ORIGINAL ARTICLE

Crizotinib versus Chemotherapy in Advanced *ALK*-Positive Lung Cancer

Alice T. Shaw, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Kazuhiko Nakagawa, M.D., Ph.D., Takashi Seto, M.D., Lucio Crinó, M.D., Myung-Ju Ahn, M.D., Tommaso De Pas, M.D., Benjamin Besse, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Fiona Blackhall, M.D., Ph.D., Yi-Long Wu, M.D., Michael Thomas, M.D., Kenneth J. O'Byrne, M.D., Denis Moro-Sibilot, M.D., D. Ross Camidge, M.D., Ph.D., Tony Mok, M.D., Vera Hirsh, M.D., Gregory J. Riely, M.D., Ph.D., Shrividya Iyer, Ph.D., Vanessa Tassell, B.S., Anna Polli, B.S., Keith D. Wilner, Ph.D., and Pasi A. Jänne, M.D., Ph.D.

ABSTRACT

BACKGROUND

In single-group studies, chromosomal rearrangements of the anaplastic lymphoma kinase gene (*ALK*) have been associated with marked clinical responses to crizotinib, an oral tyrosine kinase inhibitor targeting ALK. Whether crizotinib is superior to standard chemotherapy with respect to efficacy is unknown.

METHODS

We conducted a phase 3, open-label trial comparing crizotinib with chemotherapy in 347 patients with locally advanced or metastatic *ALK*-positive lung cancer who had received one prior platinum-based regimen. Patients were randomly assigned to receive oral treatment with crizotinib (250 mg) twice daily or intravenous chemotherapy with either pemetrexed (500 mg per square meter of body-surface area) or docetaxel (75 mg per square meter) every 3 weeks. Patients in the chemotherapy group who had disease progression were permitted to cross over to crizotinib as part of a separate study. The primary end point was progression-free survival.

RESULTS

The median progression-free survival was 7.7 months in the crizotinib group and 3.0 months in the chemotherapy group (hazard ratio for progression or death with crizotinib, 0.49; 95% confidence interval [CI], 0.37 to 0.64; P<0.001). The response rates were 65% (95% CI, 58 to 72) with crizotinib, as compared with 20% (95% CI, 14 to 26) with chemotherapy (P<0.001). An interim analysis of overall survival showed no significant improvement with crizotinib as compared with chemotherapy (hazard ratio for death in the crizotinib group, 1.02; 95% CI, 0.68 to 1.54; P=0.54). Common adverse events associated with crizotinib were visual disorder, gastrointestinal side effects, and elevated liver aminotransferase levels, whereas common adverse events with chemotherapy were fatigue, alopecia, and dyspnea. Patients reported greater reductions in symptoms of lung cancer and greater improvement in global quality of life with crizotinib than with chemotherapy.

CONCLUSIONS

Crizotinib is superior to standard chemotherapy in patients with previously treated, advanced non–small-cell lung cancer with *ALK* rearrangement. (Funded by Pfizer; ClinicalTrials.gov number, NCT00932893.)

From Massachusetts General Hospital (A.T.S.) and Lowe Center for Thoracic Oncology and Belfer Institute for Applied Cancer Science, Dana–Farber Cancer Institute (P.A.J.), Boston; Seoul National University Hospital (D.-W.K.) and Sungkyunkwan University School of Medicine, Samsung Medical Center (M.-J.A.), Seoul, South Korea; Kinki University Faculty of Medicine, Osakasayama City, Osaka (K.N.), and National Kyushu Cancer Center, Fukuoka (T.S.) — both in Japan; Azienda Ospedale Perugia, Perugia (L.C.), and European Institute of Oncology (T.D.P.) and Pfizer Italia (A.P.), Milan — all in Italy; Institut Gustave Roussy, Villejuif (B.B.), and Thoracic Oncology Unit, Centre Hospitalier Universitaire Grenoble, Grenoble (D.M.-S.) — both in France; Peter MacCallum Cancer Centre, Melbourne, VIC, Australia (B.J.S.); Christie National Health Service Foundation Trust, Manchester, United Kingdom (F.B.); Guangdong Lung Cancer Institute, Guangdong General Hospital, Guangzhou, China (Y.-L.W.); Thoraxklinik im Universitätsklinikum Heidelberg, and Translational Lung Research Center Heidelberg (Member of German Center for Lung Research), Heidelberg, Germany (M.T.); St. James's Hospital, Dublin (K.J.O.); University of Colorado, Aurora (D.R.C.); Chinese University of Hong Kong, Shatin, China (T.M.); McGill University Health Centre, Montreal (V.H.); Memorial Sloan-Kettering Cancer Center (G.J.R.) and Pfizer Oncology (S.I.), New York; and Pfizer Oncology, La Jolla, CA (V.T., K.D.W.). Address reprint requests to Dr. Shaw at Massachusetts General Hospital Cancer Center, Yawkey 7B, 32 Fruit St., Boston, MA 02114, or at ashaw1@partners.org.

Drs. Shaw and Kim contributed equally to this article.

This article was published on June 1, 2013, at NEJM.org.

N Engl J Med 2013.
DOI: 10.1056/NEJMoa1214886

Anaplastic lymphoma kinase (ALK) is a validated tyrosine kinase target in several cancers, including non–small-cell lung cancer, anaplastic large-cell lymphoma, and pediatric neuroblastoma.[1-3] *ALK* rearrangements are found in approximately 5% of cases of non–small-cell lung cancer and define a distinct molecular subtype of lung cancer.[4-7] With an estimated 1.3 million new cases of non–small-cell lung cancer worldwide each year,[8] this translates into more than 60,000 patients with *ALK*-positive non–small-cell lung cancer annually.

Crizotinib is an oral small-molecule tyrosine kinase inhibitor targeting ALK, MET, and ROS1 tyrosine kinases.[1,9,10] In two single-group studies, crizotinib showed marked antitumor activity in patients with advanced *ALK*-positive non–small-cell lung cancer, with objective response rates of approximately 60% and a median progression-free survival of 8.1 months in one of the studies and 9.7 months in the other.[11,12] In contrast, standard single-agent chemotherapies in the general population of patients with non–small-cell lung cancer have been associated with response rates of 10% or lower and median progression-free survival of 2 to 3 months.[13-15]

To date, the activity of standard chemotherapy has not been established in *ALK*-positive non–small-cell lung cancer. Retrospective studies suggest that *ALK* rearrangements may be associated with enhanced sensitivity to pemetrexed-based chemotherapy, with durations of response similar to those observed with crizotinib.[16,17]

We conducted a randomized, controlled, open-label, phase 3 trial of crizotinib, as compared with standard chemotherapy in patients with advanced, previously treated *ALK*-positive non–small-cell lung cancer.

Methods

Patients

Patients were eligible for inclusion in the study if they had locally advanced or metastatic non–small-cell lung cancer that was positive for *ALK* rearrangements. *ALK* testing was performed centrally with the use of a break-apart fluorescence in situ hybridization assay, which has an analytic sensitivity of 100% (95% confidence interval [CI], 98 to 100) and specificity of 100% (95% CI, 97 to 100).[1] Other eligibility criteria included an age of at least 18 years, progressive disease after one prior platinum-based chemotherapy regimen, measurable disease as assessed with the use of Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,[18] and an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (with 0 indicating that the patient is fully active, 1 that the patient is ambulatory but restricted in strenuous activity, and 2 that the patient is ambulatory and capable of self-care but is unable to work[19]). Patients with stable brain metastases that had been treated previously or were untreated and asymptomatic were eligible. All patients provided written informed consent.

Study Oversight

The protocol was approved by the institutional review board or independent ethics committee at each participating site and complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws. The study was designed by the sponsor (Pfizer) together with the members of the PROFILE 1007 steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The sponsor collected the data and analyzed them in conjunction with the authors. The corresponding author wrote all the drafts of the manuscript. All the authors made the decision to submit the manuscript for publication and vouch for the accuracy and completeness of the data and for the fidelity of this report to the study protocol. Editorial support was provided by a medical writer at ACUMED (New York), who was funded by the sponsor. The protocol and statistical analysis plan are available at NEJM.org.

Study Design and Treatment

Patients were randomly assigned, in a 1:1 ratio, to receive oral crizotinib (250 mg twice daily) in a 3-week cycle or intravenous chemotherapy comprising either pemetrexed (500 mg per square meter of body-surface area) or docetaxel (75 mg per square meter) every 3 weeks. Patients who were randomly assigned to chemotherapy received pemetrexed unless their prior chemotherapy regimen contained pemetrexed or unless their tumor had predominantly squamous-cell histologic features. Patients were stratified according to ECOG performance status (0 or 1 vs. 2), the presence or absence of brain metastases, and prior or no prior therapy with epidermal growth factor receptor (EGFR) kinase inhibitors.

The primary end point was progression-free

survival, as assessed by independent radiologic review. Secondary end points included overall survival, response rate (rate of partial and complete responses), safety, and patient-reported outcomes. Treatment was continued until RECIST-defined disease progression was documented, unacceptable toxic effects developed, the patient withdrew from the study, or the patient died. Patients could continue treatment beyond RECIST-defined progression at the discretion of the investigator. Patients in the chemotherapy group with RECIST-defined progression were allowed to cross over to receive crizotinib as part of a separate study (ClinicalTrials.gov number, NCT00932451).

ASSESSMENTS

Patients underwent baseline tumor imaging, including brain and bone scanning. Tumor assessments were performed every 6 weeks until RECIST-defined disease progression. RECIST, version 1.1, was used to assess tumor responses; all scans were subject to central review by independent radiologists who were unaware of the group assignments.

Adverse events, which were classified and graded according to the Common Terminology Criteria for Adverse Events, version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf), were assessed from the time the patient provided written informed consent until at least 28 days after the last dose of study drug was administered. Patient-reported symptoms, functioning, and global quality of life were assessed at baseline, on day 1 of every cycle, and at the end of treatment with the use of a validated questionnaire, the European Organization for Research and Treatment of Cancer quality-of-life questionnaire (QLQ-C30)[20] and its corresponding module for lung cancer (QLQ-LC13).[21] Scores on these questionnaires range from 0 to 100. For symptoms, higher scores indicate greater severity of symptoms; for global quality of life, higher scores indicate better global quality of life.

STATISTICAL ANALYSIS

We estimated that with a total of 217 progression events or deaths, the study would have 90% power to detect a 56% improvement in progression-free survival with crizotinib as compared with chemotherapy (i.e., median progression-free survival of 7.0 months vs. 4.5 months), at a one-sided alpha level of 0.025. Progression-free survival was defined as the time from randomization to progression of the disease, as assessed by means of independent radiologic review, or to death. The prespecified number of progression events or deaths was reached in March 2012; the date of data cutoff was March 30, 2012. One prespecified interim analysis of overall survival was performed at the time of the final analysis of progression-free survival. For the final survival analysis, we estimate that 241 events will be required for the study to have 80% power to detect a 44% increase in overall survival; this number of events is not projected to occur until 21 months after the time of data cutoff.

Efficacy end points were analyzed mainly in the intention-to-treat population. We used the Kaplan–Meier method to estimate progression-free survival and overall survival, one-sided stratified log-rank tests to compare survival curves between the two groups, and stratified Cox regression models to estimate hazard ratios. Response rates as assessed by means of independent radiologic review were compared between the treatment groups with the use of a two-sided stratified Cochran–Mantel–Haenszel test. We evaluated efficacy end points for pemetrexed and docetaxel separately in the as-treated population, which included patients who received at least one dose of study medication.

Patient-reported outcomes were evaluated in all treated patients who had completed a baseline assessment and at least one post-baseline assessment. Repeated-measures mixed-effects modeling was performed to compare the two groups with respect to the overall change from baseline scores on the QLQ-C30 and QLQ-LC13 scales. The time to deterioration was calculated as the time from randomization to the first increase of 10 points or more (indicating worsening condition) from baseline in scores for a composite end point of chest pain, dyspnea, or cough. The time to deterioration was estimated with the use of the Kaplan–Meier method and was compared between the two groups with the use of an unstratified log-rank test.

RESULTS

PATIENTS

From February 2010 through February 2012, a total of 4967 patients were screened, of whom 347 underwent randomization — 173 to crizotinib and 174 to chemotherapy (Fig. S1 in the Supplementary Appendix). The 347 patients who underwent ran-

domization comprised the intention-to-treat population. A total of 99 patients (57%) in the chemotherapy group received pemetrexed, and 72 (41%) received docetaxel. Three patients who were randomly assigned to the chemotherapy group and 1 who was randomly assigned to the crizotinib group did not receive the assigned study treatment.

Table 1. Baseline Clinical Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	Crizotinib (N=173)	Chemotherapy (N=174)
Age — yr		
Median	51	49
Range	22–81	24–85
Age distribution — no. (%)		
<65 yr	146 (84)	151 (87)
≥65 yr	27 (16)	23 (13)
Male sex — no. (%)	75 (43)	78 (45)
Race — no. (%)†		
White	90 (52)	91 (52)
Asian	79 (46)	78 (45)
Other	4 (2)	5 (3)
Smoking status — no. (%)‡		
Never smoked	108 (62)	111 (64)
Former smoker	59 (34)	54 (31)
Current smoker	5 (3)	9 (5)
Tumor histologic type — no. (%)§		
Adenocarcinoma	164 (95)	164 (94)
Non-adenocarcinoma	5 (3)	7 (4)
ECOG performance status — no. (%)¶		
0	72 (42)	65 (37)
1	84 (49)	95 (55)
2	16 (9)	14 (8)
Extent of disease — no. (%)		
Locally advanced	7 (4)	16 (9)
Metastatic	165 (95)	158 (91)
Presence of brain metastases — no. (%)	60 (35)	60 (34)

* There were no significant differences between the groups in any of the baseline characteristics listed here.
† Race was reported by the investigators.
‡ Data were missing for one patient in the crizotinib group.
§ Data were missing for seven patients: four in the crizotinib group and three in the chemotherapy group.
¶ An Eastern Cooperative Oncology Group (ECOG) performance status of 0 indicates that the patient is fully active, 1 that the patient is ambulatory but restricted in strenuous activity, and 2 that the patient is ambulatory and capable of self-care but is unable to work. Data were missing for one patient in the crizotinib group.

At the time of data cutoff, the median follow-up for overall survival was 12.2 months in the crizotinib group and 12.1 months in the chemotherapy group.

The baseline characteristics of the patients were well balanced between the two study groups (Table 1). The majority of patients were younger than 65 years of age, had never smoked, and had adenocarcinoma of the lung — characteristics that were consistent with those of patients with *ALK*-positive non–small-cell lung cancer in prior studies.[22,23] The baseline characteristics of the patients according to the type of chemotherapy they received are shown in Table S1 in the Supplementary Appendix.

EFFICACY

Among the 347 patients in the intention-to-treat population, 227 had disease progression or died by the time of data cutoff. The median progression-free survival, as determined by independent radiologic review, was 7.7 months (95% CI, 6.0 to 8.8) in the crizotinib group, as compared with 3.0 months (95% CI, 2.6 to 4.3) in the chemotherapy group (hazard ratio for disease progression or death with crizotinib, 0.49; 95% CI, 0.37 to 0.64; P<0.001) (Fig. 1A). In subgroup analyses, there was significant improvement in progression-free survival with crizotinib as compared with pemetrexed (hazard ratio for disease progression or death, 0.59; 95% CI, 0.43 to 0.80; P<0.001) and as compared with docetaxel (hazard ratio for disease progression or death, 0.30; 95% CI, 0.21 to 0.43; P<0.001) (Fig. 1B). Progression-free survival was longer with crizotinib than with chemotherapy in patient subgroups defined according to baseline characteristics and stratification factors (Fig. S2 in the Supplementary Appendix).

In the intention-to-treat population, the response rate, as verified by means of independent radiologic review, was significantly higher in the crizotinib group than in the chemotherapy group: 65% (95% CI, 58 to 72) with crizotinib as compared with 20% (95% CI, 14 to 26) with chemotherapy (P<0.001) (Table 2). In the as-treated population, the response rate was higher with crizotinib than with either type of chemotherapy (Fig. S3 in the Supplementary Appendix): 66% (95% CI, 58 to 73) with crizotinib, as compared with 29% (95% CI, 21 to 39) with pemetrexed and 7% (95% CI, 2 to 16) with docetaxel. All the

differences in response rates between crizotinib and each type of chemotherapy were significant (P<0.001).

At the time of data cutoff, 96 deaths had occurred in the intention-to-treat population — 49 (28%) in the crizotinib group and 47 (27%) in the chemotherapy group — representing 40% of the total number of events required for the final analysis of overall survival. The median overall survival was 20.3 months (95% CI, 18.1 to not reached) with crizotinib and 22.8 months (95% CI, 18.6 to not reached) with chemotherapy (hazard ratio for death in the crizotinib group, 1.02; 95% CI, 0.68 to 1.54; P=0.54) (Fig. S4 in the Supplementary Appendix). Of the 174 patients who were randomly assigned to chemotherapy, 112 (64%) subsequently received crizotinib outside the study; 34 patients (20%) discontinued chemotherapy but did not receive crizotinib, including 13 patients who died either while receiving chemotherapy or before starting follow-up therapy (Table S2 in the Supplementary Appendix).

A total of 85 patients (49%) in the crizotinib group and 28 patients (16%) in the chemotherapy group were still receiving the study treatment at the time of data cutoff. More patients in the crizotinib group than in the chemotherapy group continued treatment beyond RECIST-defined progression of disease (58 vs. 17), and the duration of such therapy was longer with crizotinib than with chemotherapy (median, 15.9 weeks [range, 2.9 to 73.4] vs. 6.9 weeks [range, 6.0 to 42.0]).

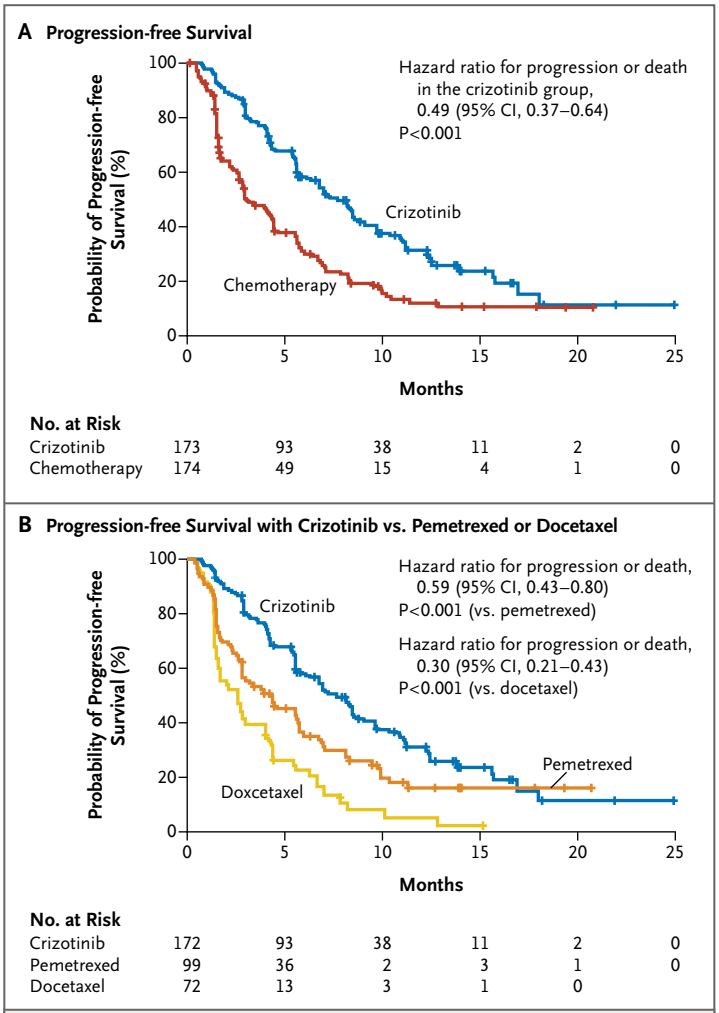

Figure 1. Progression-free Survival.

Panel A shows Kaplan–Meier estimates of progression-free survival in the intention-to-treat population. The median progression-free survival was 7.7 months with crizotinib as compared with 3.0 months with chemotherapy. Panel B shows Kaplan–Meier estimates of progression-free survival in the as-treated population (which excluded four patients who did not receive study treatment), according to the type of chemotherapy. The median progression-free survival was 7.7 months with crizotinib, as compared with 4.2 months with pemetrexed and 2.6 months with docetaxel. In both panels, tick marks on the survival curves indicate censoring of data.

SAFETY AND ADVERSE EVENTS

A total of 343 patients (the as-treated population) were included in the safety analysis. This analysis was not adjusted for the fact that patients in the crizotinib group received the assigned treatment for a longer duration than did patients in the chemotherapy group (median, 31 weeks vs. 12 weeks). The most common adverse events with crizotinib for which the incidence was at least 5% greater than that observed with chemotherapy were vision disorder (most frequently, visual impairment, photopsia, or blurred vision), diarrhea, nausea, vomiting, constipation, elevated liver aminotransferase levels, edema, upper respiratory infection, dysgeusia, and dizziness (Table 3). These events were mostly grade 1 or 2, with the exception of elevated aminotransferase levels, which were grade 3 or 4 in 27 patients (16%). The most common adverse events with chemotherapy for which the incidence was at least 5% greater than that observed with crizotinib were fatigue, alopecia, dyspnea, and rash (Table 3).

In the crizotinib group, grade 3 or 4 neutropenia occurred in 23 patients (13%), including 1 patient who had febrile neutropenia (Table S3 in the Supplementary Appendix). In the chemotherapy group, grade 3 or 4 neutropenia occurred in 33 patients (19%), including 16 patients who had febrile neutropenia.

Table 2. Summary of Responses in the Intention-to-Treat Population.*

Response	Crizotinib (N=173)	Chemotherapy (N=174)
Type of response — no. (%)		
Complete response	1 (1)	0
Partial response	112 (65)	34 (20)
Stable disease	32 (18)	63 (36)
Progressive disease	11 (6)	60 (34)
Could not be evaluated†	17 (10)	17 (10)
Rate of objective response — % (95% CI)‡	65 (58–72)	20 (14–26)
Duration of response — wk§		
Median	32.1	24.4
Range¶	2.1–72.4	3.0–43.6
Time to response — wk‖		
Median	6.3	12.6
Range	4.4–48.4	5.0–37.1

* Tumor responses were assessed with the use of Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and were confirmed by independent radiologic review.
† Responses were indeterminate in 13 patients in each group and were not available owing to early death in 4 patients in each group.
‡ P<0.001 for the comparison between the two groups.
§ The duration of response was calculated from the date of the first documentation of partial or complete response to the date of RECIST-defined progression or death, with the use of the Kaplan–Meier method.
¶ This range takes into account only patients who had subsequent disease progression or who died.
‖ The time to response was calculated from the date of randomization to the date of the first documentation of a partial or complete response.

By the time of data cutoff, 25 patients (15%) in the crizotinib group and 7 (4%) in the chemotherapy group had died from any cause during the course of the study (Table S4 in the Supplementary Appendix). The most common cause of death in both groups was disease progression, which was reported in 14 patients in the crizotinib group and 3 in the chemotherapy group. Treatment-related deaths occurred in 3 patients in the crizotinib group (with the death due to ventricular arrhythmia in 1 patient and to interstitial lung disease or pneumonitis in 2 patients), and in 1 patient in the chemotherapy group (with the death due to sepsis). In addition, in the crizotinib group, hepatic dysfunction meeting the criteria for Hy's law (a serum bilirubin level ≥3 times the upper limit of the normal range in the absence of biliary obstruction or Gilbert's syndrome)[24] developed in 1 patient, who subsequently died of hepatic failure after the data cutoff date.

Overall, more adverse events of any cause were reported in the crizotinib group than in the chemotherapy group. This increase in all-cause adverse events was still apparent after events that occurred after RECIST-defined disease progression were excluded (Table S5 in the Supplementary Appendix). The incidence of treatment-related grade 3 or 4 adverse events was similar in the two groups (33% with crizotinib and 32% with chemotherapy), as was the incidence of treatment-related serious adverse events (12% and 14% in the two groups, respectively). Treatment-related adverse events leading to permanent discontinuation of the study drug occurred in 6% and 10% of patients in the two groups, respectively.

PATIENT-REPORTED OUTCOMES

Baseline scores on the QLQ-C30 and QLQ-LC13 are summarized in Table S6 in the Supplementary Appendix. There was a significantly greater overall reduction from baseline in the symptoms of alopecia, cough, dyspnea, fatigue, chest pain, arm or shoulder pain, and pain in other parts of the body with crizotinib than with chemotherapy (P<0.001 for all comparisons, without adjustment for multiple testing) (Fig. 2A). Patients treated with crizotinib also had a significantly greater delay in the worsening of symptoms. The median time to deterioration with respect to a composite end point of three symptoms — cough, dyspnea, or chest pain — was 5.6 months with crizotinib, as compared with 1.4 months with chemotherapy (hazard ratio with crizotinib, 0.54; 95% CI, 0.40 to 0.71; P<0.001) (Fig. 2B).

There was also a significantly greater overall improvement from baseline in global quality of life among patients who received crizotinib treatment than among those who received chemotherapy (P<0.001) (Fig. 2A). In particular, in the crizotinib group a statistically significant and clinically meaningful (≥10-point) improvement from baseline in global quality of life was observed in cycle 4, and a statistically significant (although <10-point) improvement from baseline in global quality of life was observed in cycles 2 through 12 and cycle 14. In contrast, in the chemotherapy group, no significant change from baseline in global quality of life was observed at any time point. Similarly, in all domains measuring functioning, except for the domain measuring cognitive functioning, there was a significantly greater overall improvement from baseline among patients

in the crizotinib group than among patients in the chemotherapy group (Fig. S5 in the Supplementary Appendix).

DISCUSSION

We conducted a prospective, randomized, phase 3 trial comparing crizotinib therapy with standard chemotherapy in patients with advanced *ALK*-positive non–small-cell lung cancer. As compared with standard second-line chemotherapy, treatment with crizotinib resulted in significantly longer progression-free survival, significantly higher response rates, a significant reduction in symptoms, and a significant improvement in global quality of life. In this study, crizotinib was more effective than either pemetrexed or docetaxel.

The efficacy of second-line docetaxel in patients with *ALK*-positive non–small-cell lung cancer was modest, a finding that was consistent with that in previous studies involving the general population of patients with non–small-cell lung cancer.[13,15] In contrast, the response rate to pemetrexed was higher than expected — 29%, as compared with 12.8% in the general population of patients with lung adenocarcinoma who had previously been treated with chemotherapy[13,25] — though the median progression-free survival among patients in our study who received pemetrexed was only 4.2 months. Thus, patients with *ALK*-positive non–small-cell lung cancer may have a higher response rate with pemetrexed than does the general population with non–small-cell lung cancer. However, the benefit of pemetrexed is less than that originally suggested in retrospective studies[16,17] and, importantly, less than that of crizotinib, as shown in this randomized trial.

In a prespecified interim analysis, overall survival was shown to be similar in the crizotinib and chemotherapy groups. This analysis was immature, and it is likely that it was confounded by the high crossover rate among patients in the chemotherapy group. Crossover has similarly complicated the analysis of overall survival in other randomized, phase 3 studies of EGFR kinase inhibitors in patients with advanced EGFR-mutant non–small-cell lung cancer.[26-28] Despite these limitations, the median overall survival among patients in this study from the time that second-line therapy was initiated was remarkably high, at longer than 20 months, suggesting that the addition of crizotinib either before or after second-line chemotherapy may contribute to improving survival. In contrast, in a small retrospective study, the median overall survival from the time of initiation of second-line therapy among patients with *ALK*-positive non–small-cell lung cancer who had not received crizotinib was 6 months.[29]

Both crizotinib and chemotherapy were associated with toxic effects that were primarily grade 1 or 2. Two important toxic effects that were associated with crizotinib were elevated aminotransferase levels and interstitial lung disease. Treatment-related elevation of aminotransferase levels of any grade was reported in 66 patients

Table 3. Adverse Events of Any Cause.*

Adverse Event	Crizotinib (N=172)		Chemotherapy (N=171)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	no. of patients (%)			
Vision disorder†‡	103 (60)	0	16 (9)	0
Diarrhea	103 (60)	0	33 (19)	1 (1)
Nausea§	94 (55)	2 (1)	64 (37)	1 (1)
Vomiting§	80 (47)	2 (1)	30 (18)	0
Constipation	73 (42)	4 (2)	39 (23)	0
Elevated aminotransferase levels†	66 (38)	27 (16)¶	25 (15)	4 (2)
Edema†	54 (31)	0	27 (16)	0
Fatigue	46 (27)	4 (2)	57 (33)	7 (4)
Upper respiratory infection†	44 (26)	0	22 (13)	1 (<1)
Dysgeusia	44 (26)	0	16 (9)	0
Dizziness†	37 (22)	1 (1)	14 (8)	0
Dyspnea†‖	23 (13)	7 (4)	32 (19)	5 (3)
Rash	15 (9)	0	29 (17)	0
Alopecia	14 (8)	0	35 (20)	0

* Adverse events are listed here if they were reported in 15% or more of patients in either treatment group and if there was at least a 5% difference between the two groups.
† This item comprised a cluster of adverse events that may represent similar clinical symptoms or syndromes.
‡ The category of vision disorder included (in descending order of frequency) visual impairment, photopsia, blurred vision, vitreous floaters, halo vision or photophobia, chromatopsia or diplopia, and reduced visual acuity.
§ The use of antiemetic agents was significantly higher in the chemotherapy group than in the crizotinib group (67% vs. 20%).
¶ Included is one case that met the criteria for Hy's law (a serum bilirubin level of ≥3 times the upper limit of the normal range in the absence of biliary obstruction or Gilbert's syndrome), with grade 5 hepatic failure occurring after the data cutoff date.
‖ One case of grade 5 dyspnea was reported in each treatment group (<1% of patients in each group).

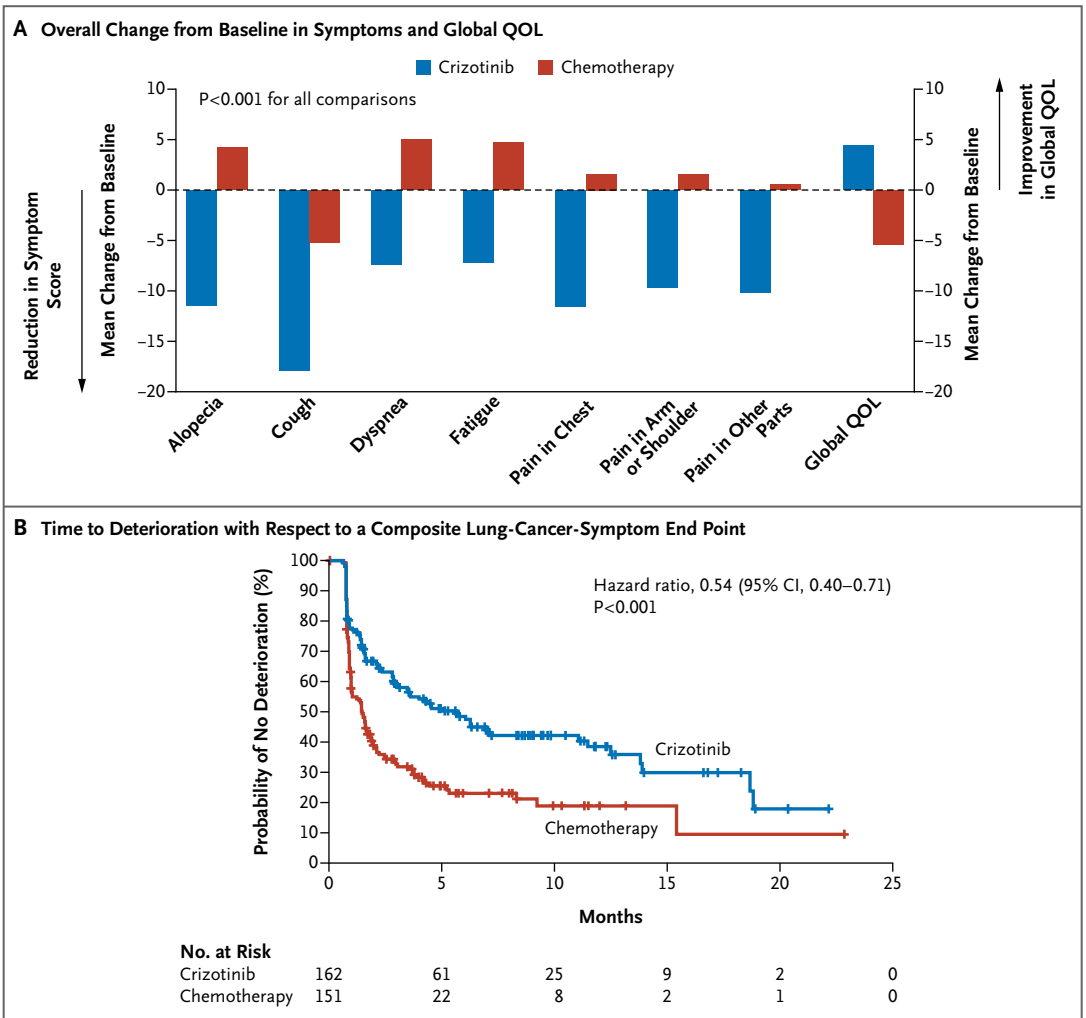

Figure 2. Patient-Reported Outcomes.

Patient-reported outcomes were assessed with the use of the European Organization for Research and Treatment of Cancer quality-of-life questionnaire (QLQ-C30) and the corresponding module for lung cancer (QLQ-LC13). The rates of completion of questionnaires ranged from 75% to 100% across cycles in both treatment groups. Panel A shows the overall change from baseline in the symptoms of alopecia, cough, dyspnea, fatigue, chest pain, arm or shoulder pain, and pain in other parts of the body, as well as in global quality-of-life (QOL) scores. Scores on the questionnaires range from 0 to 100. For symptoms, higher scores indicate greater severity of symptoms, and hence negative changes (downward bars) indicate improvement from baseline; for global quality of life, higher scores indicate better global quality of life, and hence positive changes (upward bars) indicate improvement from baseline. These analyses were based on a repeated-measures mixed-effects model with an intercept, treatment, treatment-by-time interaction, and subscale baseline score. The P values (which have not been adjusted for multiple testing) are for the between-group comparison of the overall change from baseline, as calculated with the use of repeated-measure analyses. Panel B shows Kaplan–Meier estimates of the time to deterioration with respect to a composite end point of three symptoms — cough, dyspnea, or chest pain. The median time to deterioration was 5.6 months with crizotinib and 1.4 months with chemotherapy.

(38%) in the crizotinib group, including 27 (16%) with grade 3 or 4 elevated levels; in 1 patient, concurrent elevations in bilirubin levels not related to cholestasis progressed to fatal hepatic failure. In two earlier studies of crizotinib, the incidence of elevated aminotransferase levels of grade 3 or 4 were lower, at 7% and 9%.[11,12] Although interstitial lung disease is much less common than elevated aminotransferase levels, it is a known and worrisome adverse event associated

with crizotinib. In this study, 3 patients in the crizotinib group (2%) had treatment-related interstitial lung disease of grade 3 or higher; two of the cases were fatal. Across all crizotinib studies, including this one,[11,12] the estimated incidence of treatment-related interstitial lung disease of grade 3 or higher is 1%, an incidence similar to that reported with EGFR kinase inhibitors in clinical studies.[30]

Although the incidence of treatment-related serious adverse events was similar in the crizotinib and chemotherapy groups, significantly more adverse events of any cause were observed in the crizotinib group. Two factors may have contributed to this finding. First, the duration of study treatment was significantly longer with crizotinib than with chemotherapy, and the safety analysis was not adjusted to take into account this difference in treatment durations. Second, significantly more patients in the crizotinib group continued treatment beyond RECIST-defined progression of disease, and the duration of such therapy was longer with crizotinib than with chemotherapy. These differences may have resulted in an imbalance between the two groups that could account in part for the increased incidence of all-cause adverse events seen with crizotinib (Table S5 in the Supplementary Appendix).

In conclusion, this study showed that crizotinib, as compared with chemotherapy, prolonged progression-free survival, increased response rates, and improved the quality of life in patients with advanced, previously treated *ALK*-positive non–small-cell lung cancer. The apparent lack of a survival benefit probably reflects the confounding effects of crossover, effects that have been observed in other randomized trials of molecularly targeted agents in patients with non–small-cell lung cancer.

Supported by Pfizer.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the participating patients and their families; the network of investigators (listed in the Supplementary Appendix, available at NEJM.org), research nurses, study coordinators, and operations staff; and Wendy Sacks at ACUMED (New York) for editorial assistance.

REFERENCES

1. 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. [Erratum, N Engl J Med 2011;364:588.]
2. Gambacorti-Passerini C, Messa C, Pogliani EM. Crizotinib in anaplastic large-cell lymphoma. N Engl J Med 2011; 364:775-6.
3. Mosse YP, Balis FM, Lim MS, et al. Efficacy of crizotinib in children with relapsed/refractory ALK-driven tumors including anaplastic large cell lymphoma and neuroblastoma: a Children's Oncology Group phase 1 consortium study. Presented at the Annual Meeting of the American Society of Clinical Oncology, Chicago, June 1–5, 2012. abstract.
4. 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.
5. Rikova K, Guo A, Zeng Q, et al. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. Cell 2007;131:1190-203.
6. Camidge DR, Doebele RC. Treating ALK-positive lung cancer — early successes and future challenges. Nat Rev Clin Oncol 2012;9:268-77.
7. Blackhall FH, Peters S, Kerr KM, et al. Prevalence and clinical outcomes for patients with ALK gene rearrangement in Europe: preliminary results from the European Thoracic Oncology Platform Lungscape Project. Ann Oncol 2012; 23:Suppl 9:ix73-ix94.
8. Bray F, Ren JS, Masuyer E, Ferlay J. Estimates of global cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer 2013;132:1133-45.
9. Ou SH, Kwak EL, Siwak-Tapp C, et al. Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification. J Thorac Oncol 2011;6:942-6.
10. Bergethon K, Shaw AT, Ou S-HI, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol 2012;30:863-70.
11. Camidge DR, Bang YJ, Kwak EL, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol 2012;13:1011-9.
12. Kim D-W, Ahn M-J, Shi Y, et al. Results of a global phase II study with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC). Presented at the Annual Meeting of the American Society of Clinical Oncology, Chicago, June 1–5, 2012. abstract.
13. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589-97.
14. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non–small-cell lung cancer. N Engl J Med 2005;353:123-32.
15. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095-103.
16. Camidge DR, Kono SA, Lu X, et al. Anaplastic lymphoma kinase gene rearrangements in non-small cell lung cancer are associated with prolonged progression-free survival on pemetrexed. J Thorac Oncol 2011;6:774-80.
17. Lee JO, Kim TM, Lee SH, et al. Anaplastic lymphoma kinase translocation: a predictive biomarker of pemetrexed in patients with non-small cell lung cancer. J Thorac Oncol 2011;6:1474-80.
18. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45: 228-47.
19. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.
20. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use

in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365-76.
21. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. Eur J Cancer 1994;30A:635-42.
22. Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol 2009;27:4247-53.
23. Wong DW, Leung EL, So KK, et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer 2009;115:1723-33.
24. Reuben A. Hy's law. Hepatology 2004;39:574-8.
25. Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies. Oncologist 2009; 14:253-63.
26. Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J Clin Oncol 2011;29:2866-74.
27. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non–small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380-8.
28. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239-46.
29. Shaw AT, Yeap BY, Solomon BJ, et al. Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis. Lancet Oncol 2011;12:1004-12.
30. Peerzada MM, Spiro TP, Daw HA. Pulmonary toxicities of tyrosine kinase inhibitors. Clin Adv Hematol Oncol 2011; 9:824-36.