not included; however, patients who received adjuvant treatment three months after surgery were included. Other factors required for inclusion were: age greater than 20 years; Eastern Cooperative Oncology Groups Performance Status (ECOG-PS) score of 0 to 2; creatinine level ≤ 2.0 mg/dL; and a survival expectation of at least three months. Patients with hemorrhagic lesions or anemia not related to treatment were excluded. Patients with unfavorable health conditions, as determined by their physicians, were also excluded. Demographic, disease, and treatment data were gathered from the patients' clinical records. Disease complications were categorized into 65 types. All patients provided written informed consent after receiving a thorough verbal explanation of the study protocol. The study conformed to the principles set forward in the Declaration of Helsinki and was approved by the ethics committees of each institution.

The FACT-An questionnaire survey was conducted both at baseline and at three months. The Hb levels were measured at baseline and at three months. At baseline, data including each patient's demographic background, ECOG-PS score, type of cancer treatment received, and whether the patient received any type of supportive care for anemia, such as blood transfusions, were collected at the central data center. At three months, the current status of each patient's cancer therapy and anemia treatment were reported. FACT-An questionnaires were considered to be complete if answers for all of the domains and subscales were included.

Statistical analysis

Data collection, management, and monitoring were coordinated by the Comprehensive Support Project for Oncological Research (CSPOR) data center of the Japan Clinical Research Support Unit (J-CRSU). Pearson's correlation coefficients, Mann-Whitney U test, scatter plots, and box-and-whisker plots were used to assess the strengths of the relationships between the FACT-An scores and the Hb levels. A multiple regression analysis was used to identify factors that affect QOL, using the FACT-An scores as the dependent variable. Anemia was defined as an Hb level < 11 g/dL. Treatment was classified as either platinum-based chemotherapy or non-platinum-based chemotherapy. The least squares mean (LS mean) was used to estimate the differences in FACT-An scores between the two groups. All analyses were performed with SAS Version 8.02. $P < 0.05$ was considered significant.

RESULTS

The patients' baseline demographic and clinical data are shown in Table 1. A broad spectrum of cancer types was seen, with lung cancer being the most frequent. Approximately 30% of the patients had comorbidities, with hypertension and diabetes being the most common. Most subjects (223/227, 98%) were ambulatory at baseline. The response rate at baseline, in terms of the percentage of patients who completed the questionnaire at baseline, was very high (225/227, 99%). At three months, 18 patients had dropped out of the study. The reasons for dropping out included: the patient's voluntary decision (n = 2); transfer to another hospital (n = 2); death (n = 10); or unknown (n = 4). According to the FACT Scoring Manual, the total FACT score was not calculated in three patients because the number of items to which they responded was insufficient. Over the three months, the patients' mean Hb level did not change from the baseline level (11.4 g/dL).

Univariate analyses showed weak correlations between the FACT-An score and Hb level at baseline and at three months; Pearson's correlation coefficients were 0.24(p = 0.0002) at baseline and 0.24(p = 0.0007) at three months after enrollment (Fig. 1). The patients were divided into 2 groups: anemia group (Hb < 11 g/dL) or non-anemia group (Hb ≥ 11 g/dL). The baseline FACT-An scores of the anemia (mean ± SD; 120.2 ± 24.9, n = 91) and non-anemia (130.5 ± 24.3, n = 134) groups were significantly different (Mann-Whitney U test P = 0.004) (Fig. 2 (a)). At three months, the FACT-An scores of the anemia (120.1 ± 25.2, n = 72) and non-anemia (128 ± 26.9, n = 132) groups were also significantly different (P = 0.017) (Fig. 2 (b)).

Multiple regression analyses showed that patient age, ECOG-PS score, Hb level, and the type of treatment method received (either chemotherapy with platinum or other treatments) were each predictive of a patient's baseline FACT-An score (Table 2). At three months, the patient's Hb level and whether the patient had received a blood transfusion were each predictive of the patient's FACT-An score. When measuring changes over three months, the patient's age at baseline and the change in the patient's Hb level were each predictive of the change in the patient's FACT-An score. The goodness of fit of these models was confirmed. Appropriate regression diagnostics, including examination of residuals and testing multicollinearity were performed to confirm the validity these models.

A patient's Hb level both at baseline and at three months consistently showed a predictive positive correlation with the patient's FACT-An score at each time point, while the change in the patient's Hb level was also predictive of a change in the patient's FACT-An score in the same direction. This result indicates that subjects with higher Hb levels had higher FACT-An scores, even when adjusted for other factors.

DISCUSSION

In the present study, patient age, ECOG-PS score, Hb level, and the type of treatment method received each significantly affected QOL as measured by FACT-An scores in patients with malignancy. A patient's Hb level consistently showed an effect on the patient's QOL score measured both at baseline and at three months. Additionally, the change in a patient's Hb level over three months corresponded to the change in the patient's QOL score, showing a positive correlation. The subjects who were anemic (Hb < 11.0 g/dL) consistently had lower FACT-An scores than subjects who were non-anemic (Hb ≥ 11.0 g/dL) when adjusted for other confounding factors. These results indicate that anemia is a significant factor that affects cancer patients' QOL.

Age is another factor that affected QOL in the present study. The baseline FACT-An was better in elderly patients than in younger patients. Aapro *et al.* reported

Table 1 Patients' baseline demographic and clinical characteristics (N = 227)

Characteristic	Mean ± SD (range)	Patients No	Patients %
Age (years)	59.0 ± 12.1 (27-84)	–	–
Sex		–	–
Male		126	55.3
Female		102	44.7
Cancer type		–	–
Lung		98	43.2
Breast		60	26.4
Stomach		3	1.3
Colon		4	1.8
Liver, bile, pancreas		3	1.3
Lymphoma		32	14.1
Leukemia		24	10.6
Others		3	1.3
Comorbidity		–	–
Yes		77	33.9
No		150	66.1
Performance status (ECOG)		–	–
0 (fully ambulatory without physical symptoms)		137	60.1
1 (ambulatory with symptoms)		86	37.7
2 (requiring bed rest during waking day)		5	2.2
Blood infusion		–	–
Yes		2	0.9
No		225	99.1
Treatment method		–	–
Chemotherapy (non-platinum)		141	62.1
Chemotherapy (platinum)		63	27.8
No chemotherapy		23	10.1
Hemoglobin levels (g/dL)	11.4 ± 1.8 (4.5-15.6)	–	–
< 11.0		92	40.5
< 8		13	5.7
8-9		6	2.6
9-10		25	11.0
10-11		48	21.1
> 11.0		135	59.5
11-12		38	16.7
12-13		60	26.4
> 13		37	16.3

that age was not significantly correlated with Short-Form 36 (SF-36) and FACT-An scores [7]. We consider that age alone may not always necessarily be a poor indicator of a patient's QOL. Anemia is common among the hospitalized elderly [7]. The number of elderly cancer patients is rapidly increasing in Japan, and many of these patients are able to receive chemotherapy. Earle *et al.* showed, in a large retrospective study, that chemotherapy itself did not diminish survival outcomes in elderly cancer patients [8]. Langer *et al.* reported that platinum-based chemotherapy-induced hematological toxicity was found to be more severe in elderly patients (> 70 years of age), even though these patients had a similar survival outcome [9]. Future studies to examine chemotherapy-associated anemia and QOL in this specific population are necessary.

Toxic responses to chemotherapy include anorexia, nausea, vomiting, and bone marrow dysfunction. An ideal approach for the treatment of cancer would be to maximize the effectiveness of treatment while controlling the toxic responses. The present results showed that platinum-based chemotherapy decreased QOL. Patients undergoing platinum-based chemotherapy easily become anemic [9]. An inverse correlation between accumulated doses of cisplatin and Hb levels has been reported [10]. This anemic condition is primarily caused by poor erythropoiesis and excessive synthesis of cytokines [11]. Reports have shown the incidence of anemia to be especially high among patients with lymphoma, lung cancer, and gynecologic cancer [12, 13]. Platinum-based chemotherapy has become the treatment strategy of choice for lung cancer because it has been shown to significantly reduce the risk of death when combined with other therapies [14].

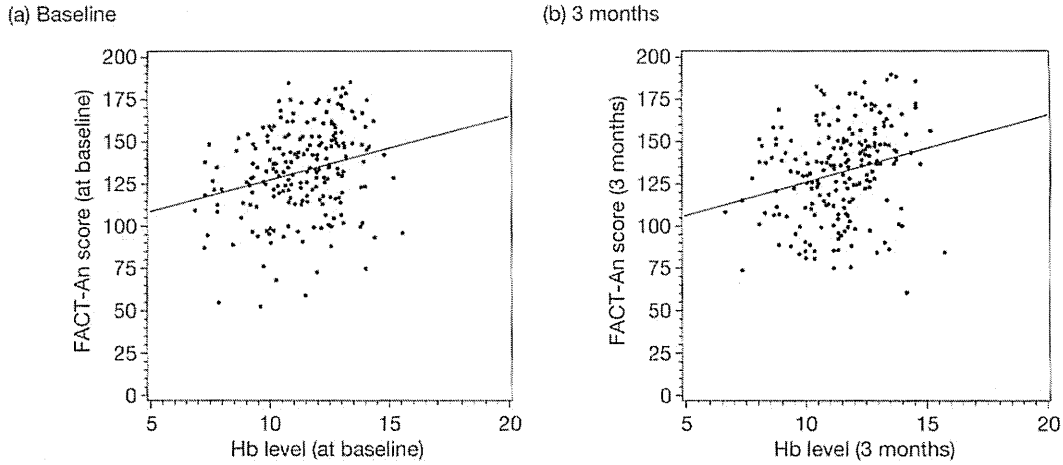

Fig. 1 Scatter plots of FACT-An scores vs. Hb levels (g/dL), measured at baseline (the left panel) and three months after enrollment (the right panel).

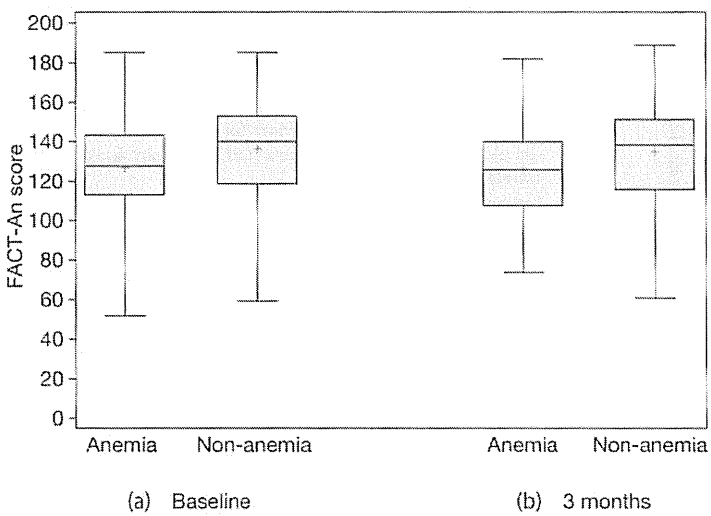

Fig. 2 Box-and-whisker plots of FACT-An scores for anemia and non-anemia patients at baseline and three months. Left two boxes show the FACT-An scores at baseline and the right boxes show the scores at three months among the anemia patients (Hb < 11 mg/dL) and the non-anemia patients (Hb ≥ 11 mg/dL). The box represents the 25th and 75th quartiles; + plots and vertical lines in the boxes represent the mean and the median, respectively. The whiskers extend from the ends of the box to the outermost data point.

In the present study, although a broad spectrum of cancer types was seen, a majority of the patients had lung cancer. These patients had an opportunity to receive platinum-based chemotherapy, and their anemic conditions partly affected their QOL.

In Japan, anemia is treated only with blood infusions, and this treatment method is restricted to renal patients or severely anemic patients. Blood infusions can lead to dangerous outcomes, such as acute lung injury, infection, or other problems [15]. Meanwhile, active intervention to reverse anemia with the use of drugs or growth factors, such as erythropoietin alpha, has provided substantial benefits for cancer patients in other countries [16]. According to a recent meta-analysis, the administration of recombinant human erythropoietins clearly showed benefits, with reduced risk of blood transfusions and improved hematologic responses in cancer patients. Conversely, treatment with these agents has also been reported to increase the risk of thrombo-embolic events, and uncertainties remain as to the influence of these agents on the overall survival of patients [17]. The clinical practice guidelines for the use of erythropoietic factors in cancer patients were revised in ASCO and ASH2007. In Japan, studies supporting the use of such growth factors are also needed. Future well-designed interventional studies to examine the QOL gains that occur with corrected anemia are necessary.

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Table 2 Multiple regression analysis with the FACT-An score as the dependent variable

Variables	Baseline		Three months		Change[a]	
	Coefficient (95%CI)	P-value	Coefficient (95%CI)	P-value	Coefficient (95%CI)	P-value
Age (65 years or over/younger)	10.27 (3.24: 17.30)	**0.004****	1.73 (- 6.56: 10.01)	0.681	- 9.19 (- 15.64: - 2.74)	**0.006****
Sex (female/male)	4.94 (- 2.07: 11.96)	0.166	6.90 (- 1.43: 15.23)	0.104	0.34 (- 6.08: 6.77)	0.916
Cancer type(leukemia/others)	7.45 (- 3.25: 18.14)	0.171	4.81 (- 7.28: 16.9)	0.434	- 2.33 (- 11.72: 7.06)	0.625
Comorbidity (Y/N)	- 1.02 (- 7.81: 5.77)	0.767	- 2.61 (- 10.33: 5.12)	0.504	- 1.17 (- 7.21: 4.86)	0.701
ECOG-PS score (2 or over/0,1)	- 30.25 (- 52.41: -8.08)	**0.008****	- 10.22 (- 40.67: 20.23)	0.509	13.08 (- 10.68: 36.85)	0.279
Blood infusion (Y/N)	13.12 (- 23.07: 49.31)	0.475	22.72 (2.17: 43.26)	**0.030***	1.65 (- 29.57: 32.87)	0.917
Latest treatment (chemo with platinum/others)	- 10.80 (- 18.20: -2.40)	**0.011***	- 1.49 (- 11.11: 8.13)	0.760	3.63 (- 3.69: 10.96)	0.329
Latest Hb level (per + 1 g/dL)	3.32 (1.35: 5.30)	**0.001****	4.69 (2.27: 7.10)	< **0.001****	0.66 (- 1.38: 2.70)	0.525
Hb level change (per + 1 g/dL) [b]					3.27 (1.09: 5.44)	**0.003****

*P ≤ 0.05; **P ≤ 0.01

[a], [b]: Change in scores over three months.

Abbreviations: ECOG-PS, Eastern Oncology Group Performance Status; Hb, Hemoglobin; CI, confidence interval.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

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Efficacy and safety analysis according to histology for S-1 in combination with carboplatin as first-line chemotherapy in patients with advanced non-small-cell lung cancer: updated results of the West Japan Oncology Group LETS study

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Background: A phase III study (Lung Cancer Evaluation of TS-1) previously demonstrated noninferiority in terms of overall survival (OS) at interim analysis for carboplatin–S-1 compared with carboplatin–paclitaxel for first-line treatment of advanced non-small-cell lung cancer (NSCLC).

Patients and methods: A total of 564 patients were randomly assigned to receive either carboplatin on day 1 plus oral S-1 on days 1–14 or carboplatin–paclitaxel on day 1 every 21 days. Updated results and *post hoc* subgroup analysis according to tumor histology are presented.

Results: The updated analysis revealed a median OS of 15.2 months in the carboplatin–S-1 arm and 13.1 months in the carboplatin–paclitaxel arm, with a hazard ratio (HR) of 0.956 [95% confidence interval (CI) 0.793–1.151], consistent with the previous primary analysis. Median OS was 14.0 months in the carboplatin–S-1 arm and 10.6 months in the carboplatin–paclitaxel arm (HR 0.713; 95% CI 0.476–1.068) for patients with squamous cell carcinoma (SCC), with corresponding values of 15.5 and 13.9 months (HR 1.060; 95% CI 0.859–1.308) for those with non-SCC.

Conclusions: These results establish the efficacy and safety of carboplatin–S-1 in patients with advanced NSCLC regardless of tumor histology.

Key words: carboplatin, histology, non-small-cell lung cancer, S-1, squamous cell carcinoma

introduction

Lung cancer is the leading cause of death related to cancer worldwide, with non-small-cell lung cancer (NSCLC) accounting for 85% of lung cancer cases [1]. Most NSCLC cases are categorized into two distinct histological subtypes: squamous cell carcinoma (SCC) and non-SCC. Treatment with pemetrexed–cisplatin was associated with a longer overall survival (OS) compared with that with gemcitabine–cisplatin in patients with non-SCC but not in those with SCC [2]. The addition of bevacizumab, a monoclonal antibody specific for vascular endothelial growth factor, to carboplatin and paclitaxel improved survival compared with chemotherapy alone in patients with non-SCC, but such treatment was contraindicated for patients with SCC because of an increased risk of fatal bleeding events [3–5]. Furthermore, the recent identification of oncogenic alterations, such as mutation of the epidermal growth factor receptor (EGFR) gene or the fusion of the genes for echinoderm microtubule-associated protein–like

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4 (EML4) and anaplastic lymphoma kinase (ALK), and of the association of such gene alterations with a clinically relevant response to corresponding tyrosine kinase inhibitors (TKIs), has had a profound impact on the treatment of advanced NSCLC [6–10]. Almost all cases of NSCLC harboring *EGFR* mutations or *ALK* rearrangements are non-SCC, with adenocarcinomas being most common. Treatment options for non-SCC have thus increased, whereas the contribution of new drugs to the treatment of SCC has been minimal. The poor outlook for advanced NSCLC patients with SCC has prompted a search for new chemotherapeutic agents and combination regimens.

S-1 (TS-1; Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) is an oral fluoropyrimidine anticancer agent that combines tegafur as the effector drug with two modulators, gimeracil, and oteracil potassium, in a molar ratio of 1 : 0.4 : 1 [11, 12]. We have recently completed a multicenter randomized phase III study comparing carboplatin and S-1 with standard carboplatin and paclitaxel combination therapy as first-line treatment in patients with advanced NSCLC [13]. The primary objective of the Lung Cancer Evaluation of TS-1 (LETS) study —determination of the noninferiority of carboplatin and S-1 compared with carboplatin and paclitaxel in terms of OS—was met at the planned interim analysis. On completion of the initially planned 2 years of follow-up, at which time an adequate number of events had been obtained, we updated the survival data of the LETS study. Given that histology (SCC or non-SCC) has recently become a key factor in the selection of chemotherapy regimens for the treatment of advanced NSCLC, we also assessed the efficacy and safety data according to the histological subtype of NSCLC by performing subgroup analyses that were not predefined in the study protocol but which address a clinically important issue.

patients and methods

patients

The design and results of the LETS study were published in 2010 [13]. In brief, the study group comprised patients aged 20–74 years who had a histopathologic diagnosis of stage IIIB or IV NSCLC, an Eastern Cooperative Oncology Group performance status of 0 or 1, and preserved functions of major organ systems. Patients had not previously received chemotherapy, and they were randomly assigned in a 1 : 1 ratio to receive carboplatin–S-1 or carboplatin–paclitaxel. In the carboplatin–S-1 group, carboplatin was given as a continuous i.v. infusion (area under the curve, 5) on day 1, and S-1 (80 mg/m^2 in two divided doses) was given orally on days 1–14. Treatment was repeated every 3 weeks for up to six cycles. Patients in the carboplatin–paclitaxel group received carboplatin (area under the curve, 6) and paclitaxel (200 mg/m^2) by continuous i.v. infusion on day 1 every 3 weeks. Treatment was repeated for up to six cycles. The primary end point was OS. Secondary end points were tumor response, safety, quality of life (QOL), and progression-free survival (PFS). Written informed consent was obtained from all patients before treatment, and the study protocol was approved by the institutional ethics committee of each of the participating institutions.

In this *post hoc* investigation, OS and PFS in the intention-to-treat population were determined from updated survival data. In addition, subgroup analyses were carried out to compare overall response rate (ORR), OS, and PFS between the treatment groups according to histological subtype (SCC versus non-SCC) of NSCLC. To assess the impact of post-study treatments with potential effects on survival, we analyzed the data according to treatment line and drugs administered (docetaxel and EGFR-TKIs). Treatment-related adverse events were also assessed according to each subgroup. QOL was assessed with the lung cancer subscale of Functional Assessment of Cancer Therapy-Lung (FACT-L) [14] and the neurotoxicity subscale of FACT/Gynecology Oncology Group-Neurotoxicity (FACT/GOG-Ntx) version 4 [15]. The maximum attainable scores on the lung cancer and neurotoxicity subscales were 28 and 44, respectively, with which a patient was considered to be asymptomatic. Patients were asked to complete each instrument at the time of enrollment and at 6 and 9 weeks after the initiation of treatment.

statistical analysis

The definition of survival was similar to that used in the initial description of the LETS study [13]. OS was defined as the interval from the date of randomization until the date of death from any cause or the final date of follow-up. At the time of data cutoff, data on survivors and on patients who were lost to follow up were censored on the final date of follow-up. PFS was defined as the interval from the date of randomization until the date on which progressive disease was first confirmed by imaging or the date of death from any cause, whichever came first. If no events had occurred, data were censored at the most recent date of follow-up.

Survival curves in each treatment group and subgroup were estimated with the Kaplan–Meier method. The 95% confidence interval (CI) for median survival was calculated with the method of Brookmeyer and Crowley. A Cox proportional-hazards model was used to calculate the hazard ratio (HR) and CI and to examine the interaction effects between study treatment and subgroup. Longitudinal QOL data were analyzed with a linear mixed-effects model. All statistical analyses were carried out with SAS for Windows, release 9.2 (SAS Institute, Cary, NC). A P value of <0.05 was considered statistically significant.

results

baseline characteristics

A total of 564 patients were enrolled into the phase III study, and 282 patients were treated in each of the carboplatin–paclitaxel and carboplatin–S-1 arms. At the time of the updated analysis, the median follow-up time was 33.4 months (range 2.1–43.6 months) and a total of 446 deaths (carboplatin–paclitaxel, $N = 219$; carboplatin–S-1, $N = 227$) had occurred. The median OS was 15.2 months (95% CI 12.3–17.8 months) in the carboplatin–S-1 group and 13.1 months (95% CI 11.7–14.9 months) in the carboplatin–paclitaxel group, with an HR for death of 0.956 (95% CI 0.793–1.151). The median PFS was 4.1 months (95% CI 3.8–4.7 months) in the carboplatin–S-1 group and 4.8 months (95% CI 4.3–5.2 months) in the carboplatin–paclitaxel group, with an HR for progression or death of 1.035 (95% CI 0.875–1.224). Of the 564 randomized patients in the phase III study population, 114 patients had SCC (carboplatin–paclitaxel, $N = 59$; carboplatin–S-1, $N = 55$) and 450 had non-SCC (carboplatin–paclitaxel, $N = 223$; carboplatin–S-1, $N = 227$). The CONSORT diagram for the study is shown in supplementary Figure S1, available at *Annals of Oncology* online. Baseline patient characteristics for both histological subtypes were generally well balanced between the treatment groups (Table 1).

Table 1. Patient demographics and characteristics according to histological subtype of NSCLC

Characteristic	Squamous		Nonsquamous	
	CBDCA–S-1 ($N = 55$)	CBDCA–PTX ($N = 59$)	CBDCA–S-1 ($N = 227$)	CBDCA–PTX ($N = 223$)
Age, median, years (range)	66 (39–74)	65 (43–74)	64 (38–74)	62 (36–74)
Sex, *N* (%)				
Male	48 (87.3)	51 (86.4)	169 (74.4)	165 (74.0)
Female	7 (12.7)	8 (13.6)	58 (25.6)	58 (26.0)
ECOG PS, *N* (%)				
0	18 (32.7)	14 (23.7)	68 (30.0)	77 (34.5)
1	37 (67.3)	45 (76.3)	159 (70.0)	146 (65.5)
Clinical stage, *N* (%)				
IIIB	20 (36.4)	27 (45.8)	48 (21.1)	41 (18.4)
IV	35 (63.6)	32 (54.2)	179 (78.9)	182 (81.6)
Smoking status, *N* (%)				
Smoker	52 (94.5)	56 (94.9)	178 (78.4)	174 (78.0)
Nonsmoker	3 (5.5)	3 (5.1)	49 (21.6)	49 (22.0)

CBDCA, carboplatin; PTX, paclitaxel; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Table 2. Summary of OS, PFS, and response rate according to histological subtype of NSCLC

	Squamous		Nonsquamous	
	CBDCA–S-1 ($N = 55$)	CBDCA–PTX ($N = 59$)	CBDCA–S-1 ($N = 227$)	CBDCA–PTX ($N = 223$)
ORR, *N* (%)	15 (27.3)	20 (33.9)	42 (18.5)	61 (27.4)
Disease control rate, *N* (%)	44 (80.0)	45 (76.3)	156 (68.7)	162 (72.6)
Median PFS (months)	4.37	4.87	4.14	4.77
95% CI	3.65–5.79	3.98–5.72	3.65–4.77	4.18–5.23
HR (95% CI)	0.938 (0.642–1.371)		1.063 (0.881–1.282)	
Median OS (months)	14	10.6	15.5	13.9
95% CI	11.4–16.7	8.7–12.6	11.7–18.4	12.1–16.8
HR (95% CI)	0.713 (0.476–1.068)		1.060 (0.859–1.308)	

efficacy results based on histology

Efficacy results according to histological subtype of NSCLC are shown in Table 2. For the non-SCC cohort, ORR was significantly higher in the carboplatin–paclitaxel arm than in the carboplatin–S-1 arm (27.4% versus 18.5%; $P = 0.027$, chi-square test), with a response rate ratio of 0.680 (95% CI 0.4805–0.960), whereas the overall disease control (complete response + partial response + stable disease) rate was similar in both treatment groups (72.6% versus 68.7%, respectively; $P = 0.393$). The ORR was 33.9% and 27.3% ($P = 0.444$), with a response rate ratio of 0.805 (95% CI 0.460–1.408), for carboplatin–paclitaxel and carboplatin–S-1, respectively, in patients with SCC. No significant interaction was noted for ORR between histology and treatment ($P = 0.686$).

The median PFS was 4.8 months with carboplatin–paclitaxel and 4.1 months with carboplatin–S-1 in patients with non-SCC (HR 1.063; 95% CI 0.881–1.282). The median PFS was similar with carboplatin–paclitaxel or carboplatin–S-1 in patients with SCC (4.9 versus 4.4 months, respectively; HR 0.938; 95% CI 0.642–1.371). No interaction was observed between histology and treatment effect for PFS ($P = 0.547$).

Figure 1 shows Kaplan–Meier analysis of OS according to treatment arm for SCC and non-SCC subgroups. Patients with SCC experienced a longer median OS in the carboplatin–S-1 group than in the carboplatin–paclitaxel group (14.0 versus 10.6 months, respectively; HR 0.713; 95% CI 0.476–1.068). Patients with non-SCC assigned to carboplatin–S-1 had a median OS of 15.5 months, whereas those assigned to carboplatin–paclitaxel had a median OS of 13.9 months (HR 1.060; 95% CI 0.859–1.308). These data were suggestive of a positive interaction between histology and treatment of OS, but it did not achieve statistical significance ($P = 0.093$).

safety results based on histology

Treatment-related adverse events according to histological subtype are shown in Table 3. Regardless of histology, carboplatin–S-1 was associated with a higher incidence of thrombocytopenia of grade 3 or 4 and a lower incidence of leukopenia, neutropenia, and febrile neutropenia of grade 3 or 4 compared with carboplatin–paclitaxel, consistent with the results previously reported for the intention-to-treat population [13].

QOL results based on histology

In general, results for QOL were similar for both histological subtypes of NSCLC (Figure 2). In patients with SCC, the adjusted mean FACT-L scores at 6 and 9 weeks were 20.8 and 21.1, respectively, for carboplatin–S-1 and 21.0 and 20.8 for carboplatin–paclitaxel ($P = 0.723$ between treatment arms). In

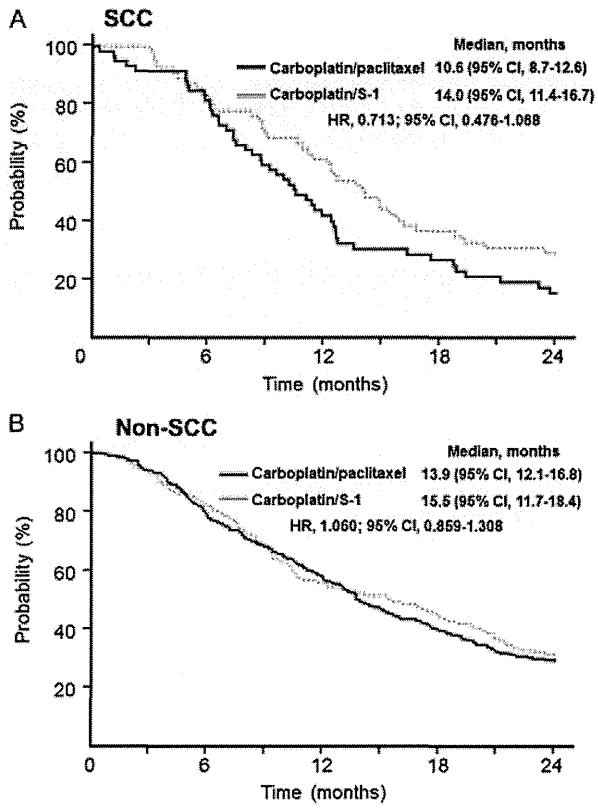

Figure 1. Kaplan–Meier curves for OS according to histological subtype of NSCLC. (A) SCC and (B) Non-SCC.

patients with non-SCC, the corresponding adjusted mean scores were 21.1 and 21.5 for carboplatin–S-1 and 21.3 and 21.3 for carboplatin–paclitaxel ($P = 0.702$). FACT/GOG-Ntx scores differed significantly between treatment arms regardless of histology. For SCC, the adjusted means were 41.1 and 41.5 at 6 and 9 weeks, respectively, for carboplatin–S-1 and 36.9 and 35.4 for carboplatin–paclitaxel ($P < 0.001$). For non-SCC, the adjusted means were 41.2 and 40.9 for carboplatin–S-1 and 38.6 and 37.6 for carboplatin–paclitaxel ($P < 0.001$).

post-study treatment based on histology

There were no major differences in post-study treatment between the two arms regardless of histological subtype (Table 4). The percentage of patients with SCC who received docetaxel as second-line treatment, however, was significantly higher for the carboplatin–S-1 arm than for the carboplatin–paclitaxel arm (58.2% versus 30.5%; $P = 0.003$, chi-square test).

discussion

The present updated analysis confirmed the noninferiority of carboplatin and S-1 compared with carboplatin and paclitaxel for the treatment of advanced NSCLC in terms of OS after completion of 2 years of follow-up and the occurrence of an adequate number of events, as planned in the original protocol. First-line treatment with carboplatin and S-1 showed a

Table 3. Treatment-related adverse events according to histological subtype of NSCLC

Event	Squamous						Nonsquamous					
	CBDCA/S-1 (*N* = 55)			CBDCA/PTX (*N* = 59)			CBDCA/S-1 (*N* = 224)			CBDCA/PTX (*N* = 221)		
	All	G3	G4	All	G3	G4	All	G3	G4	All	G3	G4
Hematologic (%)												
Leukopenia	55	2	0	85	24	7	55	6	1	86	31	2
Neutropenia	56	18	6	85	19	49	59	18	2	91	35	43
Anemia	96	13	6	85	19	3	84	16	3	82	13	2
Thrombocytopenia	91	27	16	76	12	3	86	17	13	59	6	2
Nonhematologic (%)												
Febrile neutropenia	4	4	0	19	17	2	1	1	0	4	4	0
Nausea	64	2	0	44	2	0	62	2	0	50	2	0
Vomiting	38	0	0	24	0	0	33	2	0	24	1	0
Diarrhea	40	2	0	17	0	0	31	4	0	22	1	0
Neuropathy: sensory	16	0	0	81	5	0	16	1	0	81	3	0
Arthralgia	9	0	0	59	0	0	8	0	0	69	3	0
Alopecia	11	0	0	73	0	0	9	0	0	78	0	0

favorable risk-benefit profile regardless of NSCLC histology compared with carboplatin and paclitaxel. As a first-line treatment of patients with SCC, carboplatin and S-1 showed a tendency to improve OS, with a 3.4-month increase in median OS, compared with carboplatin and paclitaxel (14.0 versus 10.6 months; HR 0.713; 95% CI 0.476–1.068). This outcome is of particular interest because of the limited therapeutic options for this patient population compared with patients with non-SCC. The current National Comprehensive Cancer Network (NCCN) guidelines highlight only cisplatin–gemcitabine and cisplatin–cetuximab–vinorelbine as treatment options for recurrence and distant metastases in patients with SCC [2, 16, 17]. Treatment of patients with SCC with gemcitabine–cisplatin versus pemetrexed–cisplatin yielded a median OS of 10.8 versus 9.4 months [2]. In the First-Line Erbitux in Lung Cancer (FLEX) trial, cetuximab–platinum-based chemotherapy was associated with a longer median OS in patients with SCC (10.2 versus 8.9 months) compared with chemotherapy alone [17]. The survival results for SCC patients treated with carboplatin and paclitaxel in our phase III trial are thus similar to those of recent previous studies. In this regard, given the historical context of NSCLC studies focusing on SCC, the survival advantage observed with carboplatin and S-1 in SCC patients is promising and warrants the performance of additional phase III studies for confirmation.

It is unclear whether the possible survival benefit conferred by carboplatin and S-1 in SCC patients is due to an intrinsic superiority of this drug combination compared with carboplatin and paclitaxel, to a reduced toxicity, or to other factors. Carboplatin–S-1 was as effective as carboplatin–paclitaxel in terms of response rate and PFS in patients with SCC. For such patients, carboplatin–S-1 was associated with a significantly lower rate of febrile neutropenia compared with carboplatin–paclitaxel (4% versus 19%, respectively; $P = 0.017$, chi-square test) as well as with a lower rate of neuropathy. SCC patients in the carboplatin–S-1 arm received docetaxel more

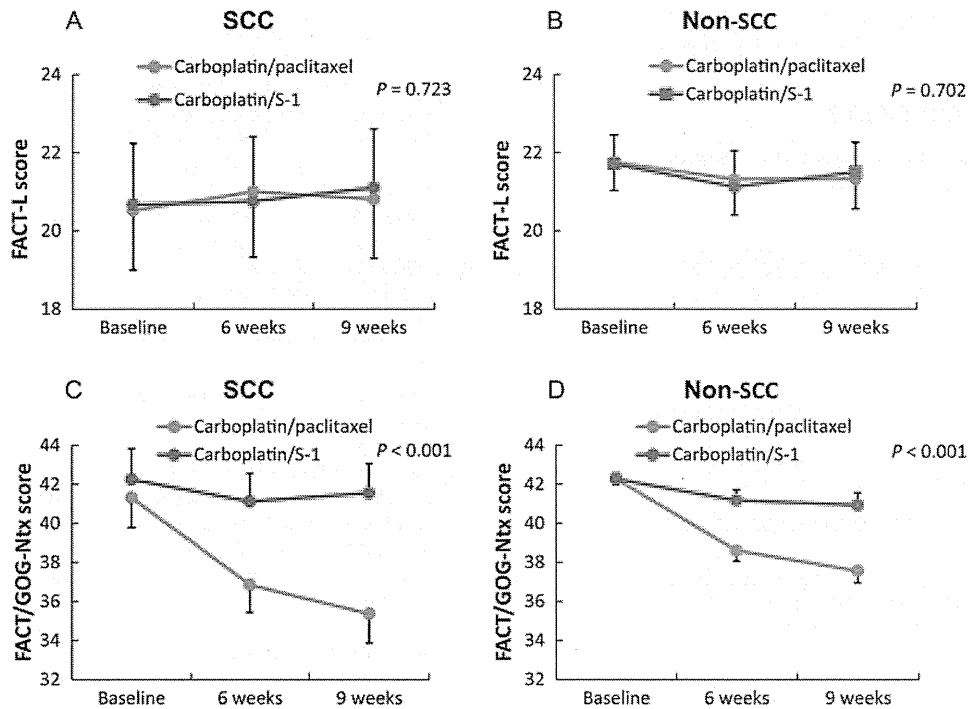

Figure 2. QOL assessments according to histological subtype of NSCLC. Assessments were carried out with the seven-item FACT-L (A and B) and 11-item FACT/GOG-Ntx (C and D) subscales for patients with SCC (A and C) or with non-SCC (B and D). Data are presented as least-square means and 95% CIs. Higher scores indicate a better QOL. *P* values were determined by analysis of variance.

Table 4. Post-treatment rate according to histological subtype of NSCLC

	Squamous			Nonsquamous		
	CBDCA–S-1 (*N* = 55)	CBDCA–PTX (*N* = 59)	*P*	CBDCA–S-1 (*N* = 227)	CBDCA–PTX (*N* = 223)	*P*
Second-line, *N* (%)	43 (78.2)	39 (66.1)	0.15	168 (74.0)	156 (70.0)	0.34
Docetaxel, *N* (%)	32 (58.2)	18 (30.5)	0.003	107 (47.1)	99 (44.4)	0.56
EGFR-TKI, *N* (%)	7 (12.7)	6 (10.2)	0.67	122 (53.7)	102 (45.7)	0.09

P values were determined by the chi-square test.

frequently as a second-line treatment than did those in the carboplatin–paclitaxel arm (58.2% versus 30.5%, respectively, $P = 0.003$), possibly because the former patients were in better condition as a result of a better tolerated first-line regimen. The reduced toxicity of carboplatin–S-1, especially with regard to neuropathy and neutropenia, may thus have allowed for more frequent application of second-line treatment with docetaxel, which has been shown to improve survival over best supportive care for the second-line setting in phase III trials [18]. Kaplan–Meier survival curves for the patients with SCC began to diverge shortly after the end of the study treatment, suggesting that the higher percentage of active second-line treatment in the carboplatin–S-1 arm of the SCC cohort may have contributed to the improved survival outcome. Given the increasing number of active drugs available for second-line treatment, subsequent therapies instituted after disease progression can have a substantial impact on OS in advanced NSCLC [19]. If multiple drugs with no large differences in effectiveness are indicated for NSCLC, treatment strategies should take into account the overall treatment plan envisioned for a given patient, including second-line and subsequent therapies as well as first-line chemotherapy.

In conclusion, we have presented the results of updated survival analysis and subgroup analysis by histology for the first phase III study of the combination of carboplatin and S-1 for the treatment of chemotherapy-naïve patients with advanced NSCLC. This regimen is therapeutically beneficial and well tolerated in such patients with either SCC or non-SCC histology. Given its efficacy and favorable toxicity profile, the combination of carboplatin and S-1 is a feasible platinum-based option to which molecularly targeted agents can be added. We are currently conducting a phase II trial of carboplatin and S-1 in combination with bevacizumab for patients with previously untreated advanced non-SCC NSCLC [20]. Furthermore, on the basis of the promising results showing a survival advantage for

SCC patients, carboplatin and S-1 should be considered among first-line treatment options for NSCLC patients with SCC.

acknowledgements

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disclosure

The authors have declared no conflicts of interest.

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ORIGINAL ARTICLE

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

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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.); ICORG, the All Ireland Cooperative Oncology Research Group, 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.

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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]).

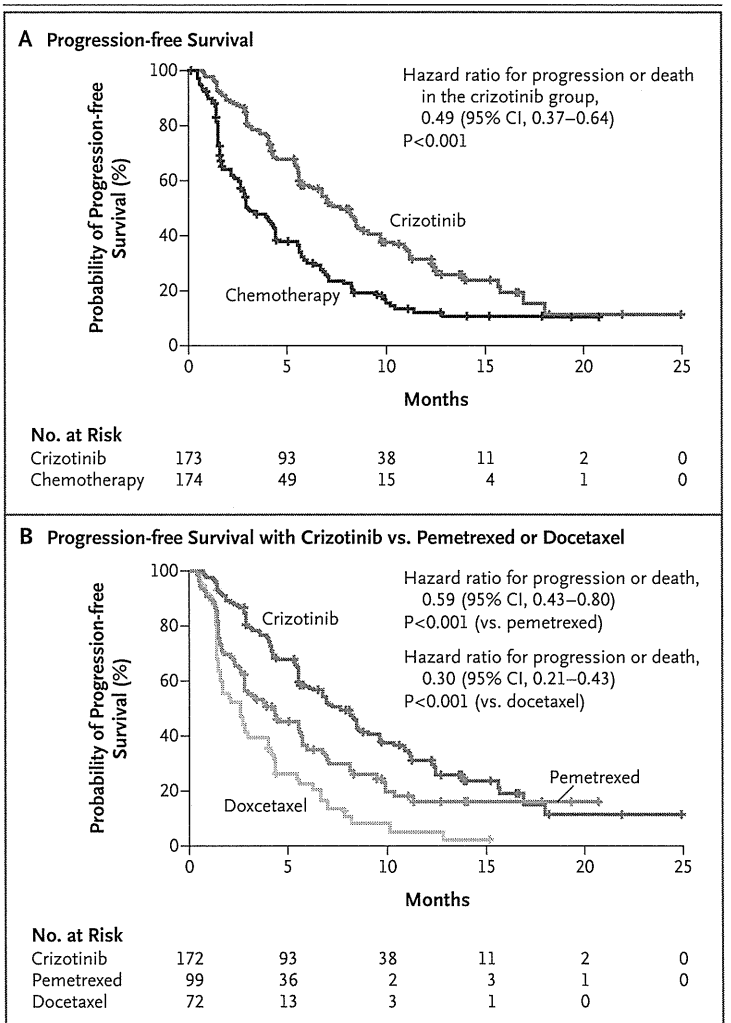

Figure 1. Progression-free Survival.

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).

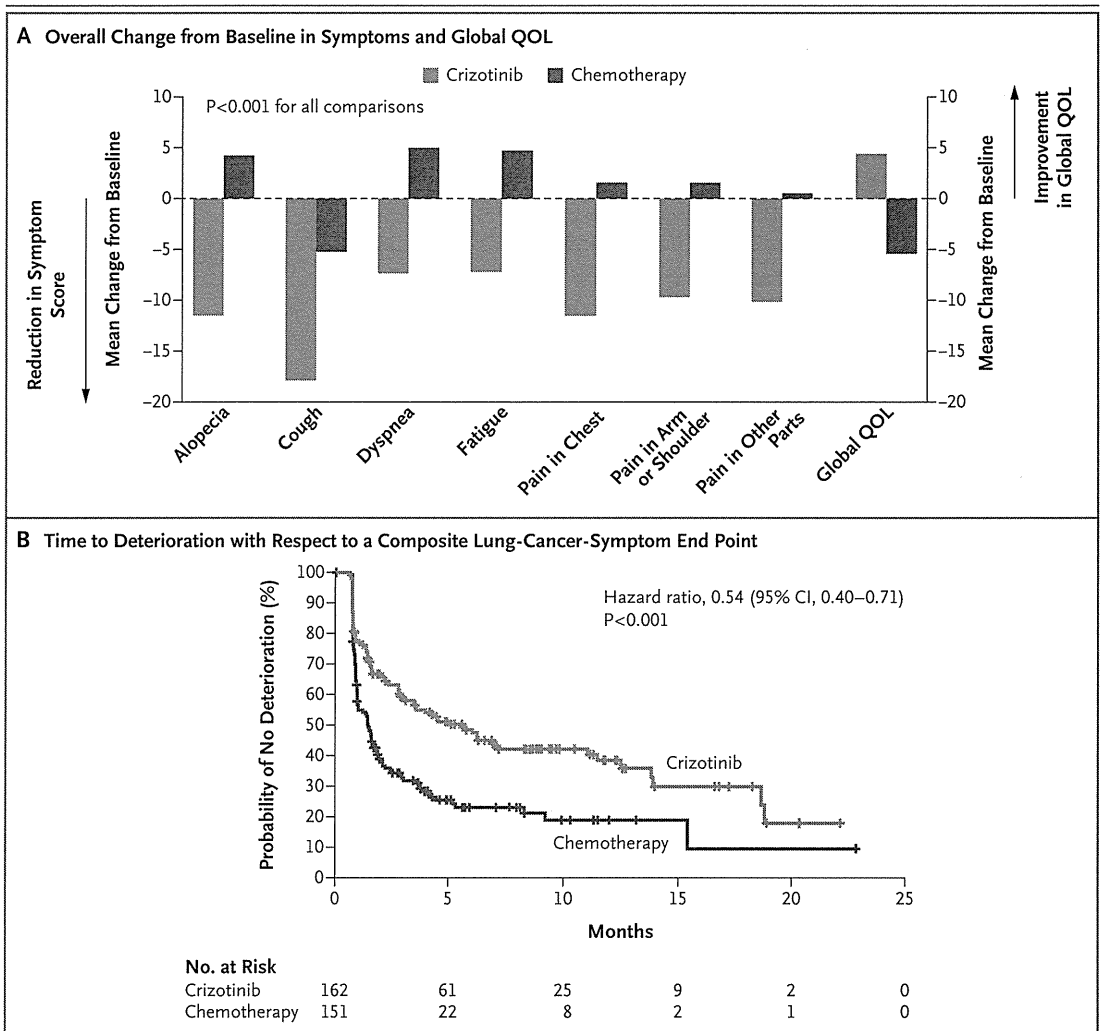

Figure 2. Patient-Reported Outcomes.

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.

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