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Sai-Hong Ignatius Ou, Jin Seok Ahn, Luigi De Petris, Ramaswamy Govindan ...+14 more authors

Institutions: University of California, Irvine, Sungkyunkwan University, Karolinska Institutet, Washington University in St. Louis ...+6 more institutions

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ORIGINAL REPORT

Alectinib in Crizotinib-Refractory *ALK*-Rearranged Non–Small-Cell Lung Cancer: A Phase II Global Study

Sai-Hong Ignatius Ou, Jin Seok Ahn, Luigi De Petris, Ramaswamy Govindan, James Chih-Hsin Yang, Brett Hughes, Hervé Lena, Denis Moro-Sibilot, Alessandra Bearz, Santiago Viteri Ramirez, Tarek Mekhail, Alexander Spira, Walter Bordogna, Bogdana Balas, Peter N. Morcos, Annabelle Monnet, Ali Zeaiter, and Dong-Wan Kim

See accompanying editorial on page 643

A B S T R A C T

Purpose

Crizotinib confers improved progression-free survival compared with chemotherapy in anaplastic lymphoma kinase *(ALK)*-rearranged non–small-cell lung cancer (NSCLC), but progression invariably occurs. We investigated the efficacy and safety of alectinib, a potent and selective ALK inhibitor with excellent CNS penetration, in patients with crizotinib-refractory *ALK*-positive NSCLC.

Patients and Methods

Alectinib 600 mg was administered orally twice daily. The primary end point was objective response rate (ORR) by central independent review committee (IRC).

Results

Of the 138 patients treated, 84 patients (61%) had CNS metastases at baseline, and 122 were response evaluable (RE) by IRC. ORR by IRC was 50% (95% CI, 41% to 59%), and the median duration of response (DOR) was 11.2 months (95% CI, 9.6 months to not reached). In 96 patients (79%) previously treated with chemotherapy, the ORR was 45% (95% CI, 35% to 55%). Median IRC-assessed progression-free survival for all 138 patients was 8.9 months (95% CI, 5.6 to 11.3 months). CNS disease control rate was 83% (95% CI, 74% to 91%), and the median CNS DOR was 10.3 months (95% CI, 7.6 to 11.2 months). CNS ORR in 35 patients with baseline measurable CNS lesions was 57% (95% CI, 39% to 74%). Of the 23 patients with baseline CNS metastases (measurable or nonmeasurable) and no prior radiation, 10 (43%) had a complete CNS response. At 12 months, the cumulative CNS progression rate (24.8%) was lower than the cumulative non-CNS progression rate (33.2%) for all patients. Common adverse events were constipation (33%), fatigue (26%), and peripheral edema (25%); most were grade 1 to 2.

Conclusion

Alectinib is highly active and well tolerated in patients with advanced, crizotinib-refractory *ALK*-positive NSCLC, including those with CNS metastases.

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Sai-Hong Ignatius Ou, University of California Irvine School of Medicine, Orange, CA; Jin Seok Ahn, Sungkyunkwan University School of Medicine; Luigi De Petris, Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden; Ramaswamy Govindan, Washington University School of Medicine, St Louis, MO; James Chih-Hsin Yang, National Taiwan University, Taipei, Taiwan; Brett Hughes, The Prince Charles Hospital, Chermside, and University of Queensland, Queensland, Australia; Hervé Lena, Centre Hospitalier Universitaire de Rennes, Rennes; Denis Moro-Sibilot, Centre Hospitalier Universitaire de Grenoble, Institut National de la Santé et de la Recherche Médicale U823, Grenoble, France; Alessandra Bearz, National Cancer Institute, Aviano, Italy; Santiago Viteri Ramirez, Quiron-Dexeus University Hospital, Barcelona, Spain; Tarek Mekhail, Florida Hospital Cancer Institute, Orlando, FL; Alexander Spira, Virginia Cancer Specialists, Fairfax, VA; and Walter Bordogna, Bogdana Balas, Peter N. Morcos, Annabelle Monnet, and Ali Zeaiter, F. Hoffmann-La Roche, Basel, Switzerland; Dong-Wan Kim, Seoul National University Hospital, Seoul, South Korea.

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Corresponding author: Sai-Hong Ignatius Ou, MD, PhD, Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, Orange, CA 92868; e-mail: ignatius.ou@uci.edu.

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INTRODUCTION

The clinical development of the anaplastic lymphoma kinase (ALK) inhibitor crizotinib has firmly established non–small-cell lung cancer (NSCLC) harboring *ALK* gene rearrangements as a distinct molecular subset of lung cancer.[1-5] Crizotinib has demonstrated superior progression-free survival benefit compared with chemotherapy in the first- or second-line setting for *ALK*-rearranged NSCLC, with a median progression-free survival (PFS) of 10.9 months and 7.7 months, respectively.[4,5] However, almost all patients invariably experience progression on crizotinib, and approximately 40% of the patients with *ALK*-rearranged NSCLC develop CNS metastases as an initial site of progression.[6] In addition, approximately 60% of patients with *ALK*-rearranged NSCLC who enrolled onto a subsequent ALK inhibitor study after experiencing progression while receiving crizotinib had baseline CNS metastases, compared with only 26% of the treatment-naïve patients with advanced *ALK*-rearranged NSCLC who enrolled onto the front-line PROFILE 1014 trial.[5,7]

Alectinib (CH5424602; Chugai/F. Hoffmann-La Roche, Basel, Switzerland) is an oral, small-molecule, ATP-competitive, tyrosine kinase inhibitor of ALK.[8] In enzymatic assays, alectinib is approximately five times more potent than crizotinib against ALK and

can inhibit most of the clinically observed acquired *ALK* resistance mutations to crizotinib.[9,10] In contrast to crizotinib, alectinib does not inhibit the kinase activity of MET or ROS1; however, it does inhibit RET with similar potency to ALK (50% inhibitory concentration [IC_{50}], 4.8 nmol/L and 1.9 nmol/L, respectively).[11] In xenograft models of *ALK*-rearranged NSCLC, alectinib showed marked antitumor activity against both crizotinib-sensitive and crizotinib-resistant tumors.[9,10] In addition, alectinib demonstrated excellent CNS tissue penetration and tumor shrinkage in a murine brain metastasis xenograft model, and it demonstrated comparable free alectinib concentrations in plasma and cerebral spinal fluid (CSF), which supports the ability of alectinib to penetrate into the CNS.[12] An ongoing North American study of alectinib in patients with *ALK*-rearranged NSCLC who had experienced progression while receiving crizotinib established the recommended phase II dose (RP2D) of alectinib as 600 mg twice daily.[13]

We conducted this global, single-arm, phase II study to determine the safety, efficacy, and pharmacokinetics (PK) of alectinib in patients with advanced *ALK*-rearranged NSCLC who had experienced progression while receiving crizotinib.

PATIENTS AND METHODS

Patients were eligible for inclusion if they had locally advanced or metastatic NSCLC harboring an *ALK* rearrangement and had experienced progression while receiving crizotinib, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients could be chemotherapy naïve or could have received prior platinum-based chemotherapy.

Study Oversight

This study was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization. The protocol was approved by the local institutional review boards/ethics committees at each participating site. Written informed consent was obtained from all patients before screening.

Study Design

The primary objectives were to determine the objective response rate (ORR) by independent review committee (IRC) in all evaluable patients and in patients previously treated with chemotherapy. Key secondary objectives were to characterize the PK profile, the safety and tolerability profile, PFS, and overall survival and to evaluate the efficacy of alectinib in the CNS.

Key eligibility criteria included histologically confirmed, advanced NSCLC with an *ALK* rearrangement previously assessed by a US Food and Drug Administration–approved test (Abbott Vysis LSI breakapart fluorescence in situ hybridization [FISH]; retesting not required), disease progression while receiving crizotinib as per RECIST 1.1, age 18 or older, Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, adequate organ function, and measurable disease according to RECIST 1.1. Patients with stable (≥ 2 weeks) treated brain and/or leptomeningeal metastases or asymptomatic (≥ 2 weeks) untreated brain and/or leptomeningeal metastases were allowed to enroll. A minimum wash-out period of 7 days was required between the last dose of crizotinib and the first dose of alectinib. Full inclusion and exclusion criteria are provided in the Data Supplement.

Study treatment was alectinib 600 mg twice daily within 30 minutes after eating. Patients continued treatment with alectinib until disease progression, unacceptable toxicity, or withdrawal of consent occurred. Treatment beyond disease progression was permitted if the treating physician considered it beneficial in consultation with the sponsor.

The first patient was enrolled on June 20, 2013, and the last patient was enrolled on April 23, 2014. The primary data cutoff was performed on August 18, 2014. An updated efficacy analysis was performed with a data cutoff of January 8, 2015.

Study Assessments

Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for AEs, version 4.0. Intensive and sparse blood samples for PK assessments were obtained.

All patients underwent tumor imaging at baseline, including computed tomography of the chest and abdomen as well as brain imaging (computed tomography or magnetic resonance imaging). Restaging scans were obtained at 8-week intervals during treatment. Brain imaging was also performed at 8-week intervals for patients with baseline brain metastases. In addition to a review of radiographs by the local investigator, a central IRC was established to perform independent radiologic review of all scans according to RECIST 1.1.[14] A central IRC was also used to assess all CNS end points.

Statistical Analysis

This was a single-arm, global, phase II study. To ensure sufficient power in the subgroup of patients who had been treated with prior chemotherapy, a sample size of 85 was chosen, such that the lower limit of the two-sided 95% CI (using an exact Clopper-Pearson CI) around the point estimate of the ORR allowed for identification of a clinically relevant response, to reject the null hypothesis that ORR equals 35%. Therefore, a total enrollment of 130 patients was planned, with a maximum of 45 chemotherapy-naïve patients, to achieve 93% power on the basis of an exact test for a single proportion, to detect a 15% increase in ORR from 35% to 50% at the 5% two-sided significance level. Hierarchical testing was used, and the primary analysis was tested in the all-patients group; if significant, a subsequent test was carried out in the subgroup of patients who had prior exposure to cytotoxic chemotherapy.

The response evaluable (RE) population comprised patients with measurable disease at baseline who had a baseline tumor assessment and who had received at least one dose of alectinib at the RP2D of 600 mg twice daily. Safety data are summarized for all patients who received at least one dose of alectinib. ORR was defined as the proportion of patients achieving a best response of complete response (CR) or partial response (PR) in the RE population. PFS was calculated from the date of first administration of alectinib until disease progression or death as a result of any cause occurred. Kaplan-Meier analyses of time-to-event data were used to estimate median event times, and the Brookmeyer-Crowley method was used to calculate two-sided 95% CIs. A competing risks model, which had a hazard-based approach that included successive nested competing-risks experiments, was used to account for the competing risks inherent in time to progression in the CNS. The probability of the first event being a CNS progression, non-CNS progression, or death was estimated by using cumulative incidence functions. All analyses were performed with the use of SAS statistical software, version 9.2 (SAS Institute, Cary, NC).

RESULTS

Patients

From June 2013 to April 2014, 138 patients were treated at 56 centers in 16 countries and were evaluable for safety, PFS, and overall survival. Sixteen patients did not have RECIST-measurable target lesions when assessed by the IRC; therefore, 122 patients were considered RE by IRC (Data Supplement). The majority of patients (61%) had CNS metastasis at study entry, of whom 42%

Table 1. Characteristics of the Evaluable Patients at Baseline

Characteristic	No. (%) of Patients: All Patients (N = 138)	No. (%) of Patients: Response Evaluable Population (n = 122)
Age, years		
Mean (standard deviation)	51.5 (11.1)	51.6 (11.1)
Median	52.0	52.2
Range	22-79	22-79
Sex		
Male	61 (44)	54 (44)
Female	77 (56)	68 (56)
Ethnicity		
White	93 (67)	80 (66)
Asian	36 (26)	33 (27)
Other	9 (7)	9 (7)
Smoking status		
Never smoker	96 (70)	87 (71)
Former smoker	39 (28)	32 (26)
Current smoker	3 (2)	3 (3)
ECOG performance status		
0	44 (32)	37 (30)
1	81 (59)	74 (61)
2	13 (9)	11 (9)
Histology		
Adenocarcinoma	133 (96)	118 (97)
Adenosquamous	2 (1)	2 (2)
Large-cell carcinoma	3 (2)	2 (2)
Baseline CNS metastasis		
Yes	84 (61)	73 (60)
Measurable	35 (25)	32 (26)
Nonmeasurable	49 (36)	41 (34)
No	54 (39)	49 (40)
Previous chemotherapy		
Yes	110 (80)	96 (79)
No	28 (20)	26 (21)
Best response on crizotinib*		
PR	75 (54)	65 (53)
SD	30 (22)	26 (21)
PD	27 (20)	25 (21)
NA/unknown	6 (4)	6 (5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NA, not available; PD, progressive disease; PR, partial response; SD, stable disease.
*Reported by investigators.

(35 of 84) had measurable CNS metastases and 73% (61 of 84) had received prior brain radiation. Of the 61 patients who received brain radiation, 64% completed radiation more than 6 months before starting alectinib, 12% completed brain radiation less than 6 months but 4 weeks or more before starting alectinib, and 8% of the patients completed radiation less than 4 weeks before starting alectinib. Furthermore, 80% of the patients had received at least one previous line of chemotherapy in addition to crizotinib (Table 1 and Data Supplement). The median duration of treatment on crizotinib for all patients was 364 days (12 months) as reported by the investigators (25th percentile, 257 days; 75th percentile, 609 days; Data Supplement). Investigator-assessed best response to crizotinib was PR (54%), stable disease (22%), progressive disease (20%), and unavailable (4%) among all enrolled patients. The median time from last dose of crizotinib to first dose of alectinib for all patients was 15 days (range, 7 to 676 days). The median follow-up time for all patients was 30 weeks (range, 2 to 53 weeks) at the primary data cutoff and was 47 weeks (range, 2 to 73 weeks) at the latest efficacy data cutoff.

Efficacy

Tumor response. Among the RE population by IRC (n = 122), the coprimary end point of ORR was met; 49% (95% CI, 40% to 58%) at the primary cutoff, and 50% (95% CI, 41% to 59%), at the updated cut-off; and the disease control rate (DCR) was 79% (95% CI, 70% to 86%; Fig 1 and Data Supplement). Among the 96 patients in the IRC RE population who had received prior chemotherapy (coprimary end point), the ORR was 44% (95% CI, 34% to 54%) at the primary cutoff, which was not statistically significant but was still clinically meaningful, and the ORR was 45% (95% CI, 35% to 55%) at the updated cutoff; the DCR was 77% (95% CI, 67% to 85%; Data Supplement). Due to the hierarchical order of testing, the overall study is considered positive, because the first coprimary end point was met. For the 26 chemotherapy-naïve patients who belonged to the IRC RE population, the ORR was 69% (95% CI, 48% to 86%; Data Supplement). At the time of the latest data cutoff, 41 (67%) of 61 responses were ongoing. ORR data obtained by investigator were consistent with the IRC data (Data Supplement).

Duration of response and progression-free survival. Among the 61 patients with PR, the median duration of response (DOR) by IRC was 11.2 months (95% CI, 9.6 months to not reached), and only 20 patients (33%) had an event (progressive disease, n = 16; death, n = 4; Fig 1B). Overall, median PFS was 8.9 months (95% CI, 5.6 to 11.3 months), and 80 (58%) of the 138 patients treated had a PFS event (Fig 1C) at time of analysis. For the 28 chemotherapy-naïve patients, the median PFS was 13.0 months (95% CI, 5.5 months to not reached). At the time of the primary data cutoff, 24 of the 138 patients had died, and the 6-month event-free rate was 87% (95% CI, 81% to 92%; Data Supplement).

CNS efficacy. Of the 84 patients with baseline CNS metastases at study entry, 61 (73%) had previous brain radiation. The majority of these 61 patients (64%) received CNS radiation more than 6 months before starting alectinib treatment (Data Supplement). Of the 35 patients with baseline measurable CNS lesions, the CNS ORR was 57% (95% CI, 39% to 74%) and included seven patients who had a CNS CR (Fig 2A and Data Supplement). Among the 84 patients with baseline CNS metastases, 23 patients (27%) achieved a CNS CR, and the overall CNS DCR was 83% (95% CI, 74% to 91%; Data Supplement). The CNS DOR for these 84 patients was 10.3 months (95% CI, 7.6 to 11.2 months; Fig 2B). Among the 23 patients who had no prior brain radiation, 10 patients achieved a CNS CR (43%). At 12 months, 33 patients (cumulative incidence rate, 24.8%) had a CNS progression, 43 patients (cumulative incidence rate, 33.2%) had a non-CNS progression, and nine patients (cumulative incidence rate, 6.6%) died without a documented progression. The incidence of non-CNS progressions increased earlier than the incidence of CNS progressions, whereas the cumulative incidence of deaths showed a slow increase over time compared with other event types (Fig 2C).

Safety. At the time of the primary data cutoff, the median duration of treatment was 27.1 weeks (range, 2.4 to 53.0 weeks). The most common AEs reported regardless of cause were constipation

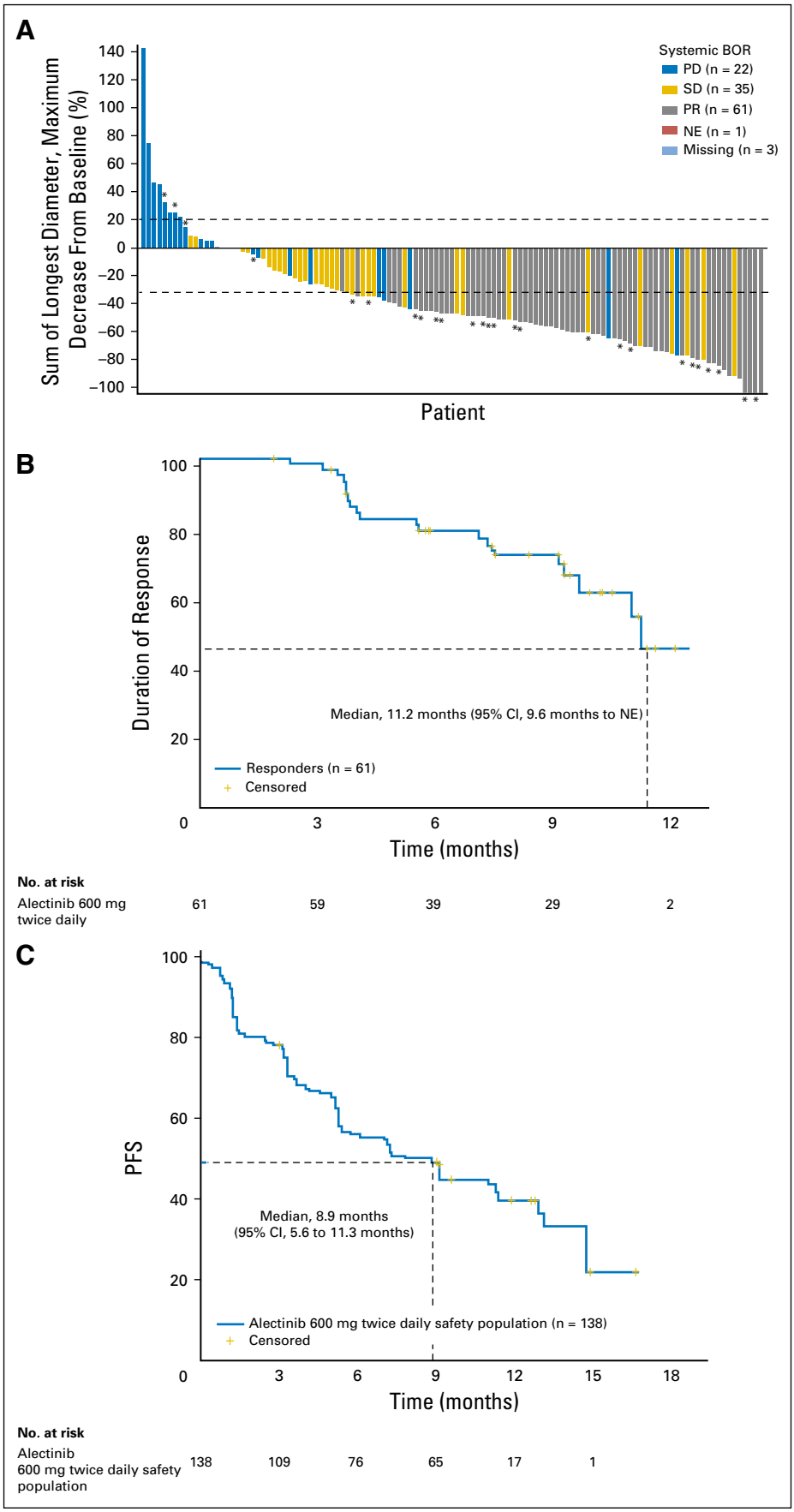

Fig 1. Response to alectinib in crizotinib-refractory *ALK*-rearranged non–small-cell lung cancer (NSCLC). (A) Waterfall plot shows the change in measurable disease size for all patients who received alectinib 600 mg twice daily. The bars indicate the largest percentage change in target lesions from baseline. The lower horizontal dashed line indicates a 30% reduction from baseline. The upper horizontal dashed line indicates a 20% increase from baseline. Asterisks below individual bars indicate chemotherapy-naïve patients. (B) Duration of response: Shown are the Kaplan-Meier estimates of the duration of response among the 61 patients who had achieved a response as assessed by the independent review committee (IRC). (C) Progression-free survival (PFS): Shown is a Kaplan-Meier estimate of PFS among patients with advanced, *ALK*-rearranged NSCLC who received alectinib 600 mg twice daily (ie, the 138 patients comprising the safety population, for whom the median PFS was 8.9 months). Vertical lines on the survival curve indicate censoring of data. BOR, best overall response; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease.

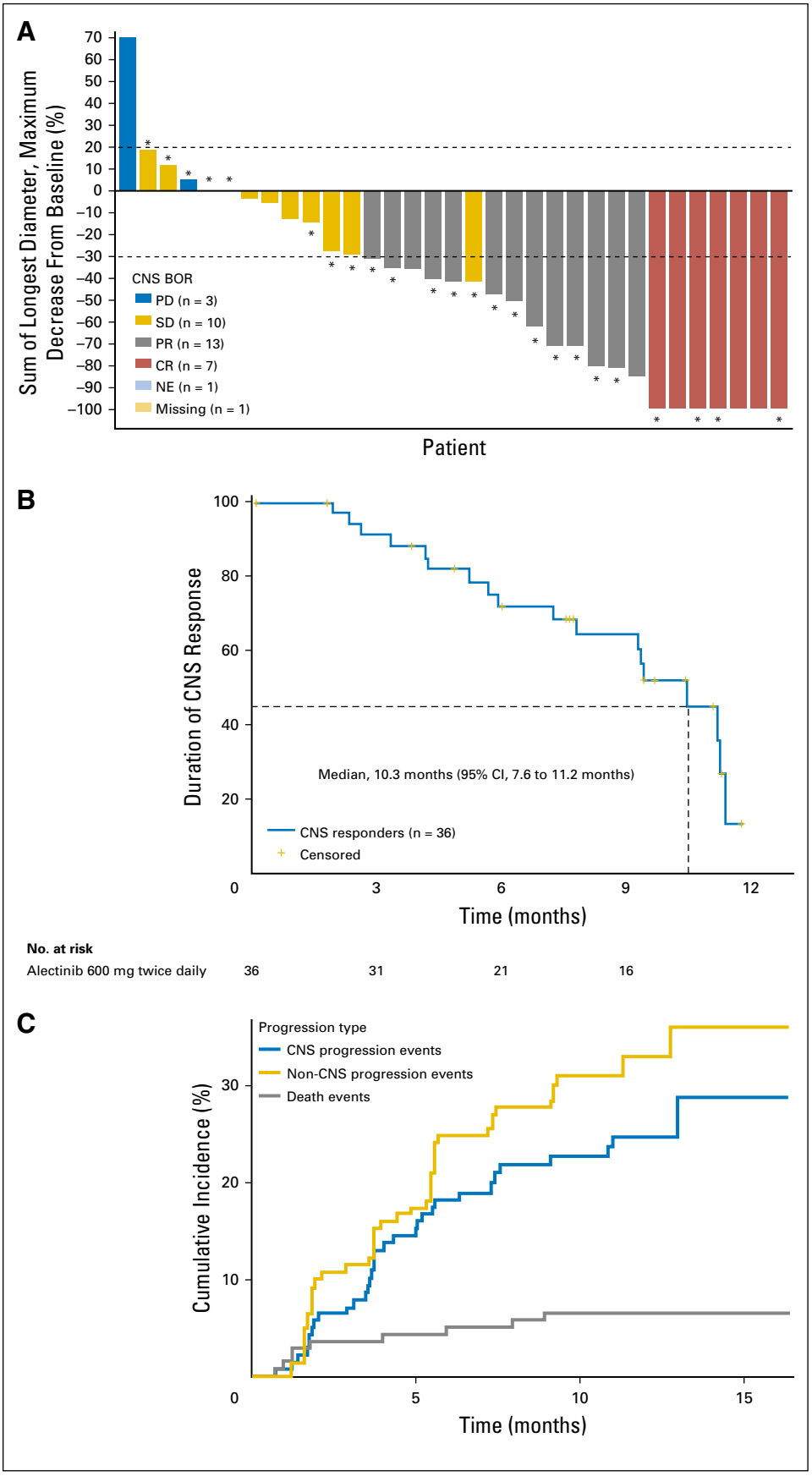

Fig 2. CNS response to alectinib. (A) The change in the cumulative CNS target lesions after patients received alectinib 600 mg twice daily. The bars indicate the largest percentage change in target lesions from baseline. The lower horizontal dashed line indicates a 30% reduction from baseline. The upper horizontal dashed line indicates a 20% increase from baseline. Asterisks below the bars indicate patients with prior brain radiation. (B) Duration of response of all patients with brain metastases at study entry. (C) The cumulative incidence rates of progression according to CNS or non-CNS progression in all patients (N = 138). The cumulative CNS progression rate is shown in blue. The cumulative non-CNS progression rate is shown in gold. The cumulative incidence of death is shown in gray. BOR, best overall response; CR, complete response; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease.

Table 2. All-Cause and Treatment-Related Adverse Events

Adverse Event	No. (%) of Patients With Adverse Event by Grade				
	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Any cause, in ≥ 10% Patients					
Constipation	39 (28)	6 (4)	0	0	45 (33)
Fatigue	26 (19)	8 (6)	2 (1)	0	36 (26)
Peripheral edema	27 (20)	6 (4)	1 (1)	0	34 (25)
Myalgia	25 (18)	5 (4)	1 (1)	0	31 (23)
Asthenia	16 (12)	8 (6)	1 (1)	0	25 (18)
Headache	16 (12)	4 (3)	2 (1)	0	22 (16)
Cough	15 (11)	4 (3)	0	0	19 (14)
Dyspnea	8 (6)	5 (4)	4 (3)	0*	18 (13)
Nausea	13 (9)	3 (2)	0	0	16 (12)
AST elevation	13 (9)	1 (1)	1 (1)	1 (1)	16 (12)
Rash	15 (11)	1 (1)	0	0	16 (12)
Vomiting	10 (7)	4 (3)	1 (1)	0	15 (11)
Diarrhea	10 (7)	3 (2)	1 (1)	0	14 (10)
ALT elevation	7 (5)	5 (4)	1 (1)	1 (1)	14 (10)
Treatment related, in ≥ 5% patients					
Myalgia	19 (14)	3 (2)	1 (1)	0	23 (17)
Constipation	17 (12)	3 (2)	0	0	20 (15)
Fatigue	16 (12)	2 (1)	1 (1)	0	19 (14)
Asthenia	12 (9)	2 (1)	1 (1)	0	15 (11)
AST elevation	11 (8)	1 (1)	1 (1)	1 (1)	14 (10)
ALT elevation	6 (4)	5 (4)	1 (1)	1 (1)	13 (9)
Peripheral edema	10 (7)	2 (1)	1 (1)	0	13 (9)
Rash	11 (8)	1 (1)	0	0	12 (9)
Photosensitivity reaction	12 (9)	0	0	0	12 (9)
Bilirubin elevation	2 (1)	7 (5)	2 (1)	0	11 (8)
Nausea	7 (5)	1 (1)	0	0	8 (6)
Dry skin	7 (5)	0	0	0	7 (5)
Diarrhea	6 (4)	0	1 (1)	0	7 (5)

NOTE. Treatment-related adverse events are defined as those deemed by the investigators to be related to treatment.
*One patient had a grade 5 event that was unrelated to treatment.

(33%), fatigue (26%), and peripheral edema (25%; Table 2). The most common treatment-related AEs were myalgia (17%), constipation (15%), fatigue (14%), and asthenia (11%). Incidence of grades 3 to 4 AEs was low in the study (Table 2).

A total of 29 (21%) of 138 patients had a dose reduction and/or interruption, mainly because of laboratory abnormalities, and the mean duration of treatment interruptions was 10 days. The mean dose intensity was 97%, which indicated that most patients were able to sustain therapeutic levels of alectinib throughout the study. In 11 (8%) of 138 patients, alectinib was permanently discontinued because of an AE. Four patients (3%) died as a result of AEs (intestinal perforation, dyspnea, pulmonary embolism, and hemorrhage). Only the intestinal perforation was considered possibly related to study treatment.

Pharmacokinetics. After multiple oral doses of alectinib 600 mg twice daily under fed conditions, the geometric mean peak-to-trough ratio of alectinib on day 21 was 1.23, which indicated an overall flat PK profile for alectinib and supported a sustained alectinib exposure throughout the dosing interval (Data Supplement). Exploratory evaluation of alectinib plasma levels at steady state between a limited number of patients (white, n = 6; Asian, n = 20) showed a large overlap in exposure, which indicated that alectinib exposures are not markedly different between white and Asian populations at 600 mg twice daily (Data Supplement).

DISCUSSION

The development of resistance to crizotinib is a major barrier to the successful long-term treatment of patients with *ALK*-rearranged NSCLC. Progression with crizotinib can be due to acquired resistance mutations in *ALK*, activation of other signaling bypass pathways, and, in approximately half of the patients treated with crizotinib, development and/or progression of brain metastases.[15,16] Crizotinib has demonstrated potential clinical activity in the CNS, but it remains to be determined whether the high frequency of CNS progression among patients on crizotinib is caused by pharmacodynamic failure of crizotinib or natural history of *ALK*-rearranged NSCLC, which could involve similar biologic mechanisms of resistance.[17-19] Therefore, novel ALK inhibitors should not only be more potent than crizotinib and able to inhibit the clinically relevant acquired resistance mutations in *ALK* but also confer sustained clinical activity in the CNS.

Oral alectinib 600 mg twice daily demonstrated potent clinical activity in patients with advanced, *ALK*-rearranged NSCLC who had experienced progression while receiving crizotinib, most of whom had also received at least one prior line of platinum-based chemotherapy. Alectinib also resulted in shrinkage of CNS metastases, with a CNS ORR of 57% in patients who had measurable CNS metastases and a CNS CR rate of 27% among all

patients who had CNS metastases; sustained durable response (median, 10.3 months) was prospectively assessed by an IRC. The observed CNS clinical activity of alectinib is consistent with the preclinical data of high CNS tissue penetration of alectinib and the comparable CSF-to–unbound plasma ratio of alectinib observed in another clinical study.[12,13] Moreover, it is consistent with the observed CNS ORR of 52% and the CNS CR rate of 29% observed in the dose-finding portion of the US phase I/II study (NP28761) of alectinib.[13] Additionally, alectinib has been reported to be effective against leptomeningeal carcinomatosis in patients with *ALK*-positive NSCLC who had experienced progression while receiving crizotinib alone[13,20] or while receiving both crizotinib and ceritinib.[21] Importantly, the cumulative incidence rate of CNS progression was lower than the cumulative incidence rate of non-CNS progression for all patients in this trial, which seems to suggest that alectinib can prevent or delay the emergence of CNS metastases. However, one caveat to this analysis is that brain imaging was not performed at a regular interval among patients without baseline CNS metastasis. Therefore, the true incidence of CNS progression could have been underestimated. Ceritinib, another novel ALK inhibitor, was recently approved in the United States and Europe for patients with *ALK*-rearranged NSCLC who have experienced progression while receiving crizotinib.[7,22] In a small number of patients with measurable brain metastases (N = 24), ceritinib achieved a CNS ORR of 29%,[23] and 42% of patients with crizotinib-resistant *ALK*-rearranged NSCLC who experienced progression while receiving ceritinib had CNS as the only site of relapse.[7] The National Cancer Institute currently is planning a master protocol to address the optimal sequential use of various ALK inhibitors, which should provide additional insight to guide treatment decisions.

Alectinib has also demonstrated impressive ORR (94%) and PFS (median not yet reached, but estimated at > 29 months) in Japanese patients with *ALK*-positive NSCLC who were ALK inhibitor naïve.[24] In the dose-finding portion of the US phase I/II alectinib study, steady state exposures of alectinib achieved at 600 mg twice daily in white patients met or exceeded the exposures of alectinib achieved with 300 mg orally twice daily in Japanese patients.[25,26] However, in this study, we did not detect marked differences in alectinib exposure at 600 mg twice daily among a small subgroup of white and Asian patients who underwent intensive pharmacokinetic analysis (Data Supplement).

Overall, the efficacy and safety profile of alectinib compare favorably with available data from other ALK inhibitors.[4,5,7,19,22,27] Common AEs were primarily myalgia, fatigue, and gastrointestinal events, which were generally of grade 1 or 2. Myalgia usually has an early onset and generally resolves within 4 weeks of starting alectinib. Less than one quarter of patients required dose modification, and no grade 3 to 4 AE occurred in more than 5% of patients treated with alectinib. Of note because the median time from the last dose of crizotinib to the start of alectinib was only 15 days, 14% of the patients had peripheral edema, which is a known adverse effect of crizotinib, as a concurrent medical condition before they started taking alectinib. This may explain the higher overall rate of peripheral edema (25%) as an AE compared with the treatment-related incidence of 9%, which is more consistent with the percentage of treatment-related peripheral edema reported in another alectinib study.[13] The clinically meaningful ORR and DOR in patients with crizotinib-resistant disease and the sustained CNS response reported from this study, as well as the good tolerability profile, support the additional development of this promising new ALK inhibitor. Alectinib is currently being investigated versus crizotinib in treatment-naïve patients with advanced NSCLC and *ALK* rearrangement in a global randomized trial with PFS as the primary end point (NCT02075840). This trial will also prospectively examine performance of brain imaging on all enrolled patients at regular fixed-time intervals, regardless of the presence of brain metastases at baseline, and should provide additional evidence about whether alectinib, compared with crizotinib, will delay and/or prevent the emergence of CNS metastases.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

Conception and design: Sai-Hong Ignatius Ou, Ramaswamy Govindan, James Chih-Hsin Yang, Walter Bordogna, Bogdana Balas, Peter N. Morcos, Ali Zeaiter

Provision of study materials or patients: Sai-Hong Ignatius Ou, Jin Seok Ahn, Luigi De Petris, Ramaswamy Govindan, James Chih-Hsin Yang, Brett Hughes, Hervé Lena, Denis Moro-Sibilot, Alessandra Bearz, Santiago Viteri Ramirez, Tarek Mekhail, Alexander Spira, Dong-Wan Kim

Collection and assembly of data: Sai-Hong Ignatius Ou, Jin Seok Ahn, Luigi De Petris, Ramaswamy Govindan, Hervé Lena, Denis Moro-Sibilot, Alessandra Bearz, Santiago Viteri Ramirez, Tarek Mekhail, Bogdana Balas, Annabelle Monnet, Ali Zeaiter, Dong-Wan Kim

Data analysis and interpretation: Sai-Hong Ignatius Ou, Brett Hughes, Tarek Mekhail, Alexander Spira, Walter Bordogna, Bogdana Balas, Peter N. Morcos, Annabelle Monnet, Ali Zeaiter, Dong-Wan Kim

Manuscript writing: All authors

Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Alectinib in Crizotinib-Refractory *ALK*-Rearranged Non–Small-Cell Lung Cancer: A Phase II Global Study

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Sai-Hong Ignatius Ou
Honoraria: Pfizer, F. Hoffmann-La Roche, Boehringer Ingelheim
Consulting or Advisory Role: Pfizer, F. Hoffmann-La Roche, Boehringer Ingelheim, ARIAD
Speakers' Bureau: F. Hoffmann-La Roche, Boehringer Ingelheim
Research Funding: Pfizer (Inst), F. Hoffmann-La Roche (Inst), Boehringer Ingelheim (Inst), AstraZeneca (Inst), Clovis Oncology (Inst), Astellas Pharma (Inst), Ignyta (Inst), Daiichi Sankyo (Inst), ARIAD (Inst)

Jin Seok Ahn
Honoraria: AstraZeneca, Janssen, Lilly, Menarini, Roche
Consulting or Advisory Role: Boehringer Ingelheim

Luigi De Petris
Consulting or Advisory Role: F. Hoffmann-La Roche (Inst), Bristol-Myers Squibb (Inst), Pfizer (Inst), Boehringer Ingelheim (Inst)

Ramaswamy Govindan
No relationship to disclose

James Chih-Hsin Yang
Honoraria: Boehringer Ingelheim
Consulting or Advisory Role: AstraZeneca, Genentech, Pfizer, Eli Lilly, Bayer, Astellas Pharma, MSD Oncology, Merck Serono, Novartis, Clovis Oncology, Celgene

Brett Hughes
Consulting or Advisory Role: F. Hoffmann-La Roche
Travel, Accommodations, Expenses: F. Hoffmann-La Roche

Hervé Lena
Honoraria: Genentech, Lilly, Bristol-Myers Squibb, AstraZeneca, Beohringer Ingelheim, MSD Oncology, Pierre Fabre, Pfizer, Novartis
Consulting or Advisory Role: Bristol-Myers Squibb, Novartis
Research Funding: Genentech (Inst)
Travel, Accommodations, Expenses: Boehringer Ingelheim, Bristol-Myers Squibb, Lilly, Amgen, Genentech, Pierre Fabre Medicament

Denis Moro-Sibilot
Honoraria: Lilly, Pfizer, Novartis, Roche, MSD, Clovis, Boehringer Ingelheim
Consulting or Advisory Role: Lilly, Roche
Research Funding: Pfizer
Travel, Accommodations, Expenses: Lilly, MSD

Alessandra Bearz
No relationship to disclose

Santiago Viteri Ramirez
Consulting or Advisory Role: Boehringer, Ingelheim, Vaxon Biotech, Astex Pharmaceuticals
Speakers' Bureau: Novartis, Pfizer, AstraZeneca Spain
Travel, Accommodations, Expenses: Celgene

Tarek Mekhail
Honoraria: Genentec, Lilly, Novartis, Celgene, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim
Consulting or Advisory Role: Genentech, Lilly, Novartis, Celgene, Brisol-Myers Squibb,
Speakers' Bureau: Genentech, Lilly, Novartis, Celegene, Bristol-Myers Squibb, Boehringer Ingelheim

Alexander Spira
Honoraria: Novartis, Roche
Research Funding: Roche, AstraZeneca, Boehringer Ingelheim, Astellas, Clovis Oncology, MedImmune
Expert Testimony: Novartis
Travel, Accommodations, Expenses: Roche

Walter Bordogna
Employment: F. Hoffmann-La Roche
Stock or Other Ownership: F. Hoffmann-La Roche

Bogdana Balas
Employment: F. Hoffmann-La Roche, F. Hoffmann-La Roche (I)
Stock or Other Ownership: F. Hoffmann-La Roche

Peter N. Morcos
Employment: F. Hoffmann-La Roche
Stock or Other Ownership: F. Hoffmann-La Roche
Research Funding: F. Hoffmann-La Roche

Annabelle Monnet
Employment: F. Hoffmann-La Roche

Ali Zeaiter
Employment: F. Hoffmann-La Roche
Leadership: F. Hoffmann-La Roche
Stock or Other Ownership: F. Hoffmann-La Roche

Dong-Wan Kim
No relationship to disclose

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