ORIGINAL ARTICLE

First-Line Lorlatinib or Crizotinib in Advanced *ALK*-Positive Lung Cancer

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ABSTRACT

BACKGROUND

Lorlatinib, a third-generation inhibitor of anaplastic lymphoma kinase (ALK), has antitumor activity in previously treated patients with *ALK*-positive non–small-cell lung cancer (NSCLC). The efficacy of lorlatinib, as compared with that of crizotinib, as first-line treatment for advanced *ALK*-positive NSCLC is unclear.

METHODS

We conducted a global, randomized, phase 3 trial comparing lorlatinib with crizotinib in 296 patients with advanced *ALK*-positive NSCLC who had received no previous systemic treatment for metastatic disease. The primary end point was progression-free survival as assessed by blinded independent central review. Secondary end points included independently assessed objective response and intracranial response. An interim analysis of efficacy was planned after approximately 133 of 177 (75%) expected events of disease progression or death had occurred.

RESULTS

The percentage of patients who were alive without disease progression at 12 months was 78% (95% confidence interval [CI], 70 to 84) in the lorlatinib group and 39% (95% CI, 30 to 48) in the crizotinib group (hazard ratio for disease progression or death, 0.28; 95% CI, 0.19 to 0.41; P<0.001). An objective response occurred in 76% (95% CI, 68 to 83) of the patients in the lorlatinib group and 58% (95% CI, 49 to 66) of those in the crizotinib group; among those with measurable brain metastases, 82% (95% CI, 57 to 96) and 23% (95% CI, 5 to 54), respectively, had an intracranial response, and 71% of the patients who received lorlatinib had an intracranial complete response. The most common adverse events with lorlatinib were hyperlipidemia, edema, increased weight, peripheral neuropathy, and cognitive effects. Lorlatinib was associated with more grade 3 or 4 adverse events (mainly altered lipid levels) than crizotinib (in 72% vs. 56%). Discontinuation of treatment because of adverse events occurred in 7% and 9% of the patients, respectively.

CONCLUSIONS

In an interim analysis of results among patients with previously untreated advanced *ALK*-positive NSCLC, those who received lorlatinib had significantly longer progression-free survival and a higher frequency of intracranial response than those who received crizotinib. The incidence of grade 3 or 4 adverse events was higher with lorlatinib than with crizotinib because of the frequent occurrence of altered lipid levels. (Funded by Pfizer; CROWN ClinicalTrials.gov number, NCT03052608.)

Chromosomal rearrangements involving the anaplastic lymphoma kinase (*ALK*) gene define a subset of non–small-cell lung cancers (NSCLCs) that are highly sensitive to small-molecule ALK tyrosine kinase inhibitors.[1,2] One trial showed that the efficacy of the first-generation ALK inhibitor crizotinib as first-line therapy was superior to that of platinum–pemetrexed chemotherapy[3]; this finding established crizotinib as a standard first-line treatment for advanced *ALK*-positive NSCLC. Subsequently, several randomized, phase 3 studies showed that more potent second-generation ALK inhibitors, including alectinib, brigatinib, and ensartinib, were superior to crizotinib as first-line therapy[4-8]; these findings led to the adoption of second-generation inhibitors as standard first-line treatments. However, despite the improved efficacy of second-generation inhibitors, drug resistance and recurrent disease[9,10] — including central nervous system (CNS) progression, a major cause of illness and death — still develop.[11-15]

Lorlatinib (Pfizer) is a novel third-generation ALK inhibitor that is more potent than second-generation inhibitors in biochemical and cellular assays and has the broadest coverage of *ALK* resistance mutations that have been identified.[9,16,17] Lorlatinib was designed to cross the blood–brain barrier in order to achieve high exposures in the CNS.[18,19] In phase 1 and 2 studies, lorlatinib had potent antitumor activity after the failure of previous ALK inhibitors (first-generation, second-generation, or both).[19,20] In particular, lorlatinib had marked intracranial activity in previously treated patients with baseline CNS disease, including leptomeningeal disease.[11,12,20] Because of its efficacy and safety, lorlatinib is a standard treatment option for *ALK*-positive patients in whom one or more ALK inhibitors have failed.

The CROWN trial is a global, randomized, phase 3 trial comparing lorlatinib with crizotinib (the standard-of-care first-line treatment at the time of trial initiation) in patients with previously untreated advanced *ALK*-positive NSCLC. Here, we report the results of a planned interim analysis of the CROWN trial.

Methods

Patients

Eligible patients (≥18 or ≥20 years of age, according to local regulations) had histologically or cytologically confirmed locally advanced or metastatic NSCLC with *ALK* status determined by means of the Ventana ALK (D5F3) CDx immunohistochemical assay. No previous systemic treatment for metastatic disease was allowed. Patients with asymptomatic treated or untreated CNS metastases were eligible. Patients had to have at least one extracranial measurable target lesion (according to the Response Evaluation Criteria in Solid Tumours [RECIST], version 1.1) that had not been previously irradiated; an Eastern Cooperative Oncology Group performance-status score of 0 to 2 (on a 5-point scale in which higher numbers reflect greater disability); and adequate bone marrow, pancreatic, renal, and liver function (as defined in the trial protocol, available with the full text of this article at NEJM.org). All the patients provided written informed consent.

A Quick Take is available at NEJM.org

Trial Oversight

The protocol and amendments were approved by the institutional review board or independent ethics committee at each site and complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and local laws. The trial was designed by the sponsor and members of the steering committee. Data were collected by the investigators and analyzed by the sponsor. The first author wrote the first draft of the manuscript. All the authors contributed to the interpretation of the data and to the development, writing, and approval of the manuscript. All the authors had full access to the raw data and vouch for the completeness and accuracy of the data reported and for the adherence of the trial to the protocol.

Trial Design and Treatment

Patients were randomly assigned in a 1:1 ratio to receive either oral lorlatinib at a dose of 100 mg daily or oral crizotinib at a dose of 250 mg twice daily (with each drug to be taken either with or without food) in a course of treatment that was measured in cycles of 28 days. Randomization was stratified according to the presence of brain metastases (yes or no) and ethnic group (Asian or non-Asian). Per protocol, crossover between the treatment groups was not permitted.

The primary end point was progression-free survival, defined as the time from randomization to RECIST-defined disease progression (as determined by blinded independent central re-

view) or death from any cause. Secondary end points included progression-free survival as assessed by the investigator, overall survival, objective response, objective intracranial response, and safety. Treatment continued until independently assessed RECIST-defined disease progression, death, withdrawal of consent, or unacceptable toxic effects. At the investigator's discretion, patients were allowed to continue treatment after RECIST-defined progression.

ASSESSMENTS

Tumor assessments were performed at screening and then every 8 weeks (±1 week) starting from randomization until independently assessed RECIST-defined disease progression. Imaging assessments included chest, abdomen, and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) and brain MRI. MRI of the CNS was required at baseline and at each tumor assessment, regardless of the patient's baseline CNS status. The intracranial response was assessed by an independent committee using a modified version of RECIST, version 1.1.[21]

Safety assessments included adverse events, vital signs, physical examination, 12-lead electrocardiography, echocardiography with multigated acquisition scanning, and laboratory assessments. Adverse events were classified and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

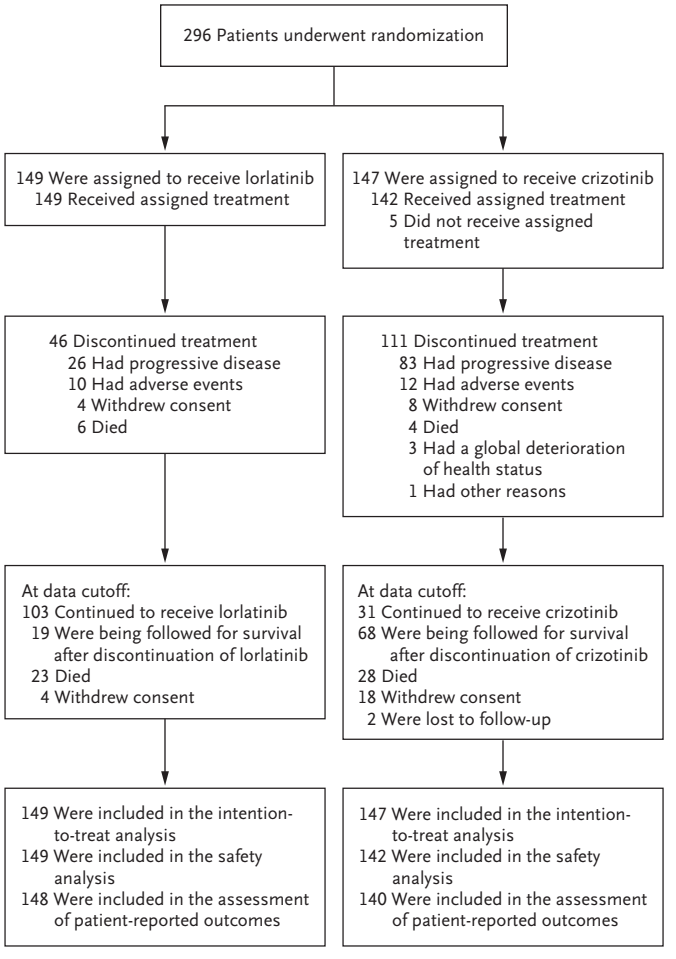


Figure 1. Randomization, Treatment, and Follow-up.

A total of 296 patients were randomly assigned to receive either lorlatinib or crizotinib. The intention-to-treat population included all the patients who underwent randomization. The as-treated population included all the patients who received at least one dose of lorlatinib or crizotinib.

STATISTICAL ANALYSIS

An interim analysis was planned after approximately 75% (133) of 177 expected events of disease progression or death had been observed. Sample-size assumptions were a median duration of progression-free survival of 18 months in the lorlatinib group and 11 months in the crizotinib group, at least 90% power to detect a hazard ratio of 0.611 with a one-sided stratified log-rank test at a significance level of 0.025 (one-sided), and a two-look, group-sequential design with a Lan–DeMets alpha-spending function with O'Brien–Fleming boundaries to determine the efficacy boundaries. For this interim analysis, the primary end point of progression-free survival was tested at a one-sided alpha level of 0.0081 based on an updated boundary corresponding to the 72% information fraction observed at the interim analysis. The data cutoff date was March 20, 2020. Overall survival was to be hierarchically tested for significance at the time of the interim or final analysis of progression-free survival, provided that the primary end point was statistically significant, favoring the lorlatinib group.

Efficacy end points were measured in the intention-to-treat population, which included all the patients who had undergone randomization. The Kaplan–Meier method was used to estimate time-to-event end points. One-sided log-rank tests, stratified according to baseline factors, were used for between-group comparisons of

progression-free survival and overall survival; stratified Cox regression models were applied to estimate hazard ratios. A one-sided stratified Cochran–Mantel–Haenszel test was used to compare the between-group difference in response. Safety evaluations were performed in the as-treated population, which included all the patients who had received at least one dose of lorlatinib or crizotinib. Safety results were not adjusted for the shorter duration of treatment in the crizotinib group.

RESULTS

PATIENTS

From May 2017 through February 2019, a total of 296 patients at 104 centers in 23 countries underwent randomization (149 to receive lorlatinib and 147 to receive crizotinib). Five patients in the crizotinib group did not receive treatment but were included in the intention-to-treat population (Fig. 1). Baseline demographic and disease characteristics were well balanced in the treatment groups (Table 1). CNS metastases at baseline, as assessed by blinded independent central review, were present in 38 patients (26%) in the lorlatinib group and 40 patients (27%) in the crizotinib group. At the time of data cutoff, 103 patients in the lorlatinib group and 31 patients in the crizotinib group were continuing to receive the assigned treatment. The median duration of follow-up for progression-free survival was 18.3 months in the lorlatinib group and 14.8 months in the crizotinib group.

EFFICACY

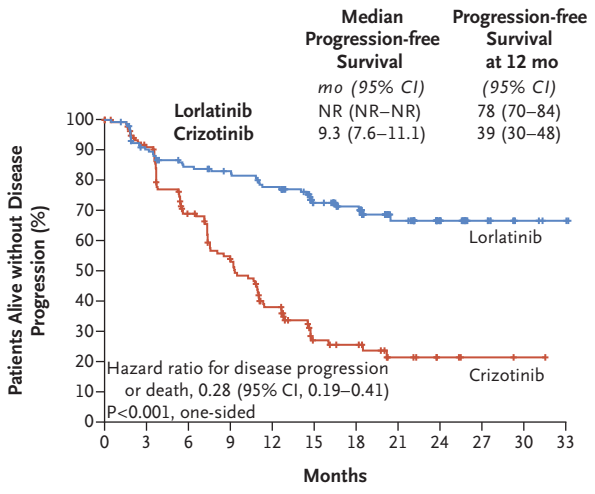
Among the 296 patients in the intention-to-treat population, 127 had had disease progression or died by the time of the data cutoff (41 of 149 patients [28%] in the lorlatinib group and 86 of 147 patients [59%] in the crizotinib group). The percentage of patients who were alive without disease progression at 12 months was 78% (95% confidence interval [CI], 70 to 84) in the lorlatinib group and 39% (95% CI, 30 to 48) in the crizotinib group (hazard ratio, 0.28; 95% CI, 0.19 to 0.41; P<0.001) (Fig. 2A). The hazard ratio favored lorlatinib over crizotinib across all prespecified patient subgroups defined according to baseline characteristics and stratification factors (Fig. S1 in the Supplementary Appendix,

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

Characteristic	Lorlatinib (N=149)	Crizotinib (N=147)
Age — yr		
Mean	59.1±13.1	55.6±13.5
Median	61	56
Interquartile range	51–69	45–66
Sex — no. (%)		
Female	84 (56)	91 (62)
Male	65 (44)	56 (38)
Race or ethnic group — no. (%)†		
White	72 (48)	72 (49)
Asian	65 (44)	65 (44)
Black	0	1 (1)
Missing	12 (8)	9 (6)
ECOG performance-status score — no. (%)‡		
0	67 (45)	57 (39)
1	79 (53)	81 (55)
2	3 (2)	9 (6)
Smoking status — no. (%)§		
Never smoked	81 (54)	94 (64)
Previous smoker	55 (37)	43 (29)
Current smoker	13 (9)	9 (6)
Current stage of disease — no. (%)		
IIIA	1 (1)	0
IIIB	12 (8)	8 (5)
IV	135 (91)	139 (95)
Other¶	1 (1)	0
Histologic type — no. (%)		
Adenocarcinoma	140 (94)	140 (95)
Adenosquamous carcinoma	6 (4)	5 (3)
Large-cell carcinoma	0	1 (1)
Squamous-cell carcinoma	3 (2)	1 (1)
Use of previous anticancer drug therapy — no. (%)‖	12 (8)	9 (6)
Previous brain radiotherapy — no. (%)	9 (6)	10 (7)
Brain metastases at baseline — no. (%)	38 (26)	40 (27)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Race or ethnic group was reported by the investigator.
‡ Eastern Cooperative Oncology Group (ECOG) scores range from 0 to 5, with higher scores indicating greater disability.
§ Smoking status was not reported for one patient in the crizotinib group.
¶ The disease stage in one patient who had locally advanced disease at trial entry was defined according to the American Joint Committee on Cancer (AJCC), version 8.0, instead of AJCC, version 7.0, as required by the protocol. This stage was therefore classified as "other."
‖ According to the protocol, previous adjuvant or neoadjuvant anticancer therapy was allowed if it had been completed more than 12 months before randomization. One patient who had received previous chemotherapy for metastatic disease was reported as having a protocol violation.

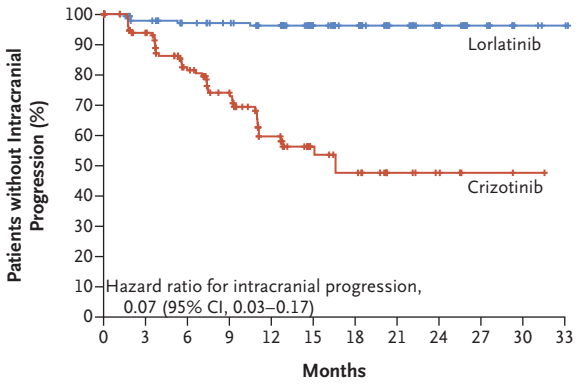
A Progression-free Survival



No. at Risk

Lorlatinib	149	129	118	113	105	73	59	33	20	11	4	2
Crizotinib	147	120	84	62	39	19	16	8	4	2	1	0

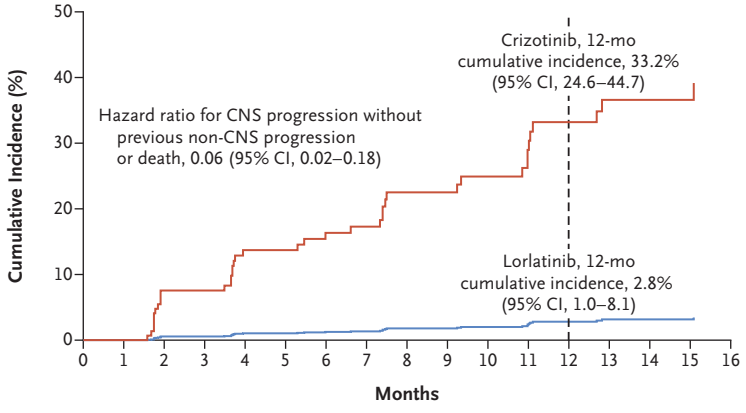
B Survival without CNS Progression



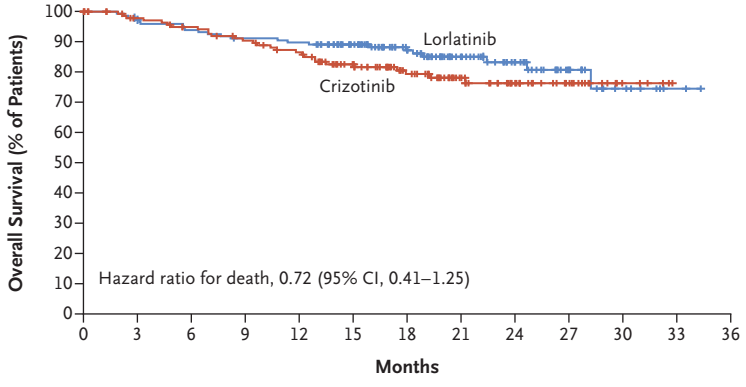
No. at Risk

Lorlatinib	149	131	122	117	110	78	65	39	25	12	4	2
Crizotinib	147	115	84	65	38	21	16	8	5	2	1	0

C Cumulative Incidence of CNS Progression as First Event



D Overall Survival



No. at Risk

Lorlatinib	149	148	141	138	135	133	131	122	101	85	63	50	38	27	13	8	4	1	0
Crizotinib	147	139	133	127	122	116	111	97	85	68	55	40	31	22	12	5	3	0	0

Figure 2 (facing page). Efficacy Outcomes in the Intention-to-Treat Population.

Panel A shows Kaplan–Meier estimates of progression-free survival, according to blinded independent central review (BICR) in the intention-to-treat population. Progression-free survival was significantly longer with lorlatinib than crizotinib; the median progression-free survival with lorlatinib was not reached. Tick marks on the survival curves indicate censoring of data. NR denotes not reached. Panel B shows Kaplan–Meier estimates of time to intracranial progression, as assessed by BICR, in the intention-to-treat population. Time to intracranial progression was defined as the time from randomization to the first objective progression of central nervous system (CNS) disease (either new brain metastases or progression of existing brain metastases). Panel C shows the cumulative incidence of CNS progression as the first event, as assessed by BICR in the intention-to-treat population. Cumulative-incidence probabilities were calculated with the use of a competing-risks approach, with values adjusted for the competing risks of non-CNS progression and death (Fig. S3 in the Supplementary Appendix). Panel D shows Kaplan–Meier curves of overall survival.

available at NEJM.org). Progression-free survival as assessed by the investigators was also significantly longer with lorlatinib than with crizotinib; the percentages of patients with progression-free survival at 12 months were 80% (95% CI, 73 to 86) and 35% (95% CI, 27 to 43), respectively (hazard ratio 0.21; 95% CI, 0.14 to 0.31) (Fig. S2).

The percentage of patients with a confirmed objective response as assessed by blinded independent central review was significantly higher with lorlatinib than with crizotinib (76% [95% CI, 68 to 83] vs. 58% [95% CI, 49 to 66]) (Table 2). A total of 70% of the patients who received lorlatinib and 27% of those who received crizotinib had a response that lasted at least 12 months. Similar responses (both the percentage of patients with a confirmed objective response and the percentage of patients with a response lasting ≥12 months) were determined by investigator assessment (Table S1).

Among the 78 patients with measurable or nonmeasurable CNS metastases at baseline, the percentage of those with a confirmed objective intracranial response as assessed by blinded independent central review was significantly higher with lorlatinib than with crizotinib (66% [95% CI, 49 to 80] vs. 20% [95% CI, 9 to 36]); 61% and 15%, respectively, had a complete intracranial response (Table 2). The percentage of patients with a duration of intracranial response of at least 12 months was 72% with lorlatinib and 0% with crizotinib. Among the 30 patients with measurable CNS metastases at baseline, 82% (95% CI, 57 to 96) in the lorlatinib group and 23% (95% CI, 5 to 54) in the crizotinib group had an intracranial response, and 71% and 8%, respectively, had a complete response (Table 2).

In the intention-to-treat population, the time to CNS progression was significantly longer with lorlatinib than with crizotinib. The percentage of patients who were alive without CNS progression at 12 months was 96% (95% CI, 91 to 98) with lorlatinib and 60% (95% CI, 49 to 69) with crizotinib (hazard ratio, 0.07; 95% CI, 0.03 to 0.17) (Fig. 2B). The cumulative incidence of CNS progression as the first event, with adjustment for the competing risks of non-CNS progression and death, was significantly lower in the lorlatinib group than in the crizotinib group. At 12 months, the cumulative incidence of CNS progression as the first event was 3% with lorlatinib and 33% with crizotinib (hazard ratio, 0.06; 95% CI, 0.02 to 0.18) (Fig. 2C).

At the time of data cutoff, overall survival data were still evolving, with deaths occurring in a total of 51 patients in the intention-to-treat population (23 patients [15%] in the lorlatinib group and 28 patients [19%] in the crizotinib group). The hazard ratio for death was 0.72 (95% CI, 0.41 to 1.25); the between-group difference in overall survival was not significant (Fig. 2D).

SAFETY

In total, 291 of 296 patients received at least one dose of lorlatinib or crizotinib. The percentage of patients who continued to receive trial treatment for at least 12 months was 76% (113 of 149) in the lorlatinib group and 35% (49 of 142) in the crizotinib group, with 69% and 22% of the patients, respectively, still receiving treatment at the time of the data cutoff. Adverse events of any grade that occurred more frequently (by more than 10 percentage points) with lorlatinib than with crizotinib included hypercholesterolemia (occurring in 70% of the patients vs. 4%), hypertriglyceridemia (in 64% vs. 6%), edema (55% vs. 39%), increased weight (38% vs. 13%), peripheral neuropathy (34% vs. 15%), cognitive

Table 2. Objective Response in the Intention-to-Treat Population and among Patients with Brain Metastases at Baseline.*

Variable	Lorlatinib	Crizotinib	Odds Ratio (95% CI)
Intention-to-treat population			
No. of patients	149	147	
Confirmed objective response			
No. of patients	113	85	
% (95% CI)	76 (68–83)	58 (49–66)	2.25 (1.35–3.89)
Complete response — no. (%)	4 (3)	0	
Partial response — no. (%)	109 (73)	85 (58)	
Stable disease — no. (%)	19 (13)	41 (28)	
Neither complete response nor progressive disease — no. (%)	3 (2)	3 (2)	
Progressive disease — no. (%)	10 (7)	7 (5)	
Could not be evaluated — no. (%)	4 (3)	11 (7)	
Median duration of response (95% CI) — mo	NE (NE–NE)	11.0 (9.0–12.9)	
Median time to tumor response (IQR) — mo	1.8 (1.7–1.9)	1.8 (1.7–1.9)	
Patients with measurable or nonmeasurable brain metastases at baseline			
No. of patients	38	40	
Confirmed CNS response			
No. of patients	25	8	
% (95% CI)	66 (49–80)	20 (9–36)	8.41 (2.59–27.23)
CNS complete response — no. (%)	23 (61)	6 (15)	
Median duration of response (95% CI) — mo	NE (NE–NE)	9.4 (6.0–11.1)	
Median time to tumor response (IQR) — mo	1.9 (1.8–3.7)	1.8 (1.7–2.7)	
Patients with measurable brain metastases at baseline			
No. of patients	17	13	
Confirmed CNS response			
No. of patients	14	3	
% (95% CI)	82 (57–96)	23 (5–54)	16.83 (1.95–163.23)
CNS complete response — no. (%)	12 (71)	1 (8)	
Median duration of response (95% CI) — mo	NE (NE–NE)	10.2 (9.4–11.1)	
Median time to tumor response (IQR) — mo	1.9 (1.8–3.5)	1.9 (1.8–1.9)	

* Responses in patients with brain metastases at baseline were assessed by blinded independent central review. An odds ratio greater than 1 indicates a better outcome with lorlatinib than with crizotinib. CI denotes confidence interval, CNS central nervous system, IQR interquartile range, and NE could not be evaluated.

effects (21% vs. 6%), anemia (19% vs. 8%), hypertension (18% vs. 2%), mood effects (16% vs. 5%), and hyperlipidemia (11% vs. 0%). Consistent with previous studies of lorlatinib, changes in cognition (including memory impairment, disturbance in attention, and amnesia) and mood (including anxiety, depression, and affect lability) were typically grade 1 and reversible with dose interruption.[19,20,22,23]

Adverse events that were more common with crizotinib than with lorlatinib included diarrhea (occurring in 52% of the patients vs. 21%), nausea (in 52% vs. 15%), vision disorder (39% vs. 18%), vomiting (39% vs. 13%), increased alanine

Table 3. Adverse Events in the Safety Population.*

Event	Lorlatinib (N=149)					Crizotinib (N=142)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
	number of patients (percent)									
Any adverse event	149 (100)	6 (4)	28 (19)	87 (58)	21 (14)	140 (99)	8 (6)	46 (32)	67 (47)	12 (8)
Hypercholesterolemia†	105 (70)	24 (16)	57 (38)	23 (15)	1 (1)	5 (4)	5 (4)	0	0	0
Hypertriglyceridemia†	95 (64)	28 (19)	37 (25)	19 (13)	11 (7)	8 (6)	5 (4)	3 (2)	0	0
Edema†	82 (55)	54 (36)	22 (15)	6 (4)	0	56 (39)	38 (27)	16 (11)	2 (1)	0
Increased weight	57 (38)	11 (7)	21 (14)	25 (17)	0	18 (13)	6 (4)	9 (6)	3 (2)	0
Peripheral neuropathy†	50 (34)	36 (24)	11 (7)	3 (2)	0	21 (15)	19 (13)	1 (1)	1 (1)	0
Cognitive effects†‡	32 (21)	20 (13)	9 (6)	3 (2)	0	8 (6)	7 (5)	1 (1)	0	0
Diarrhea	32 (21)	21 (14)	9 (6)	2 (1)	0	74 (52)	67 (47)	6 (4)	1 (1)	0
Anemia	29 (19)	16 (11)	9 (6)	4 (3)	0	11 (8)	3 (2)	4 (3)	4 (3)	0
Fatigue†	29 (19)	25 (17)	2 (1)	2 (1)	0	46 (32)	25 (18)	17 (12)	4 (3)	0
Hypertension	27 (18)	1 (1)	11 (7)	15 (10)	0	3 (2)	0	3 (2)	0	0
Vision disorder†	27 (18)	25 (17)	2 (1)	0	0	56 (39)	54 (38)	1 (1)	1 (1)	0
Increased ALT level	26 (17)	22 (15)	0	4 (3)	0	48 (34)	26 (18)	16 (11)	5 (4)	1 (1)
Constipation	26 (17)	24 (16)	2 (1)	0	0	42 (30)	30 (21)	11 (8)	1 (1)	0
Mood effects†§	24 (16)	14 (9)	8 (5)	2 (1)	0	7 (5)	4 (3)	3 (2)	0	0
Nausea	22 (15)	21 (14)	0	1 (1)	0	74 (52)	56 (39)	15 (11)	3 (2)	0
Increased AST level	21 (14)	18 (12)	0	3 (2)	0	39 (27)	30 (21)	4 (3)	5 (4)	0
Vomiting	19 (13)	16 (11)	2 (1)	1 (1)	0	55 (39)	42 (30)	11 (8)	2 (1)	0
Hyperlipidemia	16 (11)	6 (4)	7 (5)	2 (1)	1 (1)	0	0	0	0	0
Dysgeusia	8 (5)	8 (5)	0	0	0	23 (16)	20 (14)	3 (2)	0	0
Decreased appetite	5 (3)	3 (2)	2 (1)	0	0	35 (25)	23 (16)	8 (6)	4 (3)	0
Bradycardia	2 (1)	2 (1)	0	0	0	17 (12)	15 (11)	2 (1)	0	0

* Shown are adverse events that differed by more than 10 percentage points in frequency between the groups. Patients were counted only once per event. The listed events occurred after the first dose of trial treatment through the end of trial follow-up or the start of new anticancer therapy, whichever took place first. Data for all grades in the lorlatinib group are listed in decreasing order of frequency. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.
† This category comprised a cluster of adverse events that may represent similar clinical symptoms or syndromes.
‡ Cognitive effects with a frequency of at least 1% included memory impairment, disturbance in attention, confusion, amnesia, cognitive disorder, and delirium.
§ Mood effects with a frequency of at least 1% included anxiety, depression, affect lability, affective disorder, agitation, irritability, and altered mood.

aminotransferase level (34% vs. 17%), fatigue (32% vs. 19%), constipation (30% vs. 17%), increased aspartate aminotransferase level (27% vs. 14%), decreased appetite (25% vs. 3%), dysgeusia (16% vs. 5%), and bradycardia (12% vs. 1%) (Table 3).

Grade 3 or 4 adverse events occurred in 72% of the patients who received lorlatinib and 56% of those who received crizotinib (Table 3 and Table S2). The most common grade 3–4 adverse events in the lorlatinib group were elevated triglyceride levels (20%), increased weight (17%), elevated cholesterol levels (16%), and hypertension (10%). The most common grade 3–4 adverse events in the crizotinib group were laboratory abnormalities. Serious adverse events occurred in 34% of the patients in the lorlatinib group and 27% of those in the crizotinib group (Table S3). Fatal adverse events occurred in 14 patients (7 [5%] in the lorlatinib group and 7 [5%] in the crizotinib group) (Table S4).

Adverse events leading to dose interruption or

dose reduction, respectively, were reported in 49% and 21% of the patients in the lorlatinib group and in 47% and 15% of those in the crizotinib group (data on dose reductions are provided in Table S5). Adverse events leading to treatment discontinuation occurred in 7% of the patients who received lorlatinib and in 9% of those who received crizotinib (Table S6).

PATIENT-REPORTED OUTCOMES

Mean (±SE) baseline scores in measures of global quality of life were 64.6±1.82 in the lorlatinib group and 59.8±1.90 in the crizotinib group. Patients in the lorlatinib group had a significantly greater overall improvement from baseline in global quality of life than those who received crizotinib (estimated mean difference, 4.65; 95% CI, 1.14 to 8.16), although the difference was not clinically meaningful (Fig. S4A). Improvements in quality of life were seen as early as cycle 2 and were maintained over time in the lorlatinib group (Fig. S4B).

DISCUSSION

In this interim analysis of a randomized, phase 3 trial, we compared the third-generation ALK inhibitor lorlatinib with the first-generation inhibitor crizotinib in patients with previously untreated advanced *ALK*-positive NSCLC. Although crizotinib was the standard first-line therapy for advanced *ALK*-positive NSCLC[3] when the CROWN trial was initiated in 2017, it has now been supplanted by more potent second-generation ALK inhibitors.[4,5,24] In the global ALEX trial, alectinib was shown to be superior to crizotinib as first-line therapy, with a median duration of progression-free survival of 25.7 months versus 10.4 months, respectively (hazard ratio, 0.50), as assessed by an independent review committee.[4] Similarly, at the second interim analysis of the ALTA-1L (ALK in Lung Cancer Trial of Brigatinib in 1st Line) trial, progression-free survival was significantly longer among patients who received brigatinib than among those who received crizotinib, with median duration of progression-free survival of 24 months and a hazard ratio for disease progression or death of 0.49.[8] Most recently, in the eXalt3 trial, ensartinib was also shown to be superior to crizotinib, with a median duration of progression-free survival of 25.8 months and a hazard ratio for disease progression or death of 0.51.[6]

In the CROWN trial, progression-free survival was significantly longer among patients with *ALK*-positive NSCLC who received first-line lorlatinib than among those who received crizotinib. Although the length of follow-up does not allow determination of the median duration of progression-free survival, the hazard ratio for disease progression or death was 0.28, as assessed by blinded independent central review, which corresponds to a 72% lower risk of progression or death with lorlatinib than with crizotinib. Cross-trial comparisons are inherently limited because of differences in trial designs and trial populations; however, the magnitude of benefit, relative to crizotinib, appears to be at least as large for lorlatinib as for other second-generation inhibitors, all of which have been associated with an approximately 50% lower risk of progression or death than crizotinib.[4-6] The efficacy observed in the crizotinib group in the CROWN trial was similar to that observed in the crizotinib control groups in other randomized studies of next-generation inhibitors, and the median duration of follow-up in the CROWN trial was similar to that reported in the primary analysis of the global ALEX trial.[4]

Several factors may underlie the marked efficacy of lorlatinib as first-line therapy. First, multiple preclinical studies have shown that lorlatinib is more potent in inhibiting ALK than first- or second-generation inhibitors.[9,16,17] In addition, lorlatinib retains potency against all known single *ALK* resistance mutations, including *ALK* G1202R, which was the most common secondary *ALK* mutation identified after disease progression in patients who were receiving second-generation inhibitors.[9,17] Consistent with the preclinical findings, lorlatinib has had marked clinical activity in patients with tumors that progressed while they were receiving first-generation inhibitors, second-generation inhibitors, or both, with greater efficacy noted among patients with secondary *ALK* resistance mutations.[20,25] In untreated patients, lorlatinib may eliminate rare preexisting subclones harboring *ALK* resistance mutations or prevent the emergence of such resistant subclones.

Second, lorlatinib was designed to be CNS penetrant and has been shown in preclinical and

clinical studies to be highly effective in treating CNS metastases.[16,19] In a phase 2 study of lorlatinib, among patients previously treated with a second-generation inhibitor such as alectinib or brigatinib, both of which are highly CNS active, the confirmed intracranial response with lorlatinib was 53 to 56%, with a median duration of intracranial response ranging from 14.5 months to not reached.[20] Among patients previously treated with crizotinib, which has poor brain penetrance,[26] the confirmed intracranial response was even higher, at 87%.[20] The marked intracranial activity of lorlatinib after failure of first-generation ALK inhibitors, second-generation ALK inhibitors, or both suggests that as first-line therapy, lorlatinib may be particularly effective in treating and preventing brain metastases. In the CROWN trial, the intracranial response among patients with measurable brain metastases at baseline was 82%, with a complete intracranial response of 71%. In the global ALEX, ALTA-1L, and eXalt3 trials, the corresponding complete intracranial responses with alectinib, brigatinib, and ensartinib were 38%, 28%, and 27%, respectively.[4,6,8] In addition, in the CROWN trial, lorlatinib significantly decreased the cumulative incidence of CNS progression, which suggests that the prolonged progression-free survival seen with lorlatinib may be due in part to the prevention of CNS metastases.

Overall, the safety profile of lorlatinib was similar to that reported in previous studies.[19,20,27] Lorlatinib has a distinct side-effect profile as compared with other ALK inhibitors. In the patients who received lorlatinib, cognitive effects were reported in 21% and mood side effects were reported in 16%, and these side effects were predominantly low grade. As reported previously, cognitive and mood changes typically present within the first 2 months after lorlatinib administration and are managed with dose interruption and reduction.[19,20,22,23] Weight gain, which was commonly reported in patients who received lorlatinib, may be associated with increased appetite.[22] Both weight gain and cognitive and mood changes may be due to off-target inhibition of tropomyosin receptor kinase B in the CNS.[18,28] Grade 3 or 4 adverse events were more frequent with lorlatinib than with crizotinib (in 72% vs. 56%). However, more than one half of the grade 3 or 4 adverse events in the lorlatinib group were elevated levels of cholesterol, triglycerides, or both. Hypercholesterolemia and hypertriglyceridemia, the most common adverse reactions reported with lorlatinib, are usually asymptomatic and readily managed with lipid-lowering agents and dose modifications as needed (details are provided in the Management of Hyperlipidemia section in the Supplementary Appendix).[22,23] Brigatinib was associated with a similarly higher incidence of adverse events of grade 3 or higher than crizotinib (73% vs. 61%),[8] whereas alectinib showed a slightly lower incidence of grade 3 or higher adverse events than crizotinib (45% vs. 51%).[7] Despite the higher incidence of grade 3 or 4 adverse events with lorlatinib, the discontinuations of treatment because of adverse events were similar in the two groups (in 7% of the patients who received lorlatinib and 9% of those who received crizotinib). Patient-reported outcomes also supported the safety and favorable side-effect profile of lorlatinib relative to crizotinib, and patients who received lorlatinib reported a significantly greater improvement in global quality of life than those who received crizotinib.

Among patients with previously untreated, advanced *ALK*-positive NSCLC, those who received lorlatinib had significantly longer progression-free survival, a higher overall and intracranial response, and better quality of life than those who received crizotinib. The incidence of grade 3 or 4 adverse events was higher with lorlatinib than with crizotinib because of the frequent occurrence of hyperlipidemia, a known side effect of lorlatinib.

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REFERENCES

1. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming *EML4-ALK* fusion gene in non-small-cell lung cancer. Nature 2007;448:561-6.
2. Kwak EL, Bang Y-J, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non–small-cell lung cancer. N Engl J Med 2010;363:1693-703.
3. Solomon BJ, Mok T, Kim D-W, et al. First-line crizotinib versus chemotherapy in *ALK*-positive lung cancer. N Engl J Med 2014;371:2167-77.
4. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated *ALK*-positive non–small-cell lung cancer. N Engl J Med 2017;377:829-38.
5. Camidge DR, Kim HR, Ahn M-J, et al. Brigatinib versus crizotinib in *ALK*-positive non–small-cell lung cancer. N Engl J Med 2018;379:2027-39.
6. Selvaggi G, Wakelee HA, Mok T, et al. Phase III randomized study of ensartinib vs crizotinib in anaplastic lymphoma kinase (*ALK*) positive NSCLC patients: EXALT3. Presented at the International Association for the Study of Lung Cancer World Conference on Lung Cancer, Singapore, August 8, 2020. abstract.
7. Camidge DR, Dziadziuszko R, Peters S, et al. Updated efficacy and safety data and impact of the *EML4-ALK* fusion variant on the efficacy of alectinib in untreated *ALK*-positive advanced non-small cell lung cancer in the global Phase III ALEX Study. J Thorac Oncol 2019;14:1233-43.
8. Camidge DR, Kim HR, Ahn M-J, et al. Brigatinib versus crizotinib in advanced ALK inhibitor-naive *ALK*-positive non-small cell lung cancer: second interim analysis of the Phase III ALTA-1L trial. J Clin Oncol 2020 August 11 (Epub ahead of print).
9. Gainor JF, Dardaei L, Yoda S, et al. Molecular mechanisms of resistance to first- and second-generation ALK inhibitors in *ALK*-rearranged lung cancer. Cancer Discov 2016;6:1118-33.
10. Katayama R, Friboulet L, Koike S, et al. Two novel *ALK* mutations mediate acquired resistance to the next-generation ALK inhibitor alectinib. Clin Cancer Res 2014;20:5686-96.
11. Dagogo-Jack I, Oxnard GR, Fink J, et al. A phase II study of lorlatinib in patients (pts) with *ALK*-positive (ALK+) lung cancer with brain-only progression. J Clin Oncol 2020;38:Suppl 15:9595. abstract.
12. Bauer TM, Shaw AT, Johnson ML, et al. Brain penetration of lorlatinib: cumulative incidences of CNS and non-CNS pro-

gression with lorlatinib in patients with previously treated *ALK*-positive non-small-cell lung cancer. Target Oncol 2020;15:55-65.
13. Gainor JF, Chi AS, Logan J, et al. Alectinib dose escalation reinduces central nervous system responses in patients with anaplastic lymphoma kinase-positive non-small cell lung cancer relapsing on standard dose alectinib. J Thorac Oncol 2016;11:256-60.
14. Ali A, Goffin JR, Arnold A, Ellis PM. Survival of patients with non-small-cell lung cancer after a diagnosis of brain metastases. Curr Oncol 2013;20(4):e300-e306.
15. Venur VA, Ahluwalia MS. Targeted therapy in brain metastases: ready for primetime? Am Soc Clin Oncol Educ Book 2016;35:e123-e130.
16. Zou HY, Friboulet L, Kodack DP, et al. PF-06463922, an ALK/ROS1 inhibitor, overcomes resistance to first and second generation ALK inhibitors in preclinical models. Cancer Cell 2015;28:70-81.
17. Horn L, Whisenant JG, Wakelee H, et al. Monitoring therapeutic response and resistance: analysis of circulating tumor DNA in patients with ALK+ lung cancer. J Thorac Oncol 2019;14:1901-11.
18. Johnson TW, Richardson PF, Bailey S, et al. Discovery of (10*R*)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile (PF-06463922), a macrocyclic inhibitor of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) with preclinical brain exposure and broad-spectrum potency against ALK-resistant mutations. J Med Chem 2014;57:4720-44.
19. Shaw AT, Felip E, Bauer TM, et al. Lorlatinib in non-small-cell lung cancer with *ALK* or *ROS1* rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. Lancet Oncol 2017;18:1590-9.
20. Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with *ALK*-positive non-small-cell lung cancer: results from a global phase 2 study. Lancet Oncol 2018;19:1654-67.
21. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys *BRAF*-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13:1087-95.
22. Bauer TM, Felip E, Solomon BJ, et al. Clinical management of adverse events associated with lorlatinib. Oncologist 2019;24:1103-10.
23. Reed M, Rosales A-LS, Chioda MD, Parker L, Devgan G, Kettle J. Consensus recommendations for management and counseling of adverse events associated with lorlatinib: a guide for healthcare practitioners. Adv Ther 2020;37:3019-30.
24. Soria J-C, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced *ALK*-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet 2017;389:917-29.
25. Shaw AT, Solomon BJ, Besse B, et al. *ALK* resistance mutations and efficacy of lorlatinib in advanced anaplastic lymphoma kinase-positive non-small-cell lung cancer. J Clin Oncol 2019;37:1370-9.
26. Costa DB, Kobayashi S, Pandya SS, et al. CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. J Clin Oncol 2011;29(15):e443-e445.
27. Shaw AT, Solomon BJ, Chiari R, et al. Lorlatinib in advanced *ROS1*-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1-2 trial. Lancet Oncol 2019;20:1691-701.
28. Drilon A. TRK inhibitors in TRK fusion-positive cancers. Ann Oncol 2019;30:Suppl 8:viii23-viii30.