The New England Journal of Medicine

ORIGINAL ARTICLE

First-Line Crizotinib versus Chemotherapy in *ALK*-Positive Lung Cancer

Benjamin J. Solomon, M.B., B.S., Ph.D., Tony Mok, M.D., Dong-Wan Kim, M.D., Ph.D., Yi-Long Wu, M.D., Kazuhiko Nakagawa, M.D., Ph.D., Tarek Mekhail, M.D., Enriqueta Felip, M.D., Ph.D., Federico Cappuzzo, M.D., Jolanda Paolini, B.Sc., Tiziana Usari, B.Sc., Shrividya Iyer, Ph.D., Arlene Reisman, M.P.H., Keith D. Wilner, Ph.D., Jennifer Tursi, M.Sc., and Fiona Blackhall, M.D., Ph.D., for the PROFILE 1014 Investigators*

ABSTRACT

BACKGROUND

The efficacy of the ALK inhibitor crizotinib as compared with standard chemotherapy as first-line treatment for advanced *ALK*-positive non–small-cell lung cancer (NSCLC) is unknown.

METHODS

We conducted an open-label, phase 3 trial comparing crizotinib with chemotherapy in 343 patients with advanced *ALK*-positive nonsquamous NSCLC who had received no previous systemic treatment for advanced disease. Patients were randomly assigned to receive oral crizotinib at a dose of 250 mg twice daily or to receive intravenous chemotherapy (pemetrexed, 500 mg per square meter of body-surface area, plus either cisplatin, 75 mg per square meter, or carboplatin, target area under the curve of 5 to 6 mg per milliliter per minute) every 3 weeks for up to six cycles. Crossover to crizotinib treatment after disease progression was permitted for patients receiving chemotherapy. The primary end point was progression-free survival as assessed by independent radiologic review.

RESULTS

Progression-free survival was significantly longer with crizotinib than with chemotherapy (median, 10.9 months vs. 7.0 months; hazard ratio for progression or death with crizotinib, 0.45; 95% confidence interval [CI], 0.35 to 0.60; P<0.001). Objective response rates were 74% and 45%, respectively (P<0.001). Median overall survival was not reached in either group (hazard ratio for death with crizotinib, 0.82; 95% CI, 0.54 to 1.26; P=0.36); the probability of 1-year survival was 84% with crizotinib and 79% with chemotherapy. The most common adverse events with crizotinib were vision disorders, diarrhea, nausea, and edema, and the most common events with chemotherapy were nausea, fatigue, vomiting, and decreased appetite. As compared with chemotherapy, crizotinib was associated with greater reduction in lung cancer symptoms and greater improvement in quality of life.

CONCLUSIONS

Crizotinib was superior to standard first-line pemetrexed-plus-platinum chemotherapy in patients with previously untreated advanced *ALK*-positive NSCLC. (Funded by Pfizer; PROFILE 1014 ClinicalTrials.gov number, NCT01154140.)

From Peter MacCallum Cancer Centre, Melbourne, VIC, Australia (B.J.S.); State Key Laboratory of South China, Hong Kong Cancer Institute, Department of Clinical Oncology, Chinese University of Hong Kong, Shatin (T. Mok), and Guangdong Lung Cancer Institute, Guangzhou (Y.-L.W.) — both in China; Seoul National University Hospital, Seoul, South Korea (D.-W.K.); Kinki University, Osaka, Japan (K.N.); Florida Hospital Cancer Institute, Orlando (T. Mekhail); Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona (E.F.); Istituto Toscano Tumori, Livorno (F.C.), and Pfizer Oncology, Milan (J.P., T.U., J.T.) — both in Italy; Pfizer Oncology (S.I.) and Pfizer Global Innovative Pharma Business (A.R.) — both in New York; Pfizer Oncology, La Jolla, CA (K.D.W.); and the Christie Hospital and Institute of Cancer Sciences, Manchester University, Manchester, United Kingdom (F.B.). Address reprint requests to Dr. Solomon at the Department of Medical Oncology, Peter MacCallum Cancer Centre, St. Andrew's Pl., East Melbourne, VIC 3002, Australia; or at ben.solomon@petermac.org.

*A complete list of the investigators in the PROFILE 1014 trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Solomon and Mok contributed equally to this article.

This article was updated on October 15, 2015, at NEJM.org.

N Engl J Med 2014;371:2167-77.
DOI: 10.1056/NEJMoa1408440

Rearrangements of the anaplastic lymphoma kinase (*ALK*) gene are present in 3 to 5% of non–small-cell lung cancers (NSCLCs).[1,2] They define a distinct subgroup of NSCLC that typically occurs in younger patients who have never smoked or have a history of light smoking and that has adenocarcinoma histologic characteristics.[3-5]

Crizotinib is an oral small-molecule tyrosine kinase inhibitor of ALK, MET, and ROS1 kinases.[6] In phase 1 and 2 studies, crizotinib treatment resulted in objective tumor responses in approximately 60% of patients with *ALK*-positive NSCLC and in progression-free survival of 7 to 10 months.[7-9] In a randomized phase 3 trial involving patients with advanced *ALK*-positive NSCLC who had received previous platinum-based chemotherapy, crizotinib showed efficacy superior to that of single-agent second-line chemotherapy with either pemetrexed or docetaxel.[10] However, the efficacy of crizotinib as initial treatment for patients with newly diagnosed advanced *ALK*-positive NSCLC as compared with the existing standard-of-care, platinum-based double-agent chemotherapy,[11,12] is unknown.

We report the results of an ongoing international, multicenter, randomized, open-label, phase 3 study (PROFILE 1014) that compares crizotinib treatment with pemetrexed-plus-platinum chemotherapy with respect to efficacy, safety, and patient-reported outcomes in patients with previously untreated advanced *ALK*-positive NSCLC.

Methods

Patients

Patients were eligible for enrollment if they had histologically or cytologically confirmed locally advanced, recurrent, or metastatic nonsquamous NSCLC that was positive for an *ALK* rearrangement (as determined centrally with the use of a Vysis ALK Break Apart FISH Probe Kit [Abbott Molecular])[7,13] and if they had received no previous systemic treatment for advanced disease. Other eligibility criteria included an age of 18 years or older; measurable disease as assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1[14] (summarized in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org); an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (on a scale of 0 to 5, with 0 indicating that the patient is asymptomatic and higher numbers indicating increasing disability)[15]; and adequate hepatic, renal, and bone marrow function (as defined in the study protocol). Patients with treated brain metastases were eligible if the metastases were neurologically stable for at least 2 weeks before enrollment and the patient had no ongoing requirement for glucocorticoids. All patients provided written informed consent before enrollment.

Study Oversight

The protocol was approved by the institutional review board or independent ethics committee at each participating center 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) and by members of the PROFILE 1014 steering committee (see the Supplementary Appendix). The sponsor collected and analyzed the data in conjunction with the authors, all of whom had full access to the data. The manuscript was written by the first two authors, with medical writing support from ACUMED (Tytherington, United Kingdom, and New York) funded by the sponsor. All the authors vouch for the accuracy and completeness of the data and for the fidelity of this report to the study protocol. 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, at a dose of 250 mg twice daily, or intravenous chemotherapy (pemetrexed, at a dose of 500 mg per square meter of body-surface area, plus either cisplatin, at a dose of 75 mg per square meter, or carboplatin, target area under the curve of 5 to 6 mg per milliliter per minute) administered every 3 weeks for a maximum of six cycles. The choice of platinum chemotherapy was made by the investigator. Randomization was stratified according to ECOG performance status (0 or 1 vs. 2), Asian or non-Asian race, and presence or absence of brain metastases. Treatment was continued until RECIST-defined disease progression, development of unacceptable toxic effects, death, or withdrawal of consent. Continuation of crizotinib beyond disease progression was allowed for patients who had been randomly assigned to crizotinib if the patient was perceived by the investigator to be having clinical benefit.

Patients in the chemotherapy group who had disease progression as confirmed by independent radiologic review could cross over to crizotinib treatment if safety screening criteria were met.

The primary end point was progression-free survival (the time from randomization to RECIST-defined progression, as assessed by independent radiologic review, or death). Secondary end points included the objective response rate, overall survival, safety, and patient-reported outcomes.

ASSESSMENTS

Tumor assessment was performed during screening (within 28 days before randomization), every 6 weeks during treatment, and at the post-treatment follow-up visits (which were scheduled every 6 weeks) until RECIST-defined progression. For patients who crossed over to crizotinib treatment or continued crizotinib treatment beyond progression, assessments continued to be performed every 12 weeks. Brain or bone lesions that were detected at the time of screening were evaluated in all subsequent tumor assessments (i.e., every 6 weeks). In all patients, brain and bone scanning was repeated every 12 weeks to monitor for new lesions. All scans were submitted for central independent radiologic review by radiologists who were unaware of the group assignments.

Adverse events were classified and graded according to Common Terminology Criteria for Adverse Events, version 4.0. Patient-reported outcomes were assessed with the use of the European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (QLQ-C30),[16,17] the corresponding lung cancer module (QLQ-LC13),[18] and the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D).[19]

STATISTICAL ANALYSIS

We estimated that with 229 events of progression or death, the study would have 85% power to detect a 50% improvement in progression-free survival with crizotinib versus chemotherapy (from 6 months to 9 months), at a one-sided alpha level of 0.025. The prespecified number of events for the primary end point was reached in November 2013; the data cutoff date was November 30, 2013. Efficacy end points were measured in the intention-to-treat population, which included all patients who underwent randomization. The Kaplan–Meier method was used to estimate time-to-event end points. Two-sided log-rank tests stratified according to baseline stratification factors were used for between-group comparisons of progression-free survival and overall survival; stratified Cox regression models were applied to estimate hazard ratios. As prespecified in the protocol, overall survival was also analyzed with the rank-preserving structural failure time model[20-22] to explore the effect of crossover to crizotinib in the chemotherapy group. All analyses in the chemotherapy group, with the exception of the analysis of overall survival, included only data collected before crossover to crizotinib. We used a two-sided stratified Cochran–Mantel–Haenszel test to compare the objective response rate between treatment groups. Safety evaluations were performed in the as-treated population, which included all patients who received at least one dose of study medication. Safety results were not adjusted for the shorter duration of treatment in the chemotherapy group. Patient-reported outcomes were evaluated in patients in the intention-to-treat population who also had a baseline assessment and at least one post-baseline assessment. Additional details of the statistical methods are provided in the Supplementary Appendix.

RESULTS

PATIENTS

Between January 2011 and July 2013, a total of 343 patients underwent randomization — 172 to crizotinib and 171 to chemotherapy (intention-to-treat population) (Fig. S1 in the Supplementary Appendix). Three patients underwent randomization but received no study treatment, leaving 340 patients in the as-treated population — 171 patients in the crizotinib group and 169 in the chemotherapy group (with 91 patients receiving pemetrexed–cisplatin and 78 receiving pemetrexed–carboplatin). At the time of data cutoff, the median duration of follow-up for overall survival was 17.4 months for patients assigned to crizotinib and 16.7 months for those assigned to chemotherapy. The baseline characteristics in the intention-to-treat population were well balanced between the groups (Table 1).

EFFICACY

The median progression-free survival was 10.9 months (95% confidence interval [CI], 8.3 to 13.9) among patients in the crizotinib group, as compared with 7.0 months (95% CI, 6.8 to 8.2) among patients in the chemotherapy group (hazard ratio

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

Characteristic	Crizotinib (N=172)	Chemotherapy (N=171)
Age — yr		
Median	52	54
Range	22–76	19–78
Male sex — no. (%)	68 (40)	63 (37)
Race — no. (%)†		
White	91 (53)	85 (50)
Asian	77 (45)	80 (47)
Other	4 (2)	6 (4)
Smoking status — no. (%)		
Never smoked	106 (62)	112 (65)
Former smoker	56 (33)	54 (32)
Current smoker	10 (6)	5 (3)
Histologic characteristic of tumor — no. (%)		
Adenocarcinoma	161 (94)	161 (94)
Nonadenocarcinoma	11 (6)	10 (6)
ECOG performance status — no. (%)‡		
0 or 1	161 (94)	163 (95)
2	10 (6)	8 (5)
Extent of disease — no. (%)		
Locally advanced	4 (2)	3 (2)
Metastatic	168 (98)	168 (98)
Time since first diagnosis — mo		
Median	1.2	1.2
Range	0–114.0	0–93.6
Brain metastases present — no. (%)	45 (26)	47 (27)

* There were no significant differences between the groups in any of the characteristics listed in this table.
† Race was self-reported.
‡ The Eastern Cooperative Oncology Group (ECOG) performance status was assessed at the time of screening; the score was not reported for one patient in the crizotinib group. Scores range from 0 to 5, with higher scores indicating increasing disability; an 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.

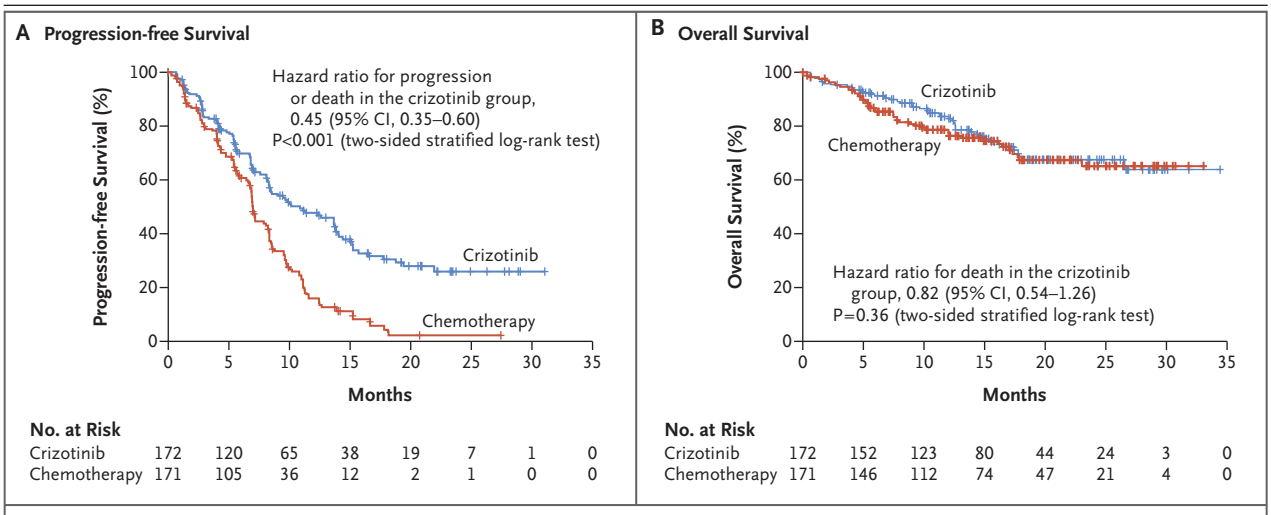
Figure 1 (facing page). Progression-free and Overall Survival.

Panel A shows Kaplan–Meier estimates of progression-free survival in the intention-to-treat population. There were 100 events of progression or death with crizotinib (89 progression events as assessed by independent radiologic review and 11 deaths without documented progression) and 137 events with chemotherapy (132 progression events as assessed by independent radiologic review and 5 deaths without documented progression). The median progression-free survival was 10.9 months with crizotinib as compared with 7.0 months with chemotherapy. The rate of progression-free survival at 18 months was 31% (95% CI, 23 to 39) in the crizotinib group and 5% (95% CI, 2 to 10) in the chemotherapy group. Panel B shows Kaplan–Meier estimates of overall survival in the intention-to-treat population. Because the rate of death from any cause at the time of data cutoff was relatively low (26%; 90 of the 343 patients who underwent randomization), the median overall survival was not reached in either group. Of the 171 patients randomly assigned to chemotherapy, 120 (70%) subsequently received crizotinib treatment. Of the 172 patients assigned to crizotinib, 21 (12%) subsequently received platinum-based chemotherapy. This analysis was not adjusted for crossover. Tick marks on the curves in Panels A and B indicate censoring of data. Panel C shows hazard ratios and 95% confidence intervals for the treatment effect on progression-free survival in subgroups of the intention-to-treat population defined according to prespecified stratification factors and baseline characteristics. Race was self-reported. Eastern Cooperative Oncology Group (ECOG) performance status scores range from 0 to 5, with higher scores indicating increasing disability; an 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 for ECOG performance status were missing for 1 patient.

for progression or death with crizotinib, 0.45; 95% CI, 0.35 to 0.60; P<0.001) (Fig. 1A). The hazard ratio favored crizotinib across most subgroups defined according to stratification factors and other baseline characteristics (Fig. 1C).

The objective response rate was significantly higher with crizotinib than with chemotherapy (74% [95% CI, 67 to 81] vs. 45% [95% CI, 37 to 53], P<0.001) (Table 2). The median duration of response was 11.3 months and 5.3 months, respectively. The best percentage change from baseline in target lesions and the best overall response in individual patients are shown in Figure S2 in the Supplementary Appendix. Intracranial lesions progressed or new intracranial lesions developed in 25 patients in the crizotinib group and in 26 patients in the chemotherapy group (15% each).

There was no significant difference in overall survival between patients in the crizotinib group and those in the chemotherapy group at the time of the progression-free survival analysis (hazard ratio for death with crizotinib, 0.82; 95% CI, 0.54 to 1.26; P=0.36) (Fig. 1B) — probably owing to the relatively low rate of death from any cause



C Progression-free Survival, According to Subgroup

Subgroup	No. of Patients	Hazard Ratio (95% CI)
Crizotinib vs. chemotherapy	343	0.45 (0.35–0.60)
Age		
≥65 yr	55	0.37 (0.17–0.77)
<65 yr	288	0.51 (0.38–0.68)
Sex		
Male	131	0.54 (0.36–0.82)
Female	212	0.45 (0.32–0.63)
Race		
Non-Asian	186	0.53 (0.36–0.76)
Asian	157	0.44 (0.30–0.65)
Smoking status		
Smoker or former smoker	125	0.64 (0.42–0.97)
Nonsmoker	218	0.41 (0.29–0.58)
Time since diagnosis		
>1 yr	35	0.14 (0.04–0.51)
≤1 yr	308	0.52 (0.40–0.68)
ECOG performance status		
2	18	0.19 (0.05–0.76)
0 or 1	324	0.47 (0.36–0.62)
Adenocarcinoma		
Yes	322	0.49 (0.37–0.64)
No	21	0.37 (0.12–1.10)
Type of disease		
Metastatic	336	0.48 (0.37–0.63)
Locally advanced	7	0.54 (0.07–3.91)
Brain metastases		
Yes	92	0.57 (0.35–0.93)
No	251	0.46 (0.34–0.63)

(26%; 90 of the 343 patients who underwent randomization) and the fact that 70% of the patients in the chemotherapy group crossed over to crizotinib treatment. The probability of 1-year survival was 84% (95% CI, 77 to 89) in the crizotinib group and 79% (95% CI, 71 to 84) in the chemotherapy group. After adjustment for crossover with the rank-preserving structural failure time model, the hazard ratio for death with crizotinib was 0.60 (95% CI, 0.27 to 1.42) as calcu-

Table 2. Response to Treatment in the Intention-to-Treat Population.*

Response	Crizotinib (N=172)	Chemotherapy (N=171)
Type of response — no. (%)		
Complete response	3 (2)	2 (1)
Partial response	125 (73)	75 (44)
Stable disease	29 (17)	63 (37)
Progressive disease	8 (5)	21 (12)
Could not be evaluated†	7 (4)	10 (6)
Objective response rate — % (95% CI)‡	74 (67–81)	45 (37–53)
Time to response — mo§		
Median	1.4	2.8
Range	0.6–9.5	1.2–8.5
Duration of response — mo¶		
Median	11.3	5.3
95% CI	8.1–13.8	4.1–5.8

* 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 could not be evaluated in 4 patients in each group because of early death.
‡ P<0.001 for the comparison between the two groups. The 95% confidence interval was calculated with the use of the exact method based on the F distribution.
§ The time to tumor response was calculated from the date of randomization to the date of the first documentation of a partial or complete response as determined by independent radiologic review.
¶ The duration of response was calculated from the date of the first documentation of a partial or complete response to the date of RECIST-defined progression or death, with the use of the Kaplan–Meier method.

lated with the Wilcoxon test (Fig. S3A in the Supplementary Appendix) and 0.67 (95% CI, 0.28 to 1.48) as calculated with the log-rank test (Fig. S3B in the Supplementary Appendix), indicating that crossover may have confounded the results of the primary overall survival analysis.

Among patients randomly assigned to crizotinib, 65 of 89 patients with progressive disease (73%) continued to receive crizotinib beyond disease progression for a median of 3.1 months (range, 0.7 to 22.6). A total of 21 patients assigned to crizotinib (12%) subsequently received platinum-based chemotherapy. At data cutoff, 79 patients who had been randomly assigned to crizotinib (46%) and 62 patients assigned to chemotherapy who had crossed over to crizotinib (36%) were still receiving crizotinib therapy. Eighteen patients in the chemotherapy group who had progressive disease did not receive follow-up therapy with crizotinib; additional details are provided in the Supplementary Appendix. Other systemic therapies received during follow-up are listed in Table S2 in the Supplementary Appendix. The baseline characteristics of the patients and the efficacy outcomes in subgroup analyses of crizotinib versus individual chemotherapy regimens were similar to those in the analysis of the overall population (Table S3 and Fig. S4 in the Supplementary Appendix).

SAFETY AND ADVERSE EVENTS

The median duration of treatment was 10.9 months (range, 0.4 to 34.3) in the crizotinib group (a median of 16 cycles started [range, 1 to 50]) and 4.1 months (range, 0.7 to 6.2) in the chemotherapy group (a median of 6 cycles of chemotherapy started [range, 1 to 6]). The most common adverse events of any cause for which the incidence was at least 5 percentage points higher in the crizotinib group than in the chemotherapy group were vision disorder (occurring in 71% of the patients), diarrhea (in 61%), and edema (in 49%); and the events for which the incidence was at least 5 percentage points higher in the chemotherapy group than in the crizotinib group were fatigue (occurring in 38% of the patients), anemia (in 32%), and neutropenia (in 30%) (Table 3). Most adverse events in the two treatment groups were grade 1 or 2 in severity. Grade 3 or 4 elevations of aminotransferase levels occurred in 24 patients in the crizotinib group (14%) and in 4 patients in the chemotherapy group (2%), but these elevations were managed primarily with dose interruptions or dose reductions. Four hepatic events resulted in permanent discontinuation of treatment in the crizotinib group: three events involved elevated aminotransferase levels only (one event of grade 3 elevation of both alanine and aspartate aminotransferase levels and one event each of grade 2 and grade 3 elevation of the alanine aminotransferase level), and one event involved a grade 2 drug-induced liver injury that met the criteria for Hy's law[23] (elevated aminotransferase and total bilirubin levels without evidence of cholestasis [i.e., no elevated serum alkaline phosphatase level]) (see the Supplementary Appendix). An additional case that met the criteria for Hy's law occurred in a patient in the chemotherapy group after crossover to crizotinib. No deaths from hepatic dysfunction occurred. Grade 3 or 4 neutropenia occurred in 11% of patients in the

Table 3. Adverse Events from Any Cause in the As-Treated Population.*

Adverse Event	Crizotinib (N=171)		Chemotherapy (N=169)†	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Higher frequency in crizotinib group				
Vision disorder‡	122 (71)	1 (1)	16 (9)	0
Diarrhea	105 (61)	4 (2)	22 (13)	1 (1)
Edema§	83 (49)	1 (1)	21 (12)	1 (1)
Vomiting	78 (46)	3 (2)	60 (36)	5 (3)
Constipation	74 (43)	3 (2)	51 (30)	0
Elevated aminotransferases§	61 (36)	24 (14)	22 (13)	4 (2)
Upper respiratory infection§	55 (32)	0	21 (12)	1 (1)
Abdominal pain§	45 (26)	0	20 (12)	0
Dysgeusia	45 (26)	0	9 (5)	0
Headache	37 (22)	2 (1)	25 (15)	0
Pyrexia	32 (19)	0	18 (11)	1 (1)
Dizziness§	31 (18)	0	17 (10)	2 (1)
Pain in extremity	27 (16)	0	12 (7)	0
Higher frequency in chemotherapy group				
Fatigue	49 (29)	5 (3)	65 (38)	4 (2)
Neutropenia§	36 (21)	19 (11)	51 (30)	26 (15)
Stomatitis§	24 (14)	1 (1)	34 (20)	2 (1)
Asthenia	22 (13)	0	41 (24)	2 (1)
Anemia§	15 (9)	0	54 (32)	15 (9)
Leukopenia§	12 (7)	3 (2)	26 (15)	9 (5)
Thrombocytopenia§	2 (1)	0	31 (18)	11 (7)
Similar frequency in the two treatment groups				
Nausea	95 (56)	2 (1)	99 (59)	3 (2)
Decreased appetite	51 (30)	4 (2)	57 (34)	1 (1)
Cough§	39 (23)	0	33 (20)	0
Neuropathy§	35 (20)	2 (1)	38 (22)	0
Dyspnea§	30 (18)	5 (3)	26 (15)	4 (2)

* Adverse events are listed here if they were reported in 15% or more of patients in either treatment group; rates were not adjusted for differences in treatment duration. Higher frequency indicates a difference of 5 percentage points or more between groups; similar frequency indicates a difference of less than 5 percentage points between groups.
† Only events that occurred before crossover to crizotinib are included.
‡ The category of vision disorder comprised a cluster of adverse events including (in descending order of frequency in the crizotinib group) visual impairment, photopsia, blurred vision, vitreous floaters, reduced visual acuity, diplopia, and photophobia.
§ This item comprised a cluster of adverse events that may represent similar clinical symptoms or syndromes.

crizotinib group and in 15% in the chemotherapy group, with no cases of febrile neutropenia reported with crizotinib and two with chemotherapy. Other grade 3 or 4 adverse events from any cause are shown in Table S4 in the Supplementary Appendix. Two patients (1%) in the crizotinib group had interstitial lung disease, resulting in permanent discontinuation of crizotinib treatment.

Adverse events from any cause that were associated with permanent discontinuation of treatment occurred in 12% of the patients in the

crizotinib group and in 14% of those in the chemotherapy group (before crossover); the corresponding rates of adverse events deemed by the investigator to be related to treatment that were associated with permanent discontinuation were 5% and 8%. One case of fatal pneumonitis, considered to be related to crizotinib treatment, occurred in a patient who had crossed over from chemotherapy. Grade 5 adverse events of any cause are shown in Table S5 in the Supplementary Appendix. With the exception of the fatal pneumonitis, described above, that occurred after crossover to crizotinib, no deaths were reported that were deemed by the investigators to be related to treatment.

PATIENT-REPORTED OUTCOMES

Baseline scores on the QLQ-C30, QLQ-LC13, and EQ-5D are summarized in Table S6 in the Supplementary Appendix. There was a significantly greater overall improvement from baseline in global quality of life among patients who received crizotinib than among those who received chemotherapy (P<0.001) (Fig. 2A, and see the Results section in the Supplementary Appendix for additional details). Crizotinib was also associated with a significantly greater overall improvement from baseline in physical, social, emotional, and role functioning domains (P<0.001) (Fig. 2A).

There was a significantly greater overall reduction from baseline with crizotinib than with chemotherapy in the symptoms of pain, dyspnea, and insomnia as assessed with the use of the QLQ-C30 (Fig. 2B) and in the symptoms of dyspnea, cough, chest pain, arm or shoulder pain, and pain in other parts of the body as assessed with the use of the QLQ-LC13 (Fig. 2C) (P<0.001 for all comparisons) (see the Results section in the Supplementary Appendix for additional details). Patients treated with crizotinib also had a significantly greater delay in the worsening of lung-cancer symptoms (a composite of cough, dyspnea, or pain in the chest) than did patients treated with chemotherapy (hazard ratio for worsening of symptoms with crizotinib, 0.59; 95% CI, 0.45 to 0.77; P<0.001; estimated probability of being event-free at 6 months, 38% vs. 22%) (Fig. S5 in the Supplementary Appendix). A significantly greater improvement from baseline was observed in EQ-5D general health status scores (as assessed with the use of a visual-analogue scale) with crizotinib than with chemotherapy (P=0.002).

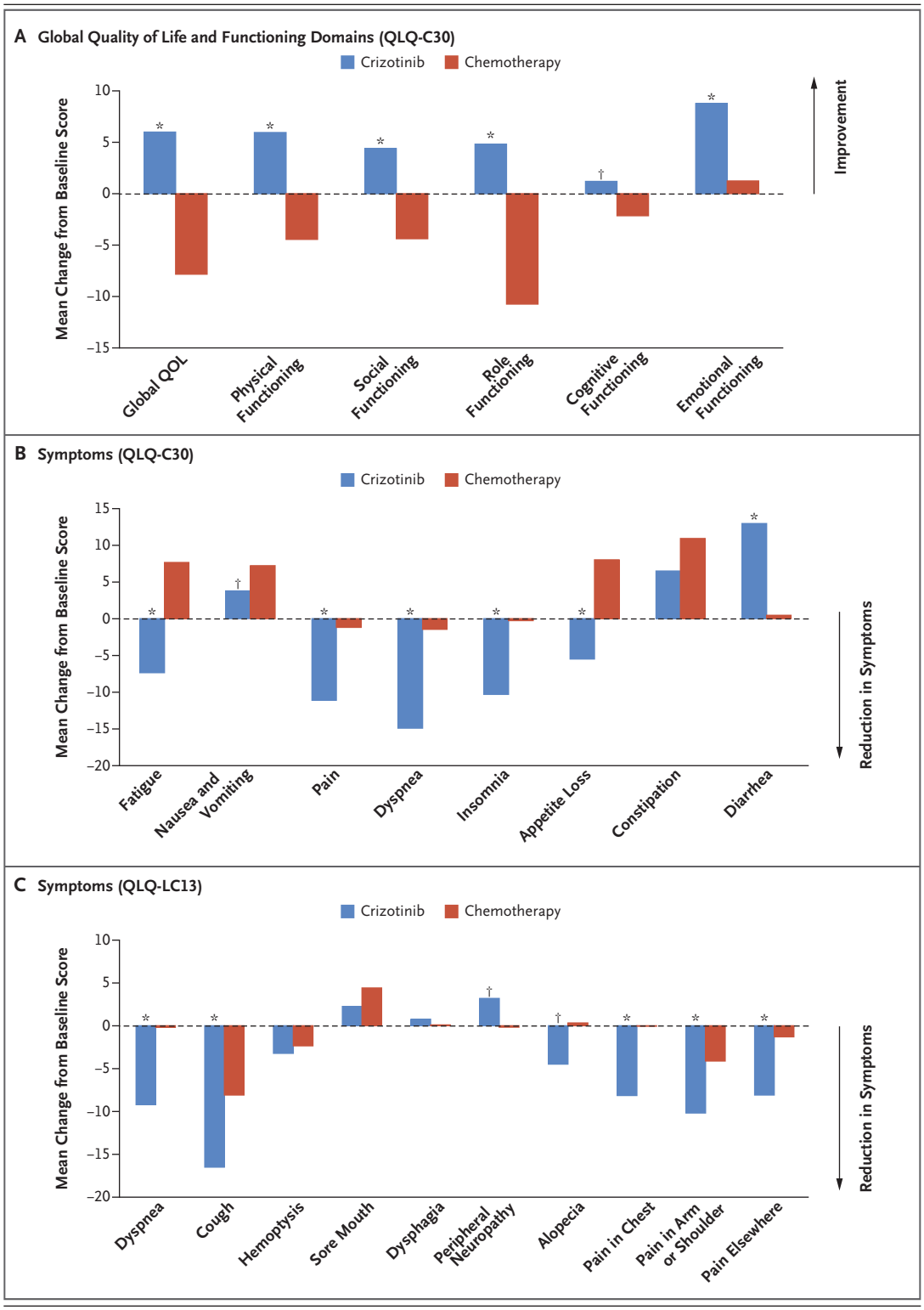
Figure 2 (facing page). Overall Change from Baseline in Global Quality of Life, Functioning Domains, and Symptoms.

Panel A shows the overall change from baseline in global quality of life (QOL) and functioning domains as assessed with the use of the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire (QLQ-C30). Panels B and C show the overall change from baseline in symptoms as assessed with the QLQ-C30 and the corresponding module for lung cancer (QLQ-LC13), respectively. Patient-reported outcomes were assessed at baseline, on days 7 and 15 of cycle 1, on day 1 of every subsequent cycle, and at the end of treatment. Scores on each scale ranged from 0 to 100. For global quality of life and functioning domains, higher scores indicate better global quality of life or functioning, and hence positive changes (upward bars) indicate improvement from baseline; for symptoms, higher scores indicate greater severity of symptoms, and hence negative changes (downward bars) indicate improvement from baseline. A change of 10 points or more is considered to be a clinically meaningful change. An asterisk indicates P<0.001, and a dagger P<0.05 for the comparison between treatment groups. In Panel C, the mean changes from the baseline score in dysphagia and in pain in the chest with chemotherapy were 0.10 and −0.05, respectively.

DISCUSSION

This study showed the superiority of first-line therapy with crizotinib over pemetrexed-plus-platinum chemotherapy in patients with previously untreated advanced *ALK*-positive NSCLC. Initial treatment with crizotinib significantly prolonged progression-free survival as compared with chemotherapy consisting of pemetrexed plus cisplatin or carboplatin. These results were independent of the type of platinum treatment administered, the performance status of the patient, the patient's race, and the presence or absence of brain metastases. Crizotinib treatment was also associated with a significantly higher response rate and significantly greater improvements in patient-reported measures of physical functioning, key lung-cancer symptoms (cough, dyspnea, chest pain, and fatigue), and global quality of life.

The standard of care for newly diagnosed NSCLC has generally been platinum-based double-agent chemotherapy,[11] except in the case of NSCLC that is positive for an epidermal growth



factor receptor (*EGFR*) mutation, for which randomized trials have shown superior efficacy of EGFR tyrosine kinase inhibitors over chemotherapy.[24-28] For tumors with nonsquamous histologic characteristics, cisplatin–pemetrexed has been shown to be superior to cisplatin–gemcitabine.[12]

Given that most advanced *ALK*-positive NSCLCs have nonsquamous histologic characteristics, pemetrexed in combination with cisplatin or carboplatin was selected as the standard chemotherapy for this trial. The efficacy of pemetrexed-based first-line chemotherapy has since been documented in *ALK*-positive NSCLC,[29,30] a finding that supports this selection. A potential limitation of our study was that pemetrexed was not continued beyond the planned six cycles of pemetrexed-plus-platinum chemotherapy, since this was not considered to be a standard approach when the study was initiated. However, in a study of patients without disease progression after four cycles of cisplatin–pemetrexed, maintenance pemetrexed therapy improved median progression-free survival over placebo by only 1.3 months (4.1 months vs. 2.8 months) from the start of maintenance therapy.[31] The way in which the use of maintenance pemetrexed therapy or other chemotherapy regimens would have affected the results in the control group of the current study is unclear.

The magnitude of the improvement in progression-free survival observed in the current study is similar to that observed in studies of *EGFR*-mutation–positive tumors treated with first-line EGFR tyrosine kinase inhibitors.[24-26] Although formal comparison across studies cannot be made, the efficacy of crizotinib in the first-line setting (median progression-free survival, 10.9 months; objective response rate, 74%) appeared to be greater than that seen with crizotinib in an otherwise similar patient population that had received previous treatment with platinum-based chemotherapy (median progression-free survival, 7.7 months; response rate, 65%).[10] Initiating crizotinib as first-line therapy in patients whose tumors test positive for *ALK* rearrangements maximizes the probability that these patients will benefit from ALK-directed therapy.

Overall survival did not differ significantly between the treatment groups at the time of this analysis, with a relatively small number of deaths reported (26%; 90 of the 343 patients who underwent randomization). As seen in randomized phase 3 studies of first-line EGFR tyrosine kinase inhibitors versus chemotherapy in *EGFR*-mutation–positive NSCLC, this finding is most likely attributable to the confounding effects of crossover treatment.[32] Of the 171 patients randomly assigned to chemotherapy, 120 received crizotinib treatment during follow-up for survival. It should be noted that the median survival had not been reached in either group, with a median follow-up of 17 months.

The safety profile of crizotinib was consistent with that reported earlier in patients with previously treated advanced *ALK*-positive NSCLC[10] and differed from that observed with chemotherapy. The incidence of adverse effects in the two treatment groups was probably affected by the fact that the duration of therapy with crizotinib was longer than that with chemotherapy and that crizotinib continued to be used in some patients beyond progression.[33] Discontinuations of therapy occurred in 5% of patients with crizotinib-related adverse events and in 8% of patients with chemotherapy-related adverse events. More serious potential adverse events previously reported with crizotinib were hepatotoxic and pulmonary toxic effects.[10] In the current study, grade 3 or 4 elevations of aminotransferase levels occurred in 14% of the patients in the crizotinib group and could be managed with dose interruptions or dose reductions. Two patients discontinued crizotinib therapy because of interstitial lung disease, and one case of fatal pneumonitis was reported in a patient who had crossed over from chemotherapy to crizotinib.

In conclusion, in patients with previously untreated *ALK*-positive NSCLC, crizotinib treatment was superior to pemetrexed-plus-platinum chemotherapy with respect to progression-free survival, objective response rate, reduction of lung-cancer symptoms, and improvement in quality of life.

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 research nurses, study coordinators, and operations staff; Joanne Fitz-Gerald and Wendy Sacks at ACUMED (Tytherington, United Kingdom, and New York) for medical writing support; and Abbott Molecular for support of the *ALK* FISH testing.

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. Rikova K, Guo A, Zeng Q, et al. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. Cell 2007;131:1190-203.
3. 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.
4. Camidge DR, Doebele RC. Treating ALK-positive lung cancer — early suc-

cesses and future challenges. Nat Rev Clin Oncol 2012;9:268-77.
5. Blackhall FH, Peters S, Bubendorf L, et al. Prevalence and clinical outcomes for patients with ALK-positive resected stage I-III adenocarcinoma: results from the European Thoracic Oncology Platform Lungscape Project. J Clin Oncol 2014;32:2780-7.
6. Christensen JG, Zou HY, Arango ME, et al. Cytoreductive antitumor activity of PF-2341066, a novel inhibitor of anaplastic lymphoma kinase and c-Met, in experimental models of anaplastic large-cell lymphoma. Mol Cancer Ther 2007;6:3314-22.
7. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non–small-cell lung cancer. N Engl J Med 2010;363:1693-703.
8. 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.
9. 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). J Clin Oncol 2012;30:Suppl. abstract.
10. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced *ALK*-positive lung cancer. N Engl J Med 2013;368:2385-94.
11. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non–small-cell lung cancer. N Engl J Med 2002;346:92-8.
12. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543-51.
13. Abbott Molecular. Vysis ALK Break Apart FISH Probe Kit package insert, 2011 (http://www.abbottmolecular.com/static/cms_workspace/pdfs/US/Vysis_ALK_FISH_Probe_Kit_PI.pdf).
14. 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.
15. 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.
16. 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.
17. Fayers P, Bottomley A. Quality of life research within the EORTC-the EORTC QLQ-C30. Eur J Cancer 2002;38:Suppl 4:S125-S133.
18. 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.
19. EuroQol Group. EuroQol — a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208.
20. Robins JM, Tsiatis A. Correcting for non-compliance in randomized trials using rank-preserving structural failure time models. Commun Stat Theory Methods 1991;20:2609-31.
21. Robins JM, Blevins D, Ritter G, Wulfsohn M. G-estimation of the effect of prophylaxis therapy for Pneumocystis carinii pneumonia on the survival of AIDS patients. Epidemiology 1992;3:319-36.
22. White IR, Babiker AG, Walker S, Darbyshire JH. Randomization-based methods for correcting for treatment changes: examples from the Concorde trial. Stat Med 1999;18:2617-34.
23. Temple R. Hy's law: predicting serious hepatotoxicity. Pharmacoepidemiol Drug Saf 2006;15:241-3.
24. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
25. 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.
26. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-34.
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. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010;11:121-8.
29. 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.
30. Shaw AT, Varghese AM, Solomon BJ, et al. Pemetrexed-based chemotherapy in patients with advanced, ALK-positive non-small cell lung cancer. Ann Oncol 2013;24:59-66.
31. Paz-Ares L, de Marinis F, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol 2012;13:247-55.
32. Mok T, Yang JJ, Lam KC. Treating patients with EGFR-sensitizing mutations: first line or second line — is there a difference? J Clin Oncol 2013;31:1081-8.
33. Shaw AT, Solomon BJ, Mok T, et al. Effect of treatment duration on incidence of adverse events (AEs) in a phase III study of crizotinib versus chemotherapy in advanced ALK-positive non-small cell lung cancer (NSCLC). Presented at the 15th World Conference on Lung Cancer, Sydney, October 27–30, 2013. abstract.