ORIGINAL ARTICLE

Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

Alectinib, a highly selective inhibitor of anaplastic lymphoma kinase (ALK), has shown systemic and central nervous system (CNS) efficacy in the treatment of *ALK*-positive non–small-cell lung cancer (NSCLC). We investigated alectinib as compared with crizotinib in patients with previously untreated, advanced *ALK*-positive NSCLC, including those with asymptomatic CNS disease.

METHODS

In a randomized, open-label, phase 3 trial, we randomly assigned 303 patients with previously untreated, advanced *ALK*-positive NSCLC to receive either alectinib (600 mg twice daily) or crizotinib (250 mg twice daily). The primary end point was investigator-assessed progression-free survival. Secondary end points were independent review committee–assessed progression-free survival, time to CNS progression, objective response rate, and overall survival.

RESULTS

During a median follow-up of 17.6 months (crizotinib) and 18.6 months (alectinib), an event of disease progression or death occurred in 62 of 152 patients (41%) in the alectinib group and 102 of 151 patients (68%) in the crizotinib group. The rate of investigator-assessed progression-free survival was significantly higher with alectinib than with crizotinib (12-month event-free survival rate, 68.4% [95% confidence interval (CI), 61.0 to 75.9] with alectinib vs. 48.7% [95% CI, 40.4 to 56.9] with crizotinib; hazard ratio for disease progression or death, 0.47 [95% CI, 0.34 to 0.65]; P<0.001); the median progression-free survival with alectinib was not reached. The results for independent review committee–assessed progression-free survival were consistent with those for the primary end point. A total of 18 patients (12%) in the alectinib group had an event of CNS progression, as compared with 68 patients (45%) in the crizotinib group (cause-specific hazard ratio, 0.16; 95% CI, 0.10 to 0.28; P<0.001). A response occurred in 126 patients in the alectinib group (response rate, 82.9%; 95% CI, 76.0 to 88.5) and in 114 patients in the crizotinib group (response rate, 75.5%; 95% CI, 67.8 to 82.1) (P=0.09). Grade 3 to 5 adverse events were less frequent with alectinib (41% vs. 50% with crizotinib).

CONCLUSIONS

As compared with crizotinib, alectinib showed superior efficacy and lower toxicity in primary treatment of *ALK*-positive NSCLC. (Funded by F. Hoffmann–La Roche; ALEX ClinicalTrials.gov number, NCT02075840.)

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The current standard first-line therapy for patients with advanced-stage non–small-cell lung cancer (NSCLC) that harbors rearrangement of the anaplastic lymphoma kinase (*ALK*) gene (*ALK*-positive NSCLC) is crizotinib.[1] The median progression-free survival with first-line crizotinib is 10.9 months.[1] Advanced *ALK*-positive NSCLC is characterized by a high lifetime risk of central nervous system (CNS) metastases[2] and a high frequency of brain metastases at diagnosis, with the CNS being the most common site of disease progression.[3] Potential mechanisms of resistance to ALK inhibitors include *ALK* mutations and "bypass" mechanisms through activation of other receptor tyrosine kinases.[4]

Alectinib (CH5424602; Chugai Pharmaceutical and F. Hoffmann–La Roche) is a potent ALK tyrosine kinase inhibitor with a 50% maximum inhibitory concentration of 1.9 nmol per liter in enzymatic analyses and with activity against the effects of several *ALK* mutations that confer resistance to crizotinib.[5-9] Unlike crizotinib, alectinib is a CNS penetrant; it is not a substrate of P-glycoprotein, a key efflux transporter located at the blood–brain barrier. In both preclinical and clinical investigations, alectinib was active in the CNS.[10-12]

The BO28984 (ALEX) trial was an international, randomized, open-label, phase 3 trial comparing alectinib (600 mg twice daily) with crizotinib in patients with previously untreated, advanced *ALK*-positive NSCLC, including those with asymptomatic CNS disease. Here we report data from the primary analysis, including the primary end point (investigator-assessed progression-free survival) and secondary end points.

Methods

Patients

Eligible patients had histologically or cytologically confirmed advanced NSCLC that was *ALK*-positive by VENTANA ALK (D5F3) immunohistochemical assay conducted at central laboratories (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Patients were 18 years of age or older, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (on a 5-point scale, with higher numbers reflecting greater disability), no previous systemic treatment for advanced NSCLC, measurable disease (according to Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1), and adequate hepatic, renal, and bone marrow function (as defined in the trial protocol, available at NEJM.org). Patients with asymptomatic brain or leptomeningeal metastases were eligible; previous CNS radiotherapy was allowed if completed at least 14 days before enrollment.

Trial Oversight

The protocol was approved by the institutional review board or ethics committee at each participating center and complied with Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and local laws. All the patients provided written informed consent before enrollment. The trial was designed by the sponsor (F. Hoffmann–La Roche) and trial investigators (listed in the Supplementary Appendix). The sponsor collected and analyzed the data in collaboration with the authors, who had full access to all the data. The manuscript was written by the first two authors and the last author, with additional writing support (sponsor-funded) from Gardiner-Caldwell Communications (Macclesfield, United Kingdom). All the authors vouch for the completeness and accuracy of the data and analyses reported and for the adherence of the trial to the protocol.

Trial Design and Treatment

Patients were randomly assigned (in a 1:1 ratio by means of a block-stratified randomization procedure with the use of an interactive or Web-based response system) to receive either oral alectinib at a dose of 600 mg twice daily (to be taken with food) or oral crizotinib at a dose of 250 mg twice daily (to be taken with or without food). Randomization was stratified according to ECOG performance status (0 or 1 vs. 2), race (Asian vs. non-Asian), and the presence or absence of CNS metastases at baseline. Per protocol, crossover between trial groups was not allowed; patients assigned to crizotinib may have received alectinib after disease progression (in countries where alectinib was already approved or available). The primary end point was investigator-assessed progression-free survival. Secondary end points were independent review committee–assessed progression-free survival, time to CNS progression, objective response rate, and overall survival. Other end points were the duration of response, rate of CNS response, duration of CNS response, and safety. All CNS end points were

assessed by the independent review committee. End-point definitions are provided in the Supplementary Appendix. Treatment was continued until disease progression, unacceptable toxic effects, withdrawal of consent, or death. Patients with isolated asymptomatic CNS progression could receive, at the investigator's discretion, a local therapy followed by continued trial treatment until systemic disease progression, symptomatic CNS progression, or both.

ASSESSMENTS

All the patients underwent tumor imaging at baseline, including scans of the brain. Subsequent tumor evaluation, including systematic brain imaging in all patients, was performed every 8 weeks until disease progression. Tumor response was assessed with the use of RECIST, version 1.1. Two assessments by the independent review committee (according to RECIST, version 1.1) were performed, one for overall systemic disease and one solely for the evaluation of CNS end points. Details regarding the selection of target lesions are provided in the Supplementary Appendix, and full details of the assessments are available in the protocol. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and were classified according to the *Medical Dictionary for Regulatory Activities*.

STATISTICAL ANALYSIS

Overall, 170 events of disease progression or death were required to achieve 80% power of the log-rank test to detect a target hazard ratio of 0.65 (corresponding to an increase in median progression-free survival from 10.9 months with crizotinib to 16.8 months with alectinib) at a two-sided alpha level of 5%. The comparison between the treatment groups with respect to progression-free survival was based on a stratified log-rank test at a 5% level of significance (two-sided). The Kaplan–Meier method was used to estimate the median progression-free survival for each treatment group with 95% confidence intervals. A stratified Cox proportional-hazards regression model was used to estimate the treatment effect, expressed as a hazard ratio with a 95% confidence interval.

Secondary end points were analyzed with the use of a hierarchical testing strategy to account for multiplicity. If the difference between the treatment groups with respect to the primary end point of investigator-assessed progression-free survival was significant, secondary end points were each tested (at a two-sided 5% significance level) in the following sequence: independent review committee–assessed progression-free survival, time to independent review committee–assessed CNS progression according to RECIST criteria, investigator-assessed response rate, and overall survival.

Efficacy end points were evaluated in the intention-to-treat population, comprising all randomly assigned patients. The safety population included all the patients who received at least one dose of trial medication.

All the patients in the intention-to-treat population were included in the analysis of time to CNS progression, regardless of status with regard to baseline CNS metastases. To account for the competing risks inherent in the comparison of CNS progression between the alectinib and crizotinib groups, a stratified two-sided log-rank test was computed on the basis of a cause-specific hazard function. The probability of CNS progression, non-CNS progression, and death were estimated with the use of cumulative-incidence functions. Statistical methods are described further in the Supplementary Appendix.

RESULTS

PATIENTS

Between August 18, 2014, and January 20, 2016, a total of 303 patients at 98 centers underwent randomization. Both the intention-to-treat and safety populations comprised 303 patients (152 in the alectinib group and 151 in the crizotinib group) (Fig. 1). Baseline characteristics were well balanced between the two treatment groups, including the presence of CNS metastases (42% in the alectinib group and 38% in the crizotinib group) (Table 1). The median duration of follow-up was 17.6 months (range, 0.3 to 27.0) in the crizotinib group and 18.6 months (range, 0.5 to 29.0) in the alectinib group. At the time of analysis, 68 patients (45%) had discontinued treatment in the alectinib group and 105 (70%) had discontinued treatment in the crizotinib group (Fig. 1).

EFFICACY

At the date of primary data cutoff (February 9, 2017), an event of disease progression or death had occurred in 164 patients in the intention-to-

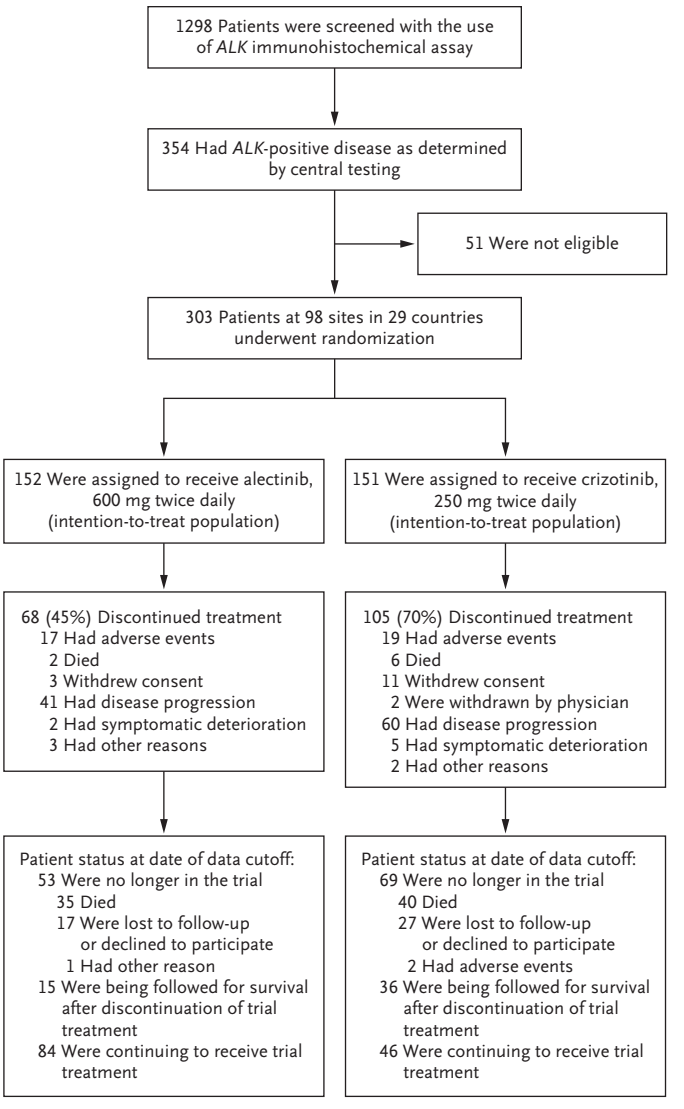

Figure 1. Screening, Enrollment, Randomization, and Follow-up.

The intention-to-treat population included all patients who were randomly assigned to trial treatment. A total of 5 patients in the alectinib group and 40 patients in the crizotinib group had isolated asymptomatic central nervous system (CNS) progression as the first progression event; 5 of these 5 patients (100%) in the alectinib group and 30 of these 40 patients (75%) in the crizotinib group continued to receive trial treatment for at least 30 days after CNS progression.

treat population (62 of 152 patients [41%] in the alectinib group and 102 of 151 patients [68%] in the crizotinib group). The rate of investigator-assessed progression-free survival was significantly higher with alectinib than with crizotinib (12-month event-free survival rate, 68.4% [95% confidence interval {CI}, 61.0 to 75.9] with alectinib vs. 48.7% [95% CI, 40.4 to 56.9] with crizotinib; hazard ratio for disease progression or death, 0.47 [95% CI, 0.34 to 0.65]; P<0.001); the median progression-free survival with alectinib was not reached (95% CI, 17.7 months to not estimable), as compared with 11.1 months (95% CI, 9.1 to 13.1) with crizotinib (Fig. 2A). Independent review committee–assessed progression-free survival was also significantly longer with alectinib than with crizotinib (median progression-free survival, 25.7 months [95% CI, 19.9 to not estimable] vs. 10.4 months [95% CI, 7.7 to 14.6]; hazard ratio for disease progression or death, 0.50 [95% CI, 0.36 to 0.70]; P<0.001) (Fig. S1 in the Supplementary Appendix). The magnitude of the treatment effect was generally consistent across the subgroups (Fig. 2B). The magnitude of benefit was lower in the subgroups of active smokers and patients with an ECOG performance status of 2, although the numbers of patients in these subgroups were small.

The time to CNS progression was significantly longer with alectinib than with crizotinib in the intention-to-treat population (cause-specific hazard ratio, 0.16; 95% CI, 0.10 to 0.28; P<0.001); 18 patients (12%) in the alectinib group had an event of CNS progression, as compared with 68 patients (45%) in the crizotinib group (Table S1 in the Supplementary Appendix). The cumulative incidence rate of CNS progression, with adjustment for the competing risks of non-CNS progression and death (Fig. S2 in the Supplementary Appendix), was consistently lower over time with alectinib than with crizotinib, and the 12-month cumulative incidence rate of CNS progression was 9.4% (95% CI, 5.4 to 14.7) versus 41.4% (95% CI, 33.2 to 49.4) (Fig. 2C).

In the intention-to-treat population, an investigator-assessed response occurred in 126 patients in the alectinib group (response rate, 82.9%; 95% CI, 76.0 to 88.5) and in 114 patients in the crizotinib group (response rate, 75.5%; 95% CI, 67.8 to 82.1) (P=0.09) (Table 2). The duration of response was longer with alectinib than with crizotinib (hazard ratio for progression or death, 0.36 [95% CI, 0.24 to 0.53]; median duration of response, not estimable [95% CI, not estimable] vs. 11.1 months [95% CI, 7.9 to 13.0]). The 12-month event-free rate was 72.5% (95% CI, 64.6 to 80.4) in the alectinib group and 44.1% (95% CI, 34.5 to 53.6) in the crizotinib group.

Among patients with measurable CNS lesions

at baseline, a CNS response occurred in 17 of 21 patients in the alectinib group (CNS response rate, 81%; 95% CI, 58 to 95) and in 11 of 22 patients in the crizotinib group (CNS response rate, 50%; 95% CI, 28 to 72); 8 patients (38%) in the alectinib group had a complete CNS response, as compared with 1 patient (5%) in the crizotinib group (Table 2). The median duration of intracranial response was 17.3 months (95% CI, 14.8 to not estimable) and 5.5 months (95% CI, 2.1 to 17.3), respectively. Among patients with measurable or nonmeasurable CNS lesions at baseline, a CNS response occurred in 38 of 64 patients in the alectinib group (CNS response rate, 59%; 95% CI, 46 to 71) and in 15 of 58 patients in the crizotinib group (CNS response rate, 26%; 95% CI, 15 to 39); 29 patients (45%) in the alectinib group had a complete CNS response, as compared with 5 patients (9%) in the crizotinib group.

At the date of data cutoff, death had occurred in 75 patients in the intention-to-treat population (35 patients [23%] in the alectinib group and 40 patients [26%] in the crizotinib group). The 12-month survival rate was 84.3% (95% CI, 78.4 to 90.2) with alectinib and 82.5% (95% CI, 76.1 to 88.9) with crizotinib. The hazard ratio for death was 0.76 (95% CI, 0.48 to 1.20), and the median overall survival was not estimable in either group (Fig. 2D).

SAFETY

The median duration of treatment was 17.9 months (range, 0 to 29) with alectinib and 10.7 months (range, 0 to 27) with crizotinib. The mean dose intensity (±SD) was 95.6±10.3% with alectinib and 92.4±14.1% with crizotinib (dose intensity is the amount of trial drug actually received divided by the expected amount).

Adverse events that occurred at a higher incidence with alectinib than with crizotinib by 5 percentage points or more were anemia (20% vs. 5%), myalgia (16% vs. 2%), increased blood bilirubin (15% vs. 1%), increased weight (10% vs. 0%), musculoskeletal pain (7% vs. 2%), and photosensitivity reaction (5% vs. 0%) (Table 3). Adverse events that were more common with crizotinib included nausea (48% vs. 14% with alectinib), diarrhea (45% vs. 12%), and vomiting (38% vs. 7%) (Table 3).

Grade 3 to 5 adverse events occurred in 41% of the patients treated with alectinib and 50% of the patients treated with crizotinib (Table S2 in

Table 1. Baseline Patient Characteristics in the Intention-to-Treat Population.*

Characteristic	Crizotinib (N=151)	Alectinib (N=152)
Age — yr		
Mean	53.8±13.5	56.3±12.0
Median	54.0	58.0
Range	18–91	25–88
Sex — no. (%)		
Male	64 (42)	68 (45)
Female	87 (58)	84 (55)
Race — no. (%)†‡		
Asian	69 (46)	69 (45)
Non-Asian	82 (54)	83 (55)
ECOG performance status — no. (%)†		
0 or 1	141 (93)	142 (93)
2	10 (7)	10 (7)
Smoking status — no. (%)		
Active smoker	5 (3)	12 (8)
Former smoker	48 (32)	48 (32)
Nonsmoker	98 (65)	92 (61)
Current stage of disease — no. (%)		
IIIB	6 (4)	4 (3)
IV	145 (96)	148 (97)
Histologic type — no. (%)		
Adenocarcinoma	142 (94)	137 (90)
Large-cell carcinoma	3 (2)	0
Mixed with predominantly adenocarcinoma component	1 (1)	0
Squamous-cell carcinoma	2 (1)	5 (3)
Undifferentiated	0	4 (3)
Other	3 (2)	6 (4)
CNS metastases — no. (%)†§		
Yes	58 (38)	64 (42)
No	93 (62)	88 (58)
Treatment for CNS metastases — no./total no. (%)		
Brain surgery	1/22 (5)	1/27 (4)
Radiosurgery	4/22 (18)	5/27 (19)
Whole-brain radiotherapy	16/22 (73)	17/27 (63)
Other¶	1/22 (5)	4/27 (15)
Previous brain radiation — no. (%)		
Yes	21 (14)	26 (17)
No	130 (86)	126 (83)

* Plus–minus values are means ±SD.
† These characteristics were defined as stratification factors for analyses. An Eastern Cooperative Oncology Group (ECOG) performance status of 2 (on a 5-point scale, with higher numbers reflecting greater disability) was not used for stratified analyses owing to low numbers of patients.
‡ Race was reported by the investigator.
§ Central nervous system (CNS) metastases were assessed by the independent review committee.
¶ One patient in the crizotinib group and three patients in the alectinib group underwent brain surgery combined with radiotherapy. An additional patient in the alectinib group underwent both radiosurgery and whole-brain radiotherapy.

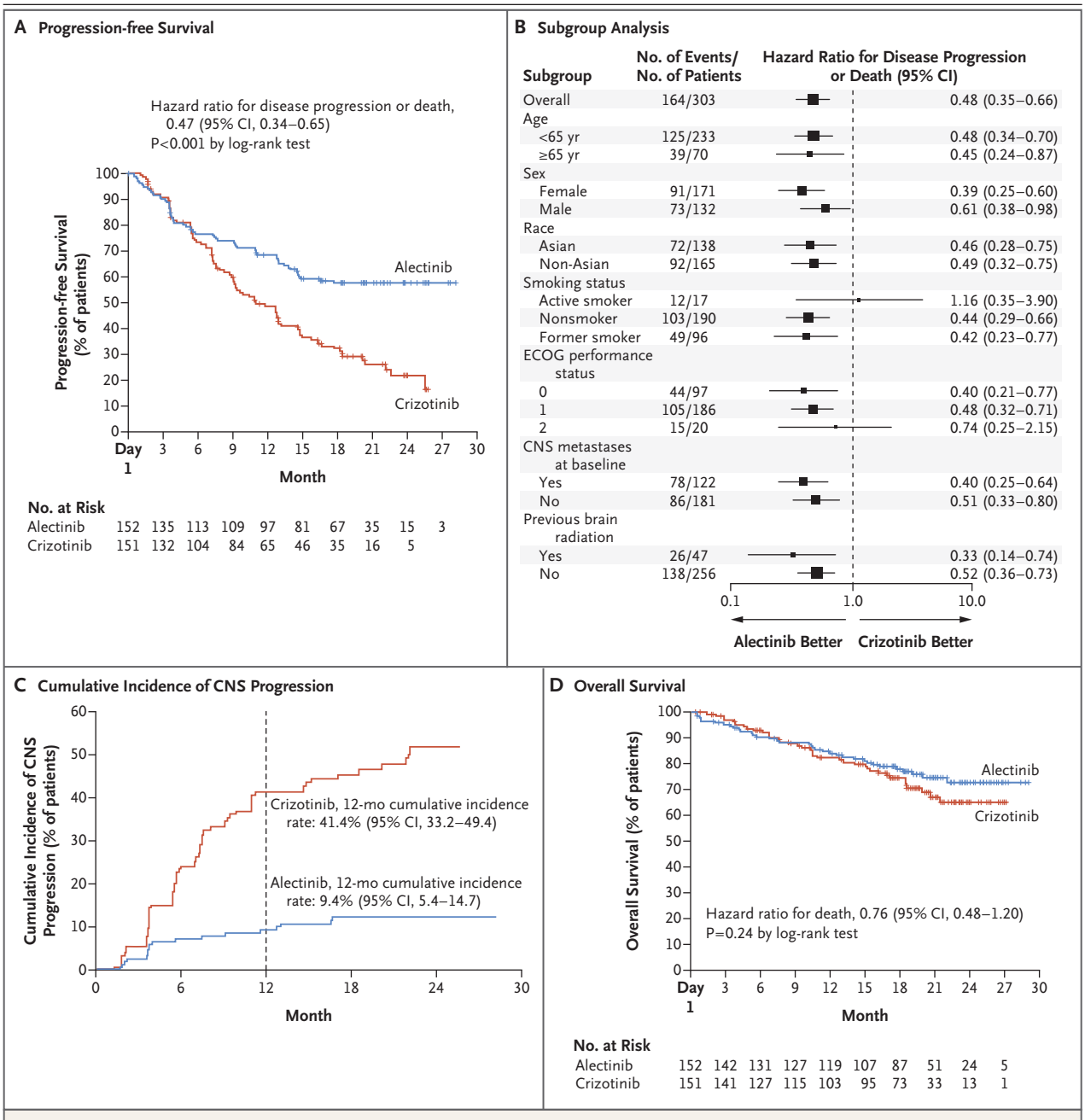

Figure 2. Efficacy Outcomes in the Intention-to-Treat Population.

Panel A shows Kaplan–Meier estimates of investigator-assessed progression-free survival, according to treatment group. The hazard ratio was estimated by means of Cox regression. The Brookmeyer and Crowley method was used to compute confidence intervals for the median progression-free survival times. The hazard ratio and P value were stratified according to race (Asian vs. non-Asian) and the presence or absence of CNS metastases at baseline, as assessed by the independent review committee. Panel B shows progression-free survival (investigator-assessed) across predefined patient subgroups. Values for the Eastern Cooperative Oncology Group (ECOG) performance status are on a 5-point scale, with higher numbers reflecting greater disability. Panel C shows the cumulative incidence of CNS progression, as assessed by the independent review committee according to Response Evaluation Criteria in Solid Tumors, version 1.1. Values were adjusted for the competing risks of non-CNS progression and death. Panel D shows overall survival.

Table 2. Objective Response Rates in the Intention-to-Treat Population and among Patients with CNS Lesions at Baseline.*

Variable	Crizotinib	Alectinib
Intention-to-treat population		
No. of patients	151	152
Response		
No. of patients	114	126
% (95% CI)	75.5 (67.8–82.1)	82.9 (76.0–88.5)†
Complete response — no. (%)	2 (1)	6 (4)
Partial response — no. (%)	112 (74)	120 (79)
Stable disease — no. (%)	24 (16)	9 (6)
Median duration of response (95% CI) — mo	11.1 (7.9–13.0)	NE (NE)
Patients with measurable CNS lesions at baseline		
No. of patients	22	21
CNS response		
No. of patients	11	17
% (95% CI)	50 (28–72)	81 (58–95)
CNS complete response — no. (%)	1 (5)	8 (38)
Median duration of response (95% CI) — mo	5.5 (2.1–17.3)	17.3 (14.8–NE)
Patients with measurable or nonmeasurable CNS lesions at baseline		
No. of patients	58	64
CNS response		
No. of patients	15	38
% (95% CI)	26 (15–39)	59 (46–71)
CNS complete response — no. (%)	5 (9)‡	29 (45)§
Median duration of response (95% CI) — mo	3.7 (3.2–6.8)	NE (17.3–NE)

* Systemic responses (in the intention-to-treat population) were assessed by the investigator. CNS responses (in patients with CNS lesions at baseline) were assessed by the independent review committee. CI denotes confidence interval, and NE not estimable.
† P=0.09 for the comparison between crizotinib and alectinib.
‡ Of the 5 patients, 1 received previous brain radiotherapy and 1 received concomitant brain radiotherapy.
§ Of the 29 patients, 5 received previous brain radiotherapy and 1 received concomitant brain radiotherapy.

the Supplementary Appendix). The most common grade 3 to 5 adverse events in both groups were laboratory abnormalities. Adverse events that occurred in at least 10% of the patients in either treatment group are shown in Table S3 in the Supplementary Appendix. Serious adverse events were reported in 28% of the patients treated with alectinib and 29% of the patients treated with crizotinib (Table S4 in the Supplementary Appendix). Fatal adverse events occurred in 3% and 5% of the patients, respectively; two deaths with crizotinib and none with alectinib were reported by investigators as being related to the trial treatment. Adverse events leading to dose reduction, interruption, or discontinuation were reported in 16%, 19%, and 11%, respectively, of the patients treated with alectinib and in 21%, 25%, and 13%, respectively, of the patients treated with crizotinib.

DISCUSSION

The ALEX trial was a global, randomized, phase 3 trial comparing alectinib with crizotinib in previously untreated patients with advanced *ALK*-positive NSCLC. Crizotinib, the first-in-class ALK

Table 3. Safety Overview and Adverse Events of Any Grade That Differed by 5 Percentage Points or More in Frequency between Groups.*

Event	Crizotinib (N=151)		Alectinib (N=152)	
	Any Grade	Grade 3–5	Any Grade	Grade 3–5
	number of patients (percent)			
Adverse event	146 (97)	76 (50)	147 (97)	63 (41)
Serious adverse event	—	44 (29)	—	43 (28)
Fatal adverse event†	—	7 (5)	—	5 (3)
Adverse event leading to treatment discontinuation	19 (13)	—	17 (11)	—
Adverse event leading to dose reduction	31 (21)	—	24 (16)	—
Adverse event leading to dose interruption	38 (25)	—	29 (19)	—
Adverse events that differed by ≥5 percentage points in frequency between groups				
Nausea	72 (48)	5 (3)	21 (14)	1 (1)
Diarrhea	68 (45)	3 (2)	18 (12)	0
Vomiting	58 (38)	5 (3)	11 (7)	0
ALT increased	45 (30)	22 (15)	23 (15)	7 (5)
AST increased	37 (25)	16 (11)	21 (14)	8 (5)
Blood bilirubin increased	2 (1)	0	23 (15)	3 (2)
Weight increased	0	0	15 (10)	1 (1)
γ-Glutamyltransferase increased	10 (7)	2 (1)	1 (1)	1 (1)
Peripheral edema	42 (28)	1 (1)	26 (17)	0
Dizziness	21 (14)	0	12 (8)	0
Dysgeusia	29 (19)	0	4 (3)	0
Visual impairment	18 (12)	0	2 (1)	0
Vision blurred	11 (7)	0	3 (2)	0
Photopsia	9 (6)	0	0	0
Myalgia	3 (2)	0	24 (16)	0
Musculoskeletal pain	3 (2)	0	11 (7)	0
Anemia	7 (5)	1 (1)	30 (20)	7 (5)
Alopecia	11 (7)	0	1 (1)	0
Photosensitivity reaction	0	0	8 (5)	1 (1)

* ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.
† Two events in the crizotinib group and none in the alectinib group were reported to be related to the trial treatment.

tyrosine kinase inhibitor, was shown to be superior to platinum–pemetrexed chemotherapy in the PROFILE 1014 trial, establishing it as the standard first-line therapy for patients with *ALK*-positive NSCLC.[1] In our trial alectinib was associated with a 53% lower risk of progressive disease or death than was crizotinib (hazard ratio, 0.47; 95% CI, 0.34 to 0.65; P<0.001; 12-month event-free rate, 68.4% with alectinib vs. 48.7% with crizotinib). The results for independent review committee–assessed progression-free survival were consistent with those for the primary end point, confirming that progression-free survival was significantly longer with alectinib than with crizotinib (median progression-free survival, 25.7 months [95% CI, 19.9 to not estimable] vs. 10.4 months [95% CI, 7.7 to 14.6]; hazard ratio, 0.50 [95% CI, 0.36 to 0.70]; P<0.001). The median progression-free survival that was achieved with crizotinib in our trial (11.1 months) was consistent with that observed in the PROFILE 1014 trial (10.9 months)[1] and the PROFILE 1029 trial

(11.1 months).[13] Overall survival data from our trial are currently immature, and a follow-up analysis will be performed when approximately 50% of the patients have died. Alectinib may increase overall survival as a result of the improved control of systemic and CNS disease; however, this needs to be confirmed in a future analysis of mature data on survival events.

The results of our trial are supported by those of the J-ALEX trial (JapicCTI-132316) involving Japanese patients with *ALK*-positive advanced NSCLC not previously treated with ALK tyrosine kinase inhibitors.[14] That trial showed the superiority of alectinib over crizotinib in terms of progression-free survival (hazard ratio for disease progression or death, 0.34; 99.7% CI, 0.17 to 0.71; P<0.001; median progression-free survival, not estimable [95% CI, 20.3 months to not estimable] with alectinib vs. 10.2 months [95% CI, 8.2 to 12.0] with crizotinib).[14] The rate of CNS metastases at baseline appears higher in our trial (38 to 42%) than in other studies of first-line treatment for *ALK*-positive NSCLC (26 to 27% in the PROFILE 1014 trial and 31 to 33% in the ASCEND-4 trial), which is possibly related to the fact that we performed systematic brain imaging at baseline.[1,15]

The method of analysis of CNS end points in our trial takes into account the competing risks inherent in evaluating CNS progression (i.e., non-CNS progression and death) and was based on an assessment by the independent review committee that was conducted solely for the purpose of assessing CNS disease. The time to CNS progression was significantly longer with alectinib than with crizotinib (cause-specific hazard ratio, 0.16, 95% CI, 0.10 to 0.28; rate of events of CNS progression, 12% with alectinib and 45% with crizotinib), and the CNS results shown in this trial confirm the efficacy of alectinib in treating *ALK*-positive disease, both in patients with and patients without CNS lesions at baseline.

The safety profile of alectinib compared favorably with that of crizotinib, despite the longer duration of treatment (median, 17.9 months vs. 10.7 months), and is consistent with that reported in previous studies.[12,16] Grade 3 to 5 adverse events were more frequent with crizotinib than with alectinib. In addition, rates of adverse events leading to dose reduction, interruption, or discontinuation were lower with alectinib.

In summary, alectinib was associated with longer progression-free survival and lower toxicity than crizotinib and showed activity against CNS disease in patients with *ALK*-positive NSCLC.

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