Supplementary Table 1).

The median TTR by BIRC assessment was 6.3 weeks (95% CI: 6.1–6.9) for ceritinib in the 450-mg fed arm, 6.3 weeks (95% CI: 6.1–9.3) for ceritinib in the 600-mg fed arm, and 6.3 weeks (95% CI: 6.1–7.1) for the 750 mg fasted arm. The DCR by BIRC was 90.4% (95% CI: 81.2–96.1), 94.1% (95% CI: 83.8–98.8), and 90.5% (95% CI: 81.5–96.1) in the 450-mg fed, 600-mg fed, and 750-mg fasted arms, respectively. The results of DCR and median TTR by investigator were consistent with the results by BIRC (Table 2).

The median PFS was NE (95% CI: 11.8–NE), 17.0 months (95% CI: 10.1–NE), and 12.2 months (95% CI: 8.2–NE) in the 450-mg fed, 600-mg fed, and 750-mg fasted arms, respectively (Table 2, Fig. 1*B*). A high proportion of patients were censored in the PFS

Table 1. Baseline Patient and Disease Characteristics, and Prior Antineoplastic Therapy (Full Analysis Set – Treatment-Naive Patients Who Are *ALK*-positive by IHC, n = 198)

Characteristics	Ceritinib 450-mg Fed (n = 73)	Ceritinib 600-mg Fed (n = 51)	Ceritinib 750-mg Fasted (n = 74)
Median age (range), years	55.0 (26-87)	52.0 (21-81)	51.0 (22-87)
Sex			
Female	41 (56.2)	20 (39.2)	35 (47.3)
Male	32 (43.8)	31 (60.8)	39 (52.7)
Race			
Asian	29 (39.7)	19 (37.3)	26 (35.1)
Caucasian	36 (49.3)	28 (54.9)	40 (54.1)
Other[a]	8 (11.0)	4 (7.8)	8 (10.8)
WHO performance status			
0	25 (34.2)	14 (27.5)	23 (31.1)
1	42 (57.5)	34 (66.7)	45 (60.8)
2	6 (8.2)	3 (5.9)	6 (8.1)
Smoking history			
Current smoker	7 (9.6)	2 (3.9)	3 (4.1)
Ex-smoker	19 (26.0)	18 (35.3)	22 (29.7)
Never smoked	47 (64.4)	30 (58.8)	49 (66.2)
Missing	0	1 (2.0)	0
Histology/cytology			
Adenocarcinoma	72 (98.6)	48 (94.1)	69 (93.2)
Stage at time of study entry			
Locally advanced (stage IIIb)	3 (4.1)	5 (9.8)	5 (6.8)
Metastatic (stage IV)	70 (95.9)	46 (90.2)	69 (93.2)
Key metastatic site of cancer			
Bone	31 (42.5)	18 (35.3)	27 (36.5)
Brain	24 (32.9)	15 (29.4)	21 (28.4)
Liver	19 (26.0)	13 (25.5)	21 (28.4)
Prior chemotherapy			
Adjuvant[b]	1 (1.4)	3 (5.9)	3 (4.1)
Neoadjuvant[b]	1 (1.4)	1 (2.0)	1 (1.4)
Therapeutic[c]	1 (1.4)	2 (3.9)	1 (1.4)
Palliative[c]	0	0	1 (1.4)
Prior radiotherapy[b]	15 (20.5)	11 (21.6)	13 (17.6)
Surgery[b]	15 (20.5)	7 (13.7)	18 (24.3)

Values are n (%) unless otherwise stated.
[a]Other includes: Black, Native American, Pacific Islander, and unknown.
[b]Allowed as per protocol.
[c]Due to mis-stratification or protocol deviation.
ALK, ALK receptor tyrosine kinase; IHC, immunohistochemistry.

analysis by BIRC: 68.5% in the 450-mg fed arm, 56.9% in the 600-mg fed arm, and 59.5% in the 750 mg-fasted arm, respectively. The majority of the censored patients were ongoing without an event (progression or death) at the time of the data cutoff: 42 of 50 censored patients in the 450-mg fed arm, in 23 of 29 censored patients in the 600-mg fed arm, and 39 of 44 censored patients in the 750-mg fasted arm. The estimated 18-month event-free rate by BIRC assessment was 50.8% (95% CI: 33.7–65.7) for the 450-mg fed arm, 48.6% (95% CI: 30.7–64.3) for the 600-mg fed arm, and 40.9% (95% CI: 23.3–57.8) for the 750-mg fasted arm. The median PFS by investigator was NE (95% CI: 2.6–NE), 17.0 months (95% CI: 10.1–NE), and 16.6 months (95% CI: 11.2–NE) in the 450-mg fed, 600-mg fed, and 750-mg fasted arms, respectively (Table 2). The estimated 18-month event-free rate by investigator assessment was 55.3% (95% CI: 38.2–69.4) in the 450-mg fed arm, 47.8% (95% CI: 29.8–63.7) in the 600-mg fed arm, and 41.4% (95% CI: 23.4–58.6) in the 750-mg fasted arm.

Safety

During the on-treatment period (from day of first dose of study treatment to 30 days after the final dose), the 450-mg fed arm presented the highest median relative dose intensity (RDI) and the lowest proportion of patients with dose reductions among the three treatment arms. The median duration of treatment exposure was 42.9 weeks (range, 0.3 weeks to 131.0 weeks) for the 450-mg fed arm, 45.6 weeks (range, 0.4 weeks to 144.9 weeks) for the 600-mg fed arm, and 42.2 weeks (range, 0.3 weeks to 134.4 weeks) for the 750-mg fasted arm (Table 3). The median RDI was 100.0% (range, 35.3% to 100.0%), 78.5% (29.4 to 100.0), and 83.7% (range, 40.9% to 100.0%) for the 450-mg fed, 600-mg fed, and 750-mg fasted arms, respectively (Table 3). The proportion of patients with at least one dose reduction was lowest in the 450-mg fed arm (24.1%) compared to the 600-mg fed arm (65.1%) and 750-mg fasted arm (60.9%). More than one dose reduction was required in 4.6%, 31.4%, and 34.5% of patients in the 450-mg fed, 600-mg fed, and 750-mg fasted arms, respectively (Table 3). The proportion of patients with at least one dose interruption was lower in the 450-mg fed arm (50.9%), than in the 600-mg fed arm (74.4%) and 750-mg fasted arm (72.7%). More than one dose interruption was required in 19.4% of patients in the 450-mg fed arm, 45.3% of patients in the 600-mg fed arm, and 52.7% of patients in the 750-mg fasted arm (Table 3).

The proportion of patients who experienced at least one AE regardless of study drug relationship was similar across treatment arms with 99.1% in the 450-mg fed arm, 97.7% in the 600-mg fed arm, and 99.1% in the 750-mg fasted arm (Supplementary Table 2). The proportion of patients with serious AEs related to study drug was similar between the 450-mg fed arm (6.5%) and the 750-mg fasted arm (9.1%) (Supplementary Table 2). The proportion of patients with AEs leading to study drug discontinuation were similar across the treatment arms with 7.4% of patients in the 450-mg fed

Table 2. Efficacy by Masked Independent Review Committee and Investigator Assessment (Full Analysis Set — Treatment-Naive Patients Who Are *ALK*-Positive by IHC, n = 198)

	Masked IRC Assessment			Investigator Assessment		
	Ceritinib 450-mg Fed (n = 73)	Ceritinib 600-mg Fed (n = 51)	Ceritinib 750-mg Fasted (n = 74)	Ceritinib 450-mg Fed (n = 73)	Ceritinib 600-mg Fed (n = 51)	Ceritinib 750-mg Fasted (n = 74)
Overall response (CR + PR), n (%) (95% CI)	57 (78.1) (66·9-86.9)	37 (72.5) (58.3-84.1)	56 (75.7) (64.3-84.9)	55 (75.3) (63.9-84.7)	38 (74.5) (60.4-85.7)	58 (78.4) (67.3-87.1)
CR	0	0	1 (1.4)	0	0	2 (2.7)
PR	57 (78.1)	37 (72.5)	55 (74.3)	55 (75.3)	38 (74.5)	56 (75.7)
SD	9 (12.3)	11 (21.6)	11 (14.9)	14 (19.2)	9 (17.6)	11 (14.9)
PD	3 (4.1)	2 (3.9)	3 (4.1)	1 (1.4)	2 (3.9)	1 (1.4)
Non-CR/Non-PD	0	0	0	0	1 (2.0)	0
Unknown[a]	4 (5.5)	1 (2.0)	4 (5.4)	3 (4.1)	1 (2.0)	4 (5.4)
Disease control (CR + PR + SD + non-CR/non-PD), n (%) (95% CI)	66 (90.4) (81·2-96.1)	48 (94.1) (83.8-98.8)	67 (90.5) (81.5-96.1)	69 (94.5) (86.6-98.5)	48 (94.1) (83.8-98.8)	69 (93.2) (84.9-97.8)
Median duration of response (in responders), months (95% CI)	M = 57 NE (11.2-NE)	M = 37 20.7 (15.8-NE)	M = 56 15.4 (8.3-NE)	M = 55 NE (14.5-NE)	M = 38 NE (12.7-NE)	M = 58 15.2 (10.3-NE)
Estimated 18-month event-free probability, % (95% CI)	52·9 (30.9-70.8)	61.1 (36.7-78.5)	36.7 (14.5-59.4)	67.8 (47.8-81.6)	53.2 (30.4-71.6)	41.9 (21.0-61.7)
Median time to response, weeks (95% CI)	6.3 (6.1-6.9)	6.3 (6.1-9.3)	6.3 (6.1-7.1)	6.3 (6.1-6.9)	6.3 (6.1-11.9)	6.1 (6.1-6.3)
Median progression-free survival, months (95% CI)	NE (11.8-NE)	17.0 (10.1-NE)	12.2 (8.2-NE)	NE (12.6-NE)	17.0 (10.1-NE)	16.6 (11.2-NE)
Estimated 18-month event-free probability, % (95% CI)	50.8 (33.7-65.7)	48.6 (30.7-64.3)	40.9 (23.3-57.8)	55.3 (38.2-69.4)	47.8 (29.8-63.7)	41.4 (23.4-58.6)

[a]One patient in 450-mg fed arm (by masked independent review committee assessment) due to progressive disease too late (> 13 weeks after randomization and not qualifying for CR, PR, SD, and non-CR/non-PD), the others due to no valid post-baseline assessment.
ALK, ALK receptor tyrosine kinase; CI, confidence interval; IHC, immunohistochemistry; NE, not estimable; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; M, number of patients included in the duration of response analysis.

arm, 5.8% of patients in the 600-mg fed arm, and 7.3% of patients in the 750-mg fasted arm (Supplementary Table 2).

The most frequently reported AEs regardless of study drug relationship were gastrointestinal related (diarrhea, vomiting, and nausea) (Table 4). There was a lower proportion of patients with AEs of all grades of diarrhea, vomiting, and nausea in the 450-mg fed arm (57.4%, 38.9%, and 41.7%, respectively) when compared to the 600-mg fed arm (65.1%, 55.8%, and 55.8%, respectively) and the 750-mg fasted arm (79.1%, 63.6%, and 57.3% respectively). The majority of the patients with gastrointestinal toxicities in the 450-mg fed arm had events of maximum grade 1, only 2.8% of patients experienced grade 3 AEs (grade 3 diarrhea in one patient and grade 3 vomiting in two patients), and no patients were reported with grade 4 gastrointestinal AEs. An overview of gastrointestinal toxicities (diarrhea, nausea, and vomiting) is shown in Table 5.

Other common AEs (≥25% of the patients in at least one of the three treatment arms, all grades) reported were increased alanine aminotransferase, increased aspartate aminotransferase, increased gamma-glutamyltransferase, fatigue, abdominal pain, and decreased appetite. The proportion of patients experiencing alanine aminotransferase increase and aspartate aminotransferase increase was similar between 450-mg fed arm (40.7% and 35.2%, respectively) and the 750-mg fasted arm (40.9% and 37.3%, respectively). The laboratory abnormalities meeting Hy's law criteria were not observed in any patients among the three treatment arms. There were also no cases of Torsades de Pointe. Only one patient (450 mg fed arm) was reported with grade 1 interstitial lung disease, which was unrelated to study drug.

In total, 11 of 108 patients in the 450-mg fed arm, 12 of 86 patients in the 600-mg fed arm, and 8 of 110 patients in the 750-mg fasted arm died during the on-treatment period. Of these, a total of 22 patients died due to study indication, and 9 patients died due to other causes.

Discussion

Ceritinib was initially approved at the recommended dose of 750 mg/d fasted for the treatment of patients

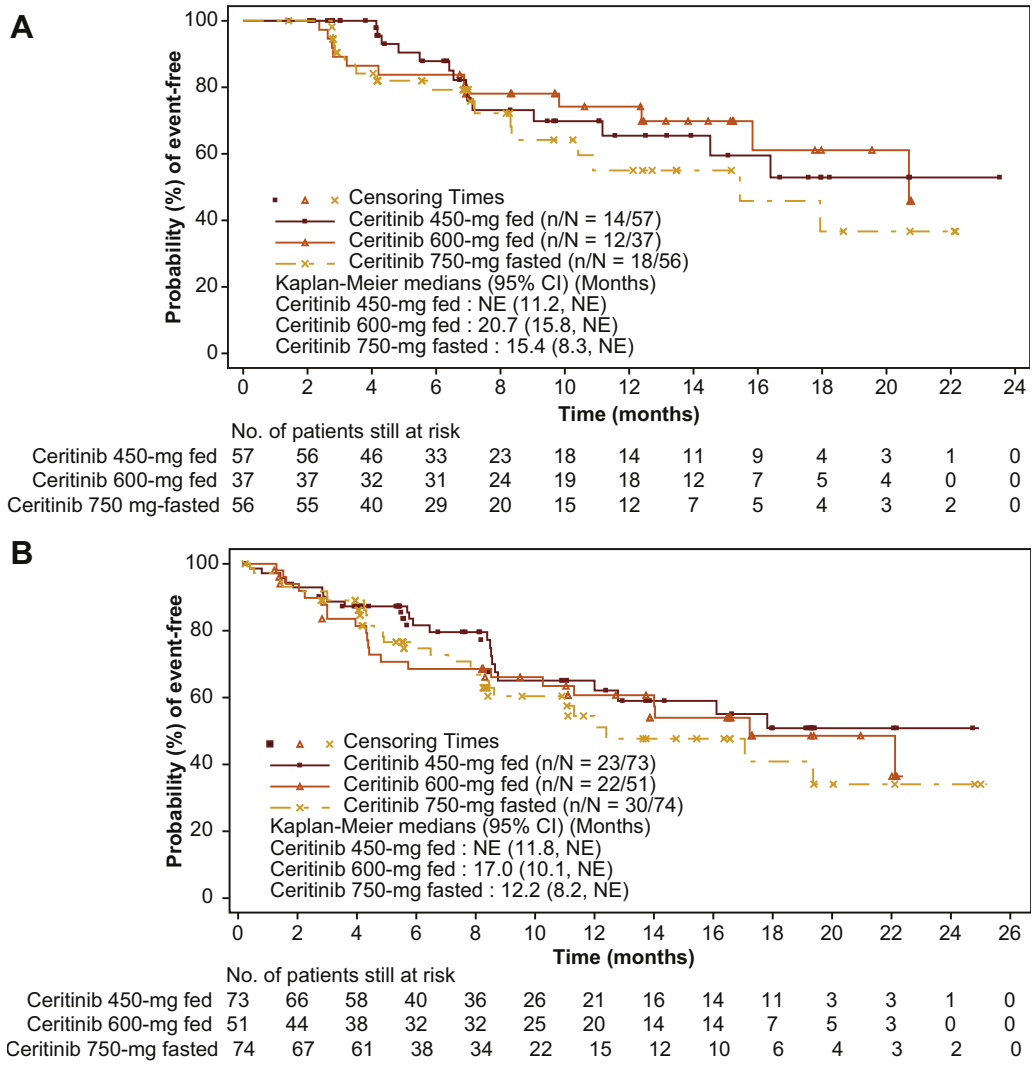

Figure 1. Duration of response per blinded independent review committee assessment by treatment arm (full analysis set — treatment-naive patients who are ALK receptor tyrosine kinase (*ALK*)-positive by immunohistochemistry (IHC) and confirmed CR or PR) and progression-free survival per blinded independent review committee assessment by treatment arm (full analysis set — treatment-naive patients who are *ALK*-positive by IHC). (*A*) Kaplan-Meier plot of duration of response per blinded independent review committee assessment by treatment arm (full analysis set — treatment-naive patients who are *ALK*-positive by IHC and confirmed CR or PR). (*B*) Kaplan-Meier plot of progression-free survival per blinded independent review committee assessment by treatment arm (full analysis set — treatment-naive patients who are *ALK*-positive by IHC). n, the total number of events included in the analysis; N, the total number of patients included in the analysis; NE, not estimable.

with *ALK*-positive NSCLC.[5-7] The available data from previous studies have shown that gastrointestinal AEs (diarrhea, nausea, and vomiting) are the most frequent AEs with ceritinib treatment.[3,8] The administration of TKIs with food has been shown to improve the gastrointestinal tolerability and increase exposure.[10,11] Similarly, two studies of ceritinib in healthy subjects have shown that dosing with food increased the systemic exposure and improved gastrointestinal tolerability.[9] Based on these observations, ASCEND-8 was designed to evaluate pharmacokinetics, efficacy, and safety of ceritinib administered at 450 mg or 600 mg with food versus 750 mg in a fasted state, in patients with *ALK*-positive NSCLC.

In addition to the comparable steady-state exposure in both the 450-mg fed arm and the 750-mg fasted arm, as observed in the pharmacokinetic analysis, ceritinib 450 mg/d with food provided at least consistent efficacy in terms of overall response, disease control, and TTR, along with clinically relevant duration of response and PFS compared to the approved dose of 750 mg in a fasted state.[12] Furthermore, safety results confirmed that ceritinib (450 mg) taken with food had the lowest frequency of dose reductions/interruptions among the

Table 3. Study Drug Exposure (Safety Set)

	Ceritinib 450-mg Fed (n = 108)	Ceritinib 600-mg Fed (n = 86)	Ceritinib 750-mg Fasted (n = 110)
Median treatment exposure, weeks (range)	42.9 (0.3-131.0)	45.6 (0.4-144.9)	42.2 (0.3-134.3)
Median relative dose intensity, % (range)	100.0 (35.3-100)	78.5 (29.4-100)	83.7 (40.9-100)
Patients with 1 dose reduction, n (%)	21 (19.4)	29 (33.7)	29 (26.4)
Patients with > 1 dose reduction, n (%)	5 (4.6)	27 (31.4)	38 (34.5)
Patients with 1 dose interruption, n (%)	34 (31.5)	25 (29.1)	22 (20.0)
Patients with > 1 dose interruption, n (%)	21 (19.4)	39 (45.3)	58 (52.7)

three treatment arms and the highest median RDI of 100%. In addition, compared to the patients in the 750-mg fasted arm, the frequency of the patients with, and the severity of gastrointestinal toxicities (diarrhea, nausea, or vomiting) were the lowest in the 450-mg fed arm. The ASCEND-8 study included both pretreated and treatment-naive patients (*ALK*-positive defined by IHC). In the pharmacokinetics analysis, for the primary objective of the study, both patients who were treatment-naive or patients who had received several prior lines of therapy were included because no exposure difference was expected based on prior treatment.[16] Because the key secondary objectives were efficacy related (ORR and DOR by BIRC), they were evaluated based on a homogeneous patient population of treatment-naïve patients. In this primary efficacy analysis, the safety analysis was based on all treated patients (both pre-treated and treatment-naïve). The study was not powered to do any statistical comparison between the treatment arms based on ORR or other efficacy endpoints. However, the sample size was calculated based on the expected ORR and ensuring a clinically relevant lower limit of the associated 95% CI (with a sample size of 70, the exact binomial 95% CI will be 53.4%, 76.7% for an observed ORR of 66%).

The results of the ORR and DCR by BIRC assessment were consistent between the 450-mg fed arm and the 750-mg fasted arm. The investigator-assessed ORR and

Table 4. All-Causality Adverse Events Occurring in Greater Than 15% (Any Treatment Arm) in Patients With *ALK*-Positive NSCLC (Safety Set, n = 304)

	Ceritinib 450-mg Fed n = 108		Ceritinib 600-mg Fed n = 86		Ceritinib 750-mg Fasted n = 110	
Preferred Term	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Diarrhea	62 (57.4)	1 (0.9)	56 (65.1)	2 (2.3)	87 (79.1)	10 (9.1)
Vomiting	42 (38.9)	2 (1.9)	48 (55.8)	1 (1.2)	70 (63.6)	4 (3.6)
Nausea	45 (41.7)	0	48 (55.8)	5 (5.8)	63 (57.3)	6 (5.5)
Alanine aminotransferase increased	44 (40.7)	19 (17.6)	41 (47.7)	25 (29.1)	45 (40.9)	25 (22.7)
Aspartate aminotransferase increased	38 (35.2)	8 (7.4)	33 (38.4)	14 (16.3)	41 (37.3)	11 (10.0)
Gamma-glutamyltransferase increased	36 (33.3)	24 (22.2)	23 (26.7)	17 (19.8)	26 (23.6)	15 (13.6)
Fatigue	24 (22.2)	1 (0.9)	27 (31.4)	2 (2.3)	30 (27.3)	5 (4.5)
Abdominal pain	22 (20.4)	0	24 (27.9)	1 (1.2)	32 (29.1)	2 (1.8)
Decreased appetite	20 (18.5)	0	23 (26.7)	1 (1.2)	27 (24.5)	3 (2.7)
Cough	25 (23.1)	0	15 (17.4)	0	24 (21.8)	1 (0.9)
Abdominal pain upper	20 (18.5)	0	11 (12.8)	1 (1.2)	27 (24.5)	0
Blood creatinine increased	23 (21.3)	0	15 (17.4)	0	17 (15.5)	0
Headache	17 (15.7)	2 (1.9)	13 (15.1)	2 (2.3)	25 (22.7)	2 (1.8)
Pyrexia	11 (10.2)	1 (0.9)	18 (20.9)	1 (1.2)	23 (20.9)	1 (0.9)
Weight decreased	14 (13.0)	0	16 (18.6)	1 (1.2)	17 (15.5)	1 (0.9)
Blood alkaline phosphatase increased	20 (18.5)	5 (4.6)	10 (11.6)	3 (3.5)	16 (14.5)	5 (4.5)
Constipation	11 (10.2)	0	15 (17.4)	0	16 (14.5)	0
Dyspnea	14 (13.0)	1 (0.9)	15 (17.4)	2 (2.3)	12 (10.9)	4 (3.6)
Back pain	14 (13.0)	1 (0.9)	9 (10.5)	0	17 (15.5)	2 (1.8)
Hyperglycaemia	13 (12.0)	8 (7.4)	9 (10.5)	5 (5.8)	17 (15.5)	10 (9.1)
Noncardiac chest pain	11 (10.2)	0	9 (10.5)	0	17 (15.5)	0
Asthenia	10 (9.3)	1 (0.9)	19 (22.1)	3 (3.5)	7 (6.4)	2 (1.8)

ALK, ALK receptor tyrosine kinase.

Table 5. Overview of Gastrointestinal Toxicities (Safety Set, n = 304)

	Ceritinib 450-mg Fed n = 108				Ceritinib 600-mg Fed n = 86				Ceritinib 750-mg Fasted n = 110			
	All Grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 or 4 n (%)
Any gastrointestinal toxicities	82 (75.9)	55 (50.9)	24 (22.2)	3 (2.8)	71 (82.6)	42 (48.8)	22 (25.6)	7 (8.1)	101 (91.8)	47 (42.7)	39 (35.5)	15 (13.6)
Diarrhea	62 (57.4)	53 (49.1)	8 (7.4)	1 (0.9)	56 (65.1)	41 (47.7)	13 (15.1)	2 (2.3)	87 (79.1)	47 (42.7)	30 (27.3)	10 (9.1)
Nausea	45 (41.7)	32 (29.6)	13 (12.0)	0	48 (55.8)	30 (34.9)	13 (15.1)	5 (5.8)	63 (57.3)	39 (35.5)	18 (16.4)	6 (5.5)
Vomiting	42 (38.9)	35 (32.4)	5 (4.6)	2 (1.9)	48 (55.8)	36 (41.9)	11 (12.8)	1 (1.2)	70 (63.6)	52 (47.3)	14 (12.7)	4 (3.6)
Gastrointestinal toxicities requiring study drug discontinuation	0	0	0	0	1 (1.2)	0	1 (1.2)	0	0	0	0	0
Gastrointestinal toxicities requiring dose adjustments/ study drug interruption												
Diarrhea	7 (6.5)	1 (0.9)	6 (5.6)	0	9 (10.5)	3 (3.5)	4 (4.7)	2 (2.3)	24 (21.8)	1 (0.9)	16 (14.5)	7 (6.4)
Nausea	1 (0.9)	1 (0.9)	0	0	13 (15.1)	4 (4.7)	4 (4.7)	5 (5.8)	14 (12.7)	1 (0.9)	7 (6.4)	6 (5.5)
Vomiting	2 (1.9)	1 (0.9)	0	1 (0.9)	12 (14.0)	5 (5.8)	6 (7.0)	1 (1.2)	14 (12.7)	4 (3.6)	6 (5.5)	4 (3.6)

DCR results were consistent with the results obtained based on BIRC assessment. These efficacy results were also similar to those reported in ceritinib treatment arm of the ASCEND-4 study.[3] In the ASCEND-4 study, ORR by BIRC assessment was 72.5% for patient treated with ceritinib 750-mg/d fasted.[3] The responses-based BIRC assessments were rapid in the trial reported here (median TTR was 6.3 weeks across all the treatment arms), which were also consistent with those reported in the ASCEND-4 study (median TTR was 6.1 weeks for patients with a confirmed response of CR or PR in the ceritinib treatment arm).[3] The DOR by BIRC results were immature because the median was not estimable in the 450-mg fed arm or unstable in the 750-mg fasted arm and few patients were left at risk at 18 months and beyond. Nevertheless, the event-free rates at 15 months or earlier between the two arms were comparable with the overlapped associated 95% CI. The event-free rates at 15 months were 59.5% (95% CI: 38.7–75.3) in the 450-mg fed arm versus 55% (95% CI: 35.3–71) in the 750-mg fasted arm. Similarly, the median PFS as assessed by BIRC was not estimable in the 450-mg fed arm or unstable in the 750-mg fasted arm and few patients were left at risk beyond 12 months. However, the event-free rates between the two arms were comparable with the overlapped associated 95% CI at 12 months (62.1% (95% CI: 46.6–74.3) in the 450-mg fed arm and 51.1% (95% CI: 35.8–64.5) in the 750-mg fasted arm) or earlier. Moreover, the median duration of follow-up (from patient randomization to data cutoff date) was only 14.3 months in treatment-naive patients who were *ALK*-positive by IHC assessed for efficacy.

In patients with brain metastases, the protocol was not designed to collect data on whether the prior treatment was received for treating brain metastases. Additionally, from pharmacokinetic perspective, the two doses (450 mg with food and 750 mg fasted) give nearly the same systemic exposure (area under the curve [0 to 24 hours], geometric mean ratio = 1.04; maximum serum concentration, geometric mean ratio = 1.03); therefore, the penetration into the brain and intracranial antitumor activity are expected to be equivalent. The reason for similar systemic exposure with the lower dose is the higher absorption of ceritinib when administered with food. The distribution pattern of the drug remains unchanged after absorption.

Consistent with the results of pharmacokinetics versus efficacy analysis reported from ASCEND-1, no apparent association between systemic exposure and best overall response could be detected in this study, indicating that the exposure ranges across the three arms were not markedly different (i.e., steady-state pharmacokinetics difference <30%) and that the fed arms led to similar efficacy as the 750-mg fasted arm.[12,17]

The 450-mg fed arm presented the lowest proportion of patients with gastrointestinal toxicities and the lowest proportion of patients reported with grades 3 or 4 gastrointestinal toxicities (diarrhea, nausea, and vomiting). In addition, only one patient in the 450-mg fed arm was reported with gastrointestinal toxicity (vomiting) leading to dose adjustment, and no patients experienced gastrointestinal toxicity leading to study drug discontinuation. All grades of AEs, serious AEs, and AEs leading to study drug discontinuation were similar between the 450-mg fed arm and the 750-mg fasted arm. Overall, the current observed safety profile of ceritinib 450 mg taken with food is consistent with those reported previously, and further, confirms the finding of improved gastrointestinal tolerability due to enhanced absorption in the gut in the fed state, which leads to less local irritation.[9,12]

In conclusion, the primary efficacy analysis results of the ASCEND-8 study show that ceritinib administered at 450 mg with food, compared to 750 mg in a fasted state, demonstrated less frequent dose reductions/interruptions, higher median RDI, and less frequent and less severe gastrointestinal AEs. The ceritinib 450-mg fed arm and the 750-mg fasted arm showed a similar robust efficacy in terms of ORR, DCR, and TTR, consistent with the results from the ASCEND-4 study, in addition to clinically relevant DOR and PFS results. Taken together, these data and the pharmacokinetic results previously reported confirm that ceritinib at a dose of 450 mg presents the most favorable gastrointestinal safety profile with similar efficacy, and thus is the preferred dosing regimen of ceritinib in patients who have *ALK*-positive NSCLC.[3,12]

Acknowledgments

This study was funded by Novartis Pharmaceuticals Corporation. The authors thank the participating patients, their families, all of the study co-investigators, and research contributors. Medical writing support was provided by Shiva Krishna Rachamadugu, 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.2019.03.002.

Data Availability Statement

Novartis will not provide access to patient-level data if there is a reasonable likelihood that individual patients could be re-identified. Phase I studies, by their nature, present a high risk of patient re-identification; therefore, patient individual results for phase I studies cannot be shared. In addition, clinical data, in some cases, have been collected subject to contractual or consent provisions that prohibit transfer to third parties. Such restrictions may preclude granting access under these provisions. Where co-development agreements or other legal restrictions prevent companies from sharing particular data, companies will work with qualified requestors to provide summary information where possible.

References

1. 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.
2. 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.
3. 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.
4. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2017;377:829–838.
5. US Food and Drug Administration. Ceritinib highlights of prescribing information. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm560873.htm. Accessed May 31, 2018.
6. US Food and Drug Administration. Ceritinib prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205755s009lbl.pdf. Accessed May 31, 2018.
7. European Medical Agency. Zykadia European public assessment report. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003819/WC500187506.pdf. Accessed May 31, 2018.
8. Shaw AT, Kim TM, Crino L, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2017;18:874–886.
9. Lau YY, Gu W, Lin T, et al. Effects of meal type on the oral bioavailability of the ALK inhibitor ceritinib in healthy adult subjects. *J Clin Pharmacol*. 2016;56:559–566.
10. Novartis Pharmaceuticals Corporation. Gleevec prescribing information. https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/gleevec_tabs.pdf. Accessed May , 2018.
11. Abbas R, Hug BA, Leister C, et al. A phase I ascending single-dose study of the safety, tolerability, and pharmacokinetics of bosutinib (SKI-606) in healthy adult subjects. *Cancer Chemother Pharmacol*. 2012;69:221–227.

12. 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.
13. Novartis Pharmaceuticals Corporation. Zykadia dosing and administration. https://www.hcp.novartis.com/products/zykadia/alk-nsclc/dosing-administration/. Accessed May 31, 2018.
14. European Medical Agency. Zykadia European public assessment report. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003819/WC500187504.pdf. Accessed August 20, 2018.
15. Brookmeyer R, Crowley J. A confidence interval for the median survival time. *Biometrics*. 1982;38:29–41.
16. Hong Y, Passos VQ, Huang PH, et al. Population pharmacokinetics of ceritinib in adult patients with tumors characterized by genetic abnormalities in anaplastic lymphoma kinase. *J Clin Pharmacol*. 2017;57:652–662.
17. Khozin S, Blumenthal GM, Zhang L, et al. FDA approval: ceritinib for the treatment of metastatic anaplastic lymphoma kinase-positive non-small cell lung cancer. *Clin Cancer Res*. 2015;21:2436–2439.