ORIGINAL ARTICLE

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

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ABSTRACT

BACKGROUND

Brigatinib, a next-generation anaplastic lymphoma kinase (ALK) inhibitor, has robust efficacy in patients with *ALK*-positive non–small-cell lung cancer (NSCLC) that is refractory to crizotinib. The efficacy of brigatinib, as compared with crizotinib, in patients with advanced *ALK*-positive NSCLC who have not previously received an ALK inhibitor is unclear.

METHODS

In an open-label, phase 3 trial, we randomly assigned, in a 1:1 ratio, patients with advanced *ALK*-positive NSCLC who had not previously received ALK inhibitors to receive brigatinib at a dose of 180 mg once daily (with a 7-day lead-in period at 90 mg) or crizotinib at a dose of 250 mg twice daily. The primary end point was progression-free survival as assessed by blinded independent central review. Secondary end points included the objective response rate and intracranial response. The first interim analysis was planned when approximately 50% of 198 expected events of disease progression or death had occurred.

RESULTS

A total of 275 patients underwent randomization; 137 were assigned to brigatinib and 138 to crizotinib. At the first interim analysis (99 events), the median follow-up was 11.0 months in the brigatinib group and 9.3 months in the crizotinib group. The rate of progression-free survival was higher with brigatinib than with crizotinib (estimated 12-month progression-free survival, 67% [95% confidence interval {CI}, 56 to 75] vs. 43% [95% CI, 32 to 53]; hazard ratio for disease progression or death, 0.49 [95% CI, 0.33 to 0.74]; P<0.001 by the log-rank test). The confirmed objective response rate was 71% (95% CI, 62 to 78) with brigatinib and 60% (95% CI, 51 to 68) with crizotinib; the confirmed rate of intracranial response among patients with measurable lesions was 78% (95% CI, 52 to 94) and 29% (95% CI, 11 to 52), respectively. No new safety concerns were noted.

CONCLUSIONS

Among patients with *ALK*-positive NSCLC who had not previously received an ALK inhibitor, progression-free survival was significantly longer among patients who received brigatinib than among those who received crizotinib. (Funded by Ariad Pharmaceuticals; ALTA-1L ClinicalTrials.gov number, NCT02737501.)

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Rearrangements of the oncogenic anaplastic lymphoma kinase (*ALK*) gene occur in 3 to 5% of patients with non–small-cell lung cancer (NSCLC).[1-3] A previous phase 3 trial showed that progression-free survival was significantly longer among patients who received crizotinib, a first-generation ALK inhibitor, than among those who received platinum-based, double-agent chemotherapy (median progression-free survival, 10.9 months vs. 7.0 months).[4] Disease progression in the central nervous system (CNS) in patients receiving crizotinib is common, probably because of its poor brain penetration.[5-7] Progression beyond the CNS in patients receiving crizotinib and other ALK inhibitors can occur through the emergence of *ALK* mutations, which are detectable in 20% of patients who have received crizotinib and in 56% of patients who have received next-generation inhibitors. Progression also occurs in patients through other mechanisms that are not related to *ALK* mutations.[8-10]

Brigatinib (Ariad Pharmaceuticals) is a next-generation ALK inhibitor that targets a broad range of *ALK* mutations and *ROS1* rearrangements. It is also the only ALK inhibitor with activity in cell lines with mutations in the gene encoding epidermal growth factor receptor (*EGFR*).[11-14] Step-up dosing of brigatinib over a period of 7 days is used to abrogate the risk of uncommon early-onset pulmonary events.[13] In the ALK in Lung Cancer Trial of AP26113 (ALTA) involving 222 patients with disease that was refractory to crizotinib, brigatinib administered at the recommended dosing regimen of 180 mg once daily (with a 7-day lead-in period at 90 mg in 110 patients) was associated with high systemic and CNS response rates and a median progression-free survival of 16.7 months.[15-18] The same regimen was associated with similar progression-free survival (16.3 months) among patients who had received crizotinib in the phase 1–2 trial.[13,15,19] These median rates of progression-free survival are higher than those associated with other next-generation ALK inhibitors (including alectinib, ceritinib, ensartinib, and lorlatinib) among such patients.[17,19-24]

The ALK in Lung Cancer Trial of Brigatinib in 1st Line (ALTA-1L) is a phase 3 trial comparing the efficacy and safety of brigatinib with those of crizotinib in patients with *ALK*-positive NSCLC who had not received previous treatment with an ALK inhibitor. Here we report the results of the first prespecified interim analysis.

METHODS

PATIENTS

Eligible patients were at least 18 years of age, had locally advanced or metastatic NSCLC with at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,[25] and had not previously received ALK-targeted therapy. Patients with asymptomatic, untreated CNS metastases were not excluded. Patients were eligible for trial entry on the basis of locally determined ALK testing. Patients were excluded if they had previously received more than one systemic anticancer therapy regimen for advanced disease or chemotherapy or radiation therapy (other than stereotactic radiosurgery or stereotactic body radiation therapy) within 14 days before the first dose of the trial drug. Complete inclusion and exclusion criteria are provided in the trial protocol, available with the full text of this article at NEJM.org.

TRIAL OVERSIGHT

This trial was conducted in accordance with the ethical standards of the Declaration of Helsinki and the International Council for Harmonisation guidelines for Good Clinical Practice. All patients provided written informed consent. The protocol and informed-consent documents were approved by the local institutional review board or ethics committee at each site. The trial was designed by the sponsor, Ariad Pharmaceuticals, in collaboration with the first author. Data were collected and trial procedures were overseen by the trial investigators (listed in the Supplementary Appendix, available at NEJM.org). The sponsor analyzed the data, and all the authors had full access to the data and participated in the interpretation of the data. The manuscript was written by the authors with medical writing assistance paid for by the sponsor. All the authors vouch for the completeness and accuracy of the data reported and for the adherence of the trial to the protocol and statistical analysis plan.

TRIAL DESIGN

ALTA-1L is an open-label, multicenter, randomized, international, phase 3 trial conducted at 124 centers in 20 countries. Patients were stratified

according to baseline brain metastases (present or absent) and completion of at least one full cycle of previous chemotherapy for locally advanced or metastatic disease (yes or no). They were randomly assigned (in a 1:1 ratio) to receive oral brigatinib at a dose of 180 mg once daily after a 7-day lead-in period of 90 mg once daily or oral crizotinib at a dose of 250 mg twice daily.

Patients continued treatment until they had progressive disease as assessed by an independent review committee whose members were unaware of the trial-drug assignments, had unacceptable toxic effects, or had another discontinuation criterion. In the crizotinib group, crossover to brigatinib was permitted after progression assessed by means of blinded independent review (with a 10-day washout period from crizotinib). At the investigator's discretion, treatment in the brigatinib group could be continued after disease progression. Dose interruptions or reductions were permitted for treatment-related adverse events. Adverse events were categorized with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Disease assessment (according to RECIST, version 1.1) included imaging of the chest and abdomen with the use of computed tomography or magnetic resonance imaging (MRI) with contrast material and imaging of the head with the use of MRI with contrast material. Assessment was performed at screening, every 8 weeks through cycle 14 (28 days per cycle), and then every 12 weeks until the end of treatment. Two independent review committees whose members were unaware of the trial-drug assignments performed disease assessments: one for all disease according to RECIST, version 1.1,[25] and one exclusively for the evaluation of intracranial CNS end points. Responses were confirmed at least 4 weeks after the initial response.

OUTCOMES

The primary end point was progression-free survival as assessed by blinded independent review according to RECIST, version 1.1. Secondary end points included the objective response rate and intracranial response. A complete list of secondary end points is provided in the trial protocol.

STATISTICAL ANALYSIS

Interim analyses were planned after approximately 50% (99 events) and 75% (149 events) of all 198 expected events (disease progression or death) were observed. A Lan–DeMets alpha spending function with O'Brien–Fleming boundaries[26] was used to control the overall alpha level at 0.05 (two-sided). Assuming an estimated median progression-free survival of 10 months among patients who received crizotinib in sample-size calculations,[4] a total of 198 events (disease progression or death among approximately 270 patients who underwent randomization) was required for the trial to have approximately 90% power at the final analysis of the primary end point to detect a 6-month increase in progression-free survival (hazard ratio for disease progression or death, 0.625).

For the first interim analysis, the primary end point of progression-free survival was tested at a two-sided alpha level of 0.0031. Efficacy was evaluated in the intention-to treat population. Patients who received at least one dose of a trial drug constituted the safety population. For time-to-event efficacy analyses, median values and two-sided 95% confidence intervals were estimated with the use of Kaplan–Meier methods. The primary end point was compared between the brigatinib and crizotinib groups with the use of a two-sided log-rank test stratified according to the presence or absence of baseline brain metastases and the use or nonuse of previous chemotherapy in patients with locally advanced or metastatic disease.

Efficacy and safety data are reported as of February 19, 2018. Statistical analyses were performed with the use of Base 9.4 SAS/STAT software, version 13.1. Statistical methods are described further in the statistical analysis plan and in the Supplementary Methods section in the Supplementary Appendix.

RESULTS

PATIENTS

Between April 2016 and August 2017, a total of 275 patients were enrolled; 137 patients were randomly assigned to brigatinib and 138 were randomly assigned to crizotinib (Fig. 1). Two patients (1 per group) did not receive treatment but were included in the intention-to-treat analyses. Baseline factors, including sex, Eastern Cooperative Oncology Group performance-status score, use of a Food and Drug Administration–approved ALK diagnostic test, and the use of previous

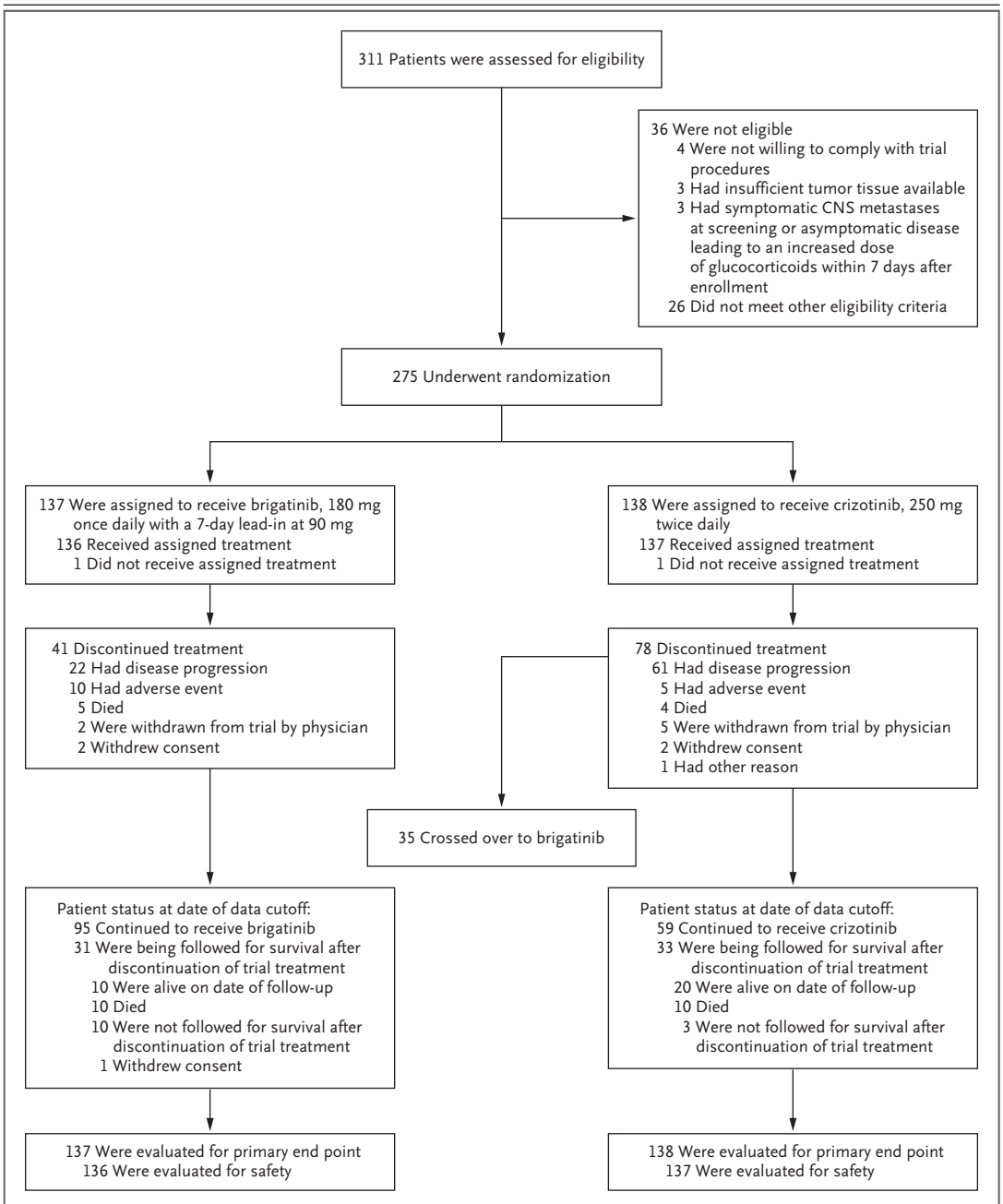

Figure 1. Screening, Enrollment, Randomization, and Follow-up.

Data reported as of the cutoff date for the first interim analysis (February 19, 2018) are shown. In the brigatinib group, 18 patients had documented disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and 4 had clinical disease progression. In the crizotinib group, 54 patients had documented disease progression according to RECIST, version 1.1, and 7 had clinical disease progression. Crossover from crizotinib to brigatinib was permitted for patients who had objective progression as assessed by blinded independent review. Patients who discontinued crizotinib for other reasons (e.g., progression according to investigator assessments) and then began to receive brigatinib were not included in the number of crossover patients. CNS denotes central nervous system.

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

Characteristic	Brigatinib (N=137)	Crizotinib (N=138)	Total (N=275)
Age — yr			
Median	58	60	59
Range	27–86	29–89	27–89
Female sex — no. (%)	69 (50)	81 (59)	150 (55)
Race — no. (%)†			
Non-Asian	78 (57)	89 (64)	167 (61)
Asian	59 (43)	49 (36)	108 (39)
ECOG performance-status score — no. (%)‡			
0 or 1	131 (96)	132 (96)	263 (96)
2	6 (4)	6 (4)	12 (4)
History of tobacco use — no. (%)			
Never smoked	84 (61)	75 (54)	159 (58)
Former smoker	49 (36)	56 (41)	105 (38)
Current smoker	4 (3)	7 (5)	11 (4)
Stage of disease at trial entry — no. (%)			
IIIB	8 (6)	12 (9)	20 (7)
IV	129 (94)	126 (91)	255 (93)
Histologic type — no. (%)			
Adenocarcinoma	126 (92)	137 (99)	263 (96)
Adenosquamous carcinoma	3 (2)	1 (1)	4 (1)
Squamous-cell carcinoma	4 (3)	0	4 (1)
Large-cell carcinoma	2 (1)	0	2 (1)
Other	2 (1)	0	2 (1)
ALK status assessed locally with the use of FDA-approved test — no. %§	123 (90)	112 (81)	235 (85)
Brain metastases — no. (%)¶	40 (29)	41 (30)	81 (29)
Previous radiotherapy to brain — no. (%)	18 (13)	19 (14)	37 (13)
Previous chemotherapy in patients with locally advanced or metastatic disease — no. (%)‖	36 (26)	37 (27)	73 (27)

* Percentages may not sum to 100 because of rounding. FDA denotes Food and Drug Administration.
† Race was reported by the investigator.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher numbers indicating increasing impairment in activities of daily living.
§ *ALK*-positive status was confirmed locally by fluorescence in situ hybridization (Vysis) or immunohistochemical assay (Ventana).
¶ The presence of brain metastases was assessed by the investigator.
‖ Previous chemotherapy was defined as completion of at least one full cycle of chemotherapy in patients with locally advanced or metastatic disease. Among 36 patients who received previous chemotherapy in the brigatinib group, 2 (6%) had a complete response, 9 (25%) had a partial response, 10 (28%) had stable disease, and 8 (22%) had progressive disease; the best response to previous chemotherapy was "other or unknown" in 7 patients (19%). Among 37 patients who received previous chemotherapy in the crizotinib group, 2 (5%) had a complete response, 8 (22%) had a partial response, 13 (35%) had stable disease, and 7 (19%) had progressive disease; the best response to previous chemotherapy was "other or unknown" in 7 patients (19%).

chemotherapy (and best response to chemotherapy) were well balanced between the groups (Table 1, and Table S1 in the Supplementary Appendix). Of 275 patients, 81 (29%) had brain metastases at baseline (29% in the brigatinib group and 30% in the crizotinib group), with

similar rates of CNS radiotherapy before enrollment.

As of February 19, 2018, a total of 95 patients (69%) in the brigatinib group and 59 patients (43%) in the crizotinib group continued to receive trial treatment, with a median follow-up of 11.0 months (range, 0 to 20.0) and 9.3 months (range, 0 to 20.9), respectively. The median duration of treatment was 9.2 months (range, 0.1 to 18.4) in the brigatinib group and 7.4 months (range, 0.1 to 19.2 months) in the crizotinib group. A total of 35 patients who discontinued crizotinib because of disease progression crossed over to brigatinib treatment as part of the trial (see the Supplementary Results section in the Supplementary Appendix).

EFFICACY

At the first interim data cutoff, a total of 99 events for the primary end point (disease progression or death) had occurred in the intention-to-treat population (36 of 137 patients [26%] in the brigatinib group and 63 of 138 patients [46%] in the crizotinib group). For blinded independent review–assessed progression-free survival, brigatinib met the prespecified threshold for statistical superiority over crizotinib (estimated 12-month progression-free survival, 67% [95% confidence interval {CI}, 56 to 75] in the brigatinib group and 43% [95% CI, 32 to 53] in the crizotinib group; hazard ratio for progression or death, 0.49 [95% CI, 0.33 to 0.74]; P<0.001 by the log-rank test) (Fig. 2A). According to investigator assessment, progression-free survival was also longer among patients who received brigatinib (estimated 12-month progression-free survival, 69% [95% CI, 59 to 76] in the brigatinib group and 40% [95% CI, 30 to 50] in the crizotinib group; hazard ratio for disease progression or death, 0.45 [95% CI, 0.30 to 0.68]). Efficacy consistently favored brigatinib across subgroups (Fig. 2B, and Fig. S1 in the Supplementary Appendix).

The confirmed objective response rate assessed by blinded independent review was 71% (95% CI, 62 to 78) in the brigatinib group and 60% (95% CI, 51 to 68) in the crizotinib group (Table 2). The overall objective response rate (objective response at one or more assessments, including confirmed and unconfirmed responses) was 76% (95% CI, 68 to 83) in the brigatinib group and 73% (95% CI, 65 to 80) in the crizotinib group. Changes from baseline in target lesions are shown in Figure 2C. The estimated rate of the 12-month duration of response in patients with a confirmed response was 78% (95% CI, 67 to 86) in the brigatinib group and 48% (95% CI, 31 to 63) in the crizotinib group (Fig. S2 in the Supplementary Appendix).

Of 275 patients, 90 had brain metastases at baseline, as assessed by blinded independent review, and 39 had measurable brain metastases (≥10 mm in diameter). The confirmed rate of intracranial objective response among patients with measurable baseline brain metastases was 78% (95% CI, 52 to 94) (14 of 18 patients) with brigatinib and 29% (95% CI, 11 to 52) (6 of 21 patients) with crizotinib (Table 2), and the over-

Figure 2 (facing page). Efficacy of Brigatinib and Crizotinib in Patients with *ALK*-Positive NSCLC Who Had Not Previously Received an ALK Inhibitor.

Panel A shows Kaplan–Meier estimates of blinded independent review–assessed progression-free survival among patients in the intention-to-treat population. Of the 137 patients in the brigatinib group, 36 (26%) had an event; of the 138 patients in the crizotinib group, 63 (46%) had an event. Tick marks indicate censored data. NR denotes not reached. Panel B shows hazard ratios for disease progression or death across prespecified patient subgroups. The hazard ratio was not calculated for patients who were current smokers (4 in the brigatinib group and 7 in the crizotinib group) because of insufficient patient numbers according to the statistical analysis plan. Values for the Eastern Cooperative Oncology Group (ECOG) performance-status score are on a 5-point scale, with higher numbers reflecting greater disability. The hazard ratio was not calculated for patients who had an ECOG performance-status score of 2 (6 in the brigatinib group and 6 in the crizotinib group) because of insufficient patient numbers according to the statistical analysis plan. The presence of brain metastases at baseline was assessed by the investigator. The "previous chemotherapy" category is previous chemotherapy in patients with locally advanced or metastatic disease. Panel C shows the best percentage change from baseline in the sum of the longest diameters of target lesions in patients who underwent follow-up imaging and could be evaluated for a response (121 patients in the brigatinib group and 122 patients in the crizotinib group). Assessments were based on blinded independent review. All trial assessments were used in these calculations. The solid line at –30% indicates the threshold for partial response according to RECIST, version 1.1. Panel D shows survival without intracranial disease progression among patients with brain metastases at baseline. Of the 43 patients in the brigatinib group, 11 (26%) had an event; of the 47 patients in the crizotinib group, 28 (60%) had an event. Tick marks indicate censored data.

Table 2. Rates of Systemic and Intracranial Objective Response, Assessed by Blinded Independent Review.*

Variable	Brigatinib	Crizotinib	Odds Ratio (95% CI)
Intention-to-treat population			
No. of patients	137	138	
Confirmed objective response			
No. of patients	97	83	
% (95% CI)	71 (62–78)	60 (51–68)	1.59 (0.96–2.62)
Complete response — no. (%)	5 (4)	7 (5)	
Partial response — no. (%)	92 (67)	76 (55)	
Rate of objective response at ≥1 assessment — % (95% CI)	76 (68–83)	73 (65–80)	1.13 (0.66–1.97)
Complete response — no. (%)	9 (7)	11 (8)	
Partial response — no. (%)	95 (69)	90 (65)	
Median duration (95% CI) of confirmed response — mo	NR (NR–NR)	11.1 (9.2–NR)	
12-mo rate (95% CI) of maintaining response	75 (63–83)	41 (26–54)	
Patients with measurable brain metastases at baseline, as assessed by blinded independent review†			
No. of patients	18	21	
Confirmed intracranial objective response			
No. of patients	14	6	
% (95% CI)	78 (52–94)	29 (11–52)	10.42 (1.90–57.05)
Intracranial complete response — no. (%)	2 (11)	0	
Intracranial partial response — no. (%)	12 (67)	6 (29)	
Rate of intracranial objective response at ≥1 assessment — % (95% CI)	83 (59–96)	33 (15–57)	9.29 (1.88–45.85)
Intracranial complete response — no. (%)	2 (11)	0	
Intracranial partial response — no. (%)	13 (72)	7 (33)	
Patients with any brain metastases at baseline, as assessed by blinded independent review			
No. of patients	43	47	
Confirmed intracranial objective response			
No. of patients	29	8	
% (95% CI)	67 (51–81)	17 (8–31)	13.00 (4.38–38.61)
Intracranial complete response — no. (%)	16 (37)	2 (4)	
Intracranial partial response — no. (%)	13 (30)	6 (13)	
Rate of intracranial objective response at ≥1 assessment — % (95% CI)	79 (64–90)	23 (12–38)	16.30 (5.32–49.92)
Intracranial complete response — no. (%)	19 (44)	4 (9)	
Intracranial partial response — no. (%)	15 (35)	7 (15)	

* NR denotes not reached.
† Measurable brain metastases were at least 10 mm in diameter.

all rate of intracranial objective response (objective response at one or more assessments, including confirmed and unconfirmed responses) in this population was 83% (95% CI, 59 to 96) with brigatinib and 33% (95% CI, 15 to 57) with crizotinib. Overall, 9% (12 of 137 patients) in the brigatinib group and 19% (26 of 138 patients) in the crizotinib group had intracranial disease progression as the first site of disease progression, alone or with concurrent systemic progression. In patients without brain metastases at baseline, 1% (1 of 94 patients) in the brigatinib group and 5% (5 of 91 patients) in the crizotinib group had intracranial disease progression as the first site of disease progression.

The estimated rate of 12-month survival with-

out intracranial disease progression among patients with baseline brain metastases was 67% (95% CI, 47 to 80) in the brigatinib group and 21% (95% CI, 6 to 42) in the crizotinib group; the estimated rate of 12-month survival without intracranial disease progression in the intention-to-treat population was 78% (95% CI, 68 to 85) in the brigatinib group and 61% (95% CI, 50 to 71) in the crizotinib group. The rate of survival without intracranial disease progression among patients with baseline brain metastases was higher in the brigatinib group than in the crizotinib group (hazard ratio for intracranial disease progression or death, 0.27; 95% CI, 0.13 to 0.54) (Fig. 2D), and the rate of survival without intracranial disease progression among patients in the intention-to-treat population was higher in the brigatinib group than in the crizotinib group (hazard ratio, 0.42; 95% CI, 0.24 to 0.70). An exploratory competing-risks analysis of intracranial disease progression, systemic progression, and death in the intention-to-treat population showed that the cause-specific hazard ratio for time to progression of intracranial disease was 0.30 (95% CI, 0.15 to 0.60) (Fig. S3 in the Supplementary Appendix).

At data cutoff, 34 patients in the intention-to-treat population had died (17 patients in the brigatinib group [12%] and 17 patients in the crizotinib group [12%]). The 1-year rate of overall survival was 85% (95% CI, 76 to 91) with brigatinib and 86% (95% CI, 77 to 91) with crizotinib (Fig. S4 in the Supplementary Appendix). The median overall survival was not reached in either group.

SAFETY

The most common (>25% of patients overall) adverse events of any grade that occurred during treatment were gastrointestinal symptoms, increased blood creatine kinase levels, and increased alanine aminotransferase levels (Table 3, and Table S2 in the Supplementary Appendix). Adverse events that occurred at a higher incidence by more than 5 percentage points with brigatinib than with crizotinib included an increased creatine kinase level (brigatinib [39%] vs. crizotinib [15%]), cough (25% vs. 16%), hypertension (23% vs. 7%), and an increased lipase level (19% vs. 12%). Adverse events that were more common with crizotinib than with brigatinib included nausea (crizotinib [56%] vs. brigatinib [26%]), diarrhea (55% vs. 49%), constipation (42% vs. 15%), peripheral edema (39% vs. 4%), vomiting (39% vs. 18%), an increased alanine aminotransferase level (32% vs. 19%), decreased appetite (20% vs. 7%), photopsia (20% vs. 1%), dysgeusia (19% vs. 4%), and visual impairment (16% vs. 0%). Grade 3 to 5 adverse events occurred in 61% of patients in the brigatinib group and in 55% of patients in the crizotinib group. No cases of pancreatitis were reported. Symptoms possibly related to increased creatine kinase levels (myalgia and muscle pain) did not differ substantially between the groups, nor were they apparently related to the grade of increased creatine kinase levels (Table 3).

Fourteen patients had adverse events leading to death within 30 days after the last dose of the trial drug (7 [5%] in the brigatinib group and 7 [5%] in the crizotinib group); none of the events were deemed by the investigators to be related to trial treatment. Interstitial lung disease or pneumonitis at any time occurred in 4% (5 of 136) of patients in the brigatinib group and 2% (3 of 137) of patients in the crizotinib group. Grade 3 or 4 interstitial lung disease or pneumonitis occurred in 3% (4 of 136) and 0.7% (1 of 137), respectively. Interstitial lung disease or pneumonitis of any grade with early onset (defined as occurring within 14 days after the initiation of treatment) was observed in 4 of 136 patients (3%) in the brigatinib group (onset on days 3 to 8) and was not observed in patients who received crizotinib. All 4 patients discontinued brigatinib after the pulmonary event, according to the protocol. Among patients who crossed over from crizotinib to brigatinib, the rate of interstitial lung disease or pneumonitis of any grade was 3% (1 of 35 patients), and it occurred on day 3.

An investigator- or protocol-mandated dose reduction for any adverse events occurred in 29% of treated patients in the brigatinib group and 21% of treated patients in the crizotinib group. The most common adverse events leading to dose reduction are shown in Table S3 in the Supplementary Appendix. A total of 12% of patients who received brigatinib and 9% of patients who received crizotinib discontinued treatment owing to adverse events.

DISCUSSION

In ALTA-1L, brigatinib, as compared with crizotinib, had superior efficacy against systemic and intracranial disease. At the first interim analysis,

Table 3. Adverse Events of Any Grade That Differed by More Than 5 Percentage Points in Frequency between Groups.

Event	Brigatinib (N=136)		Crizotinib (N=137)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	132 (97)	83 (61)	137 (100)	76 (55)
Diarrhea	67 (49)	2 (1)	75 (55)	3 (2)
Increased blood creatine kinase level*	53 (39)	22 (16)	21 (15)	2 (1)
Nausea	36 (26)	2 (1)	77 (56)	4 (3)
Cough	34 (25)	0	22 (16)	0
Hypertension	31 (23)	13 (10)	10 (7)	4 (3)
Increased alanine aminotransferase level	26 (19)	2 (1)	44 (32)	13 (9)
Increased lipase level†	26 (19)	18 (13)	16 (12)	7 (5)
Vomiting	25 (18)	1 (1)	54 (39)	3 (2)
Constipation	20 (15)	0	57 (42)	1 (1)
Increased amylase level†	19 (14)	7 (5)	9 (7)	1 (1)
Pruritus	18 (13)	1 (1)	6 (4)	1 (1)
Rash	14 (10)	0	3 (2)	0
Decreased appetite	10 (7)	1 (1)	27 (20)	4 (3)
Dermatitis acneiform	9 (7)	0	2 (1)	0
Dyspepsia	8 (6)	0	18 (13)	0
Epistaxis	8 (6)	0	0	0
Bradycardia	7 (5)	1 (1)	17 (12)	0
Peripheral edema	6 (4)	1 (1)	53 (39)	1 (1)
Dysgeusia	6 (4)	0	26 (19)	0
Upper abdominal pain	6 (4)	1 (1)	18 (13)	2 (1)
Pain in extremity	6 (4)	0	17 (12)	1 (1)
Increased blood creatinine level	3 (2)	0	19 (14)	1 (1)
Neutropenia	2 (1)	0	12 (9)	6 (4)
Pleural effusion	2 (1)	1 (1)	9 (7)	2 (1)
Photopsia	1 (1)	0	28 (20)	1 (1)
Gastroesophageal reflux disease	1 (1)	0	12 (9)	0
Visual impairment	0	0	22 (16)	0
Deep-vein thrombosis	0	0	8 (6)	0

* Myalgia was reported in 6% of patients in the brigatinib group and 4% of patients in the crizotinib group; musculoskeletal pain was reported in 4% and 6% of the patients, respectively. No myalgia or musculoskeletal pain of grade 3 or greater was reported in either group.
† No clinical cases of pancreatitis were reported in either group.

the prespecified threshold for significance for the primary end point of blinded independent review–assessed progression-free survival with brigatinib was met. With a median follow-up of 11.0 months in the brigatinib group and 9.3 months in the crizotinib group, brigatinib was associated with a 51% lower risk of disease progression or death than crizotinib (hazard ratio, 0.49; P<0.001). The rate of progression-free survival at 12 months was 67% in the brigatinib group (median not reached) and 43% in the crizotinib group (median, 9.8 months, consistent with results seen in other randomized trials).[4,27]

The hazard ratio for disease progression or death was 0.55 (95% CI, 0.34 to 0.88) among patients who had not received chemotherapy and 0.35 (95% CI, 0.14 to 0.85) among those who had received previous chemotherapy. One of the

lowest hazard ratios for disease progression or death was noted among patients with baseline brain metastases (0.20; 95% CI, 0.09 to 0.46). Although the hazard ratio for disease progression or death did not reach significance among patients without baseline brain metastases (0.72; 95% CI, 0.44 to 1.18), this interim analysis may emphasize differences in early progression. Because of the known poor efficacy of crizotinib in the CNS, CNS progression events may tend to have an earlier onset than other events; therefore, differences in early progression-free survival will be most apparent among patients with baseline brain disease.

Randomized, phase 3 trial data show that treatment options for patients with advanced NSCLC who have not previously received ALK inhibitors include crizotinib, alectinib, and ceritinib.[4,27,28] Despite shorter follow-up, these initial results for brigatinib as compared with crizotinib in patients who had not previously received ALK inhibitors appear similar to results from the phase 3 BO28984 (ALEX) trial, which compared alectinib, a second-generation ALK inhibitor, with crizotinib. Both the rates of progression-free survival and overall response were similar in the crizotinib groups in both trials.[27] Previous chemotherapy was not permitted in the ALEX trial as it was in ALTA-1L, and *ALK* status was centrally confirmed by Ventana immunohistochemical analysis.[27] Crossover from crizotinib at progression was not permitted in the ALEX trial[27] as it was in ALTA-1L.

The primary end point of the ALEX trial was investigator-assessed progression-free survival. Analysis by an independent review committee was conducted only at the primary analysis time point.[27,29] Investigator-assessed progression-free survival with a median follow-up of 17.6 to 18.6 months was associated with 12-month event-free survival rates of 68.4% (95% CI, 61.0 to 75.9) in the alectinib group and 48.7% (95% CI, 40.4 to 56.9) in the crizotinib group (hazard ratio, 0.47; 95% CI, 0.34 to 0.65; P<0.001), with no median reached in the alectinib group. The analysis of the independent review committee showed median progression-free survival of 25.7 months (95% CI, 19.9 to could not be estimated) in the alectinib group and 10.4 months (95% CI, 7.7 to 14.6) in the crizotinib group (hazard ratio, 0.53; 95% CI, 0.38 to 0.73; P<0.001).[27,30] A post hoc analysis with an additional 10 months of follow-up showed investigator-assessed median progression-free survival of 34.8 months among patients in the alectinib group (hazard ratio, 0.43; 95% CI, 0.32 to 0.58); this shows that efficacy in these patients can improve over time because of the greater emergence of plateaus in the Kaplan–Meier curve in the experimental group than in the control group.[29]

The safety profiles of brigatinib and crizotinib were consistent with those in previous studies.[4,16,27,31] Elevated creatine kinase levels were not associated with the frequency or severity of myalgia or musculoskeletal pain, and there were no cases of clinical pancreatitis. The rate of dose reduction because of any adverse events was 29% in the brigatinib group and 21% in the crizotinib group, in part reflecting more stringent protocol-mandated dose modifications for laboratory abnormalities with brigatinib as compared with crizotinib modifications, which followed standard labeling (Table S3 in the Supplementary Appendix, and the trial protocol). Early-onset pulmonary events (interstitial lung disease and pneumonitis) were observed with brigatinib but not crizotinib. The rate of these events with brigatinib among patients who had not previously received ALK inhibitors (3%) appears to be lower than among patients with disease that was refractory to crizotinib (6% in ALTA),[16] despite similar drug exposures (Fig. S5 in the Supplementary Appendix). Consistent with a multivariate analysis indicating that a longer washout period (≥7 days) from crizotinib reduced the risk of these events,[16] the rate of early-onset pulmonary events among patients who crossed over from crizotinib to brigatinib (3%), which required a 10-day minimum washout period, appeared to be lower than the rate observed in ALTA.

A key strength of this open-label trial is that progression-free survival was assessed by a blinded independent review committee, minimizing the potential for bias associated with investigator assessments. In addition, *ALK* positivity defined with the use of real-world assays was incorporated, potentially increasing the applicability of these data, and patients could have received previous chemotherapy. A limitation of this analysis is that overall survival data will be confounded by crossover of patients in the crizotinib group to brigatinib during the trial and subsequent use of other tyrosine kinase inhibitors after discontinuation of the trial by patients from either group. With further follow-up, data in both groups will mature and help to better contextu-

alize the role of brigatinib as compared with other next-generation ALK inhibitors.

In conclusion, among patients with *ALK*-positive NSCLC who had not previously received an ALK inhibitor, progression-free survival was significantly longer among those who received brigatinib than among those who received crizotinib.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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