Patient-Reported Outcomes and Quality of Life in PROFILE 1007: A Randomized Trial of Crizotinib Compared with Chemotherapy in Previously Treated Patients with *ALK*-Positive Advanced Non–Small-Cell Lung Cancer

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Introduction: The main objective of the current post hoc analysis was to compare patient-reported outcomes between crizotinib (N = 172) and chemotherapy subgroups (pemetrexed [N = 99] and docetaxel [N = 72]) in previously treated patients with advanced *ALK*-positive non–small-cell lung cancer, in PROFILE 1007 study (Pfizer; NCT0093283).

Methods: Patient-reported outcomes were assessed at baseline, day 1 of each cycle, and end of treatment. General health status was measured using the EuroQol-5D visual analog scale and health utility index scores were assessed using the EuroQol-5D descriptive system. Functioning, lung cancer symptoms, and global quality of life (QOL) were assessed using European Organisation for Research and Treatment of Cancer QLQ-C30 and the QLQ-LC13 lung cancer module. Repeated measures mixed-effects analyses compared overall scores and change from baseline scores, controlling for baseline scores.

Results: The overall mean EQ-5D health utility index scores (95% CI) on treatment were significantly greater ($p < 0.05$) for crizotinib (0.82 [0.79−0.85]) than for chemotherapy (0.73 [0.70−0.77]; 0.74 [0.70−0.79] for pemetrexed and 0.66 [0.58−0.74] for docetaxel). A significantly greater improvement from baseline was observed with crizotinib versus pemetrexed and versus docetaxel treatment groups for general health status, physical functioning, global QOL, dyspnea, fatigue, and pain. Improvement rates for fatigue, cough, pain, dyspnea, and global QOL were significantly greater on crizotinib compared with pemetrexed and docetaxel, respectively. Worsening rates for diarrhea and constipation were higher with crizotinib.

Conclusion: The benefits of crizotinib in improving symptoms and QOL are demonstrated regardless of whether the comparator is pemetrexed or docetaxel.

Key Words: Patient-reported outcomes, Quality of life, Crizotinib, Non–small-cell lung cancer.

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The majority of patients with lung cancer are symptomatic at initial diagnosis,[1] most often with fatigue, dyspnea, cough, and pain.[2] In addition to respiratory symptom clusters,[3] nonrespiratory symptoms of psychological distress (worry, anxiety) and general physical symptoms, such as loss of appetite, are frequent[4] and difficult to palliate with current supportive treatments. While improving survival is a major goal of treatment, palliative therapy to alleviate symptoms and optimize well-being without adding toxicity is prioritized by patients.[5]

Crizotinib (Pfizer, Inc., New York, NY) is an oral small-molecule tyrosine kinase inhibitor (TKI) targeting ALK, MET, and ROS1 tyrosine kinases.[6,7] The results of primary analyses from a randomized, controlled, open-label, phase III trial (PROFILE 1007) of crizotinib compared with chemotherapy in patients with advanced, previously treated *ALK*-positive non–small-cell lung cancer (NSCLC), were previously reported.[8] In the chemotherapy arm, patients received either docetaxel or pemetrexed depending on prior first-line treatment and/or tumor histology. These drugs have distinctly different side-effect profiles.[9] Crizotinib was associated with a longer progression-free survival (PFS; 7.7 months versus 3.0 months for chemotherapy, hazard ratio [HR], 0.49,

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95% confidence interval [CI], 0.37–0.64, $p < 0.001$), higher response rates (65% [95% CI, 58–72] versus 20% [95% CI, 14–26] for chemotherapy; $p < 0.001$), and significantly greater improvement in patient-reported symptoms, global quality of life (QOL), and delayed time to deterioration (TTD) of prespecified lung cancer symptoms compared with chemotherapy.[8] The original publication did not include the results for patient-reported general (disease nonspecific) health status and health utility index for crizotinib compared with the chemotherapy arm. Nor were results for patient-reported general health status, health utility scores, patient-reported symptoms, functioning, and QOL for crizotinib compared with the specific chemotherapy drug in the comparator arm, i.e., crizotinib versus pemetrexed and crizotinib versus docetaxel presented. Here, we present these results.

PATIENTS AND METHODS

Patient Population, Study Design, and Treatment

In brief, all patients had locally advanced or metastatic NSCLC positive for *ALK* rearrangement. Key eligibility criteria were progressive disease after one platinum-based chemotherapy regimen and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. 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/m^2) or docetaxel (75 mg/m^2) every 3 weeks. The primary end point was PFS and secondary end points included patient-reported outcomes (PROs). This study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guidelines on Good Clinical Practice, and applicable local regulatory requirements and laws. All participants provided informed consent. The protocol, amendments, and informed consent forms were approved by an institutional review board or independent site-specific ethics committee (see Shaw et al.[8] for full details).

Questionnaires to measure PROs were self-administered at baseline (day 1 cycle 1) and on day 1 of every subsequent cycle until end of treatment prior to any testing, treatment, or discussion with the physician or clinic personnel. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core module (EORTC QLQ-C30)[10] comprises 30 questions assessing global QOL, functioning, and symptoms of both multi-item and single-item measures. The EORTC QLQ 13-item lung cancer module (LC-13) module comprises 13 questions assessing lung cancer-specific symptoms.[11] For each domain and item, a linear transformation was applied to standardize the raw score to a range from 0 to 100, with 100 representing best possible function/QOL, and highest symptom severity. A 10-point change from baseline in an item or domain is established to be clinically meaningful.[12] The EQ-5D questionnaire is a generic, non-cancer-specific tool that consists of the EQ-5D descriptive system that can be used to calculate a health utility index score and a visual analog scale (EQ-5D VAS) in which patients rate their current general health status on a scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).[13]

Analyses

The number and percentage of patients of the total number eligible at each cycle who completed the QLQ-C30, QLQ-LC13, and EQ-5D were summarized for crizotinib, pemetrexed, and docetaxel at each time point. The questionnaire domains and items were scored according to the respective scoring algorithm.[14] Comparison of the EORTC QLQ-C30 and LC-13 scores between crizotinib and each of the chemotherapy subgroups was performed as follows: (1) mean change from baseline scores across cycles; (2) proportion of patients with improved, stable, or worsened outcomes; and (3) median TTD in symptoms of cough, dyspnea, and pain. Comparisons were performed between crizotinib and the pemetrexed and docetaxel subgroups. No comparisons were performed between the pemetrexed and docetaxel subgroups. Patients who had completed at least one question at baseline and at least at one time point on treatment (referred to as the PRO-evaluable population) were included in these analyses.

Mean Overall On-Treatment and Change from Baseline Scores

Repeated measures mixed-effects analyses[15] were performed to compare between-treatment EQ-5D index on-treatment scores, the EORTC QLQ C-30 and LC-13 item and domain scores, and EQ-5D VAS change from baseline scores so as to adjust for correlation between data collected across multiple data points for an individual. Baseline scores were included as control variables within the regression model. No adjustments were made for multiplicity of testing.

Proportion of Patients with Improved or Worse Outcome

Patients were classified as improved or worse for all symptom and function domains, global QOL, and single items based on a longitudinal analysis across all time points for an individual patient, and using a 10-point or greater change, previously validated to be clinically meaningful.[12] For analysis of functioning domains and global QOL, a patient was classified as improved if a 10-point or greater increase was observed in the average change from baseline scores across all available time points on treatment for that patient. Similarly, a patient was classified as worse if a decrement of 10 points or worse was observed in the average change from baseline scores across all available time points for an individual patient. For analysis of symptom domains and single items, the classification into improved/worse categories was the reverse, such that a positive change indicates worsening (i.e., greater symptom severity) and a negative change indicates symptom improvement. Improvement and worsening rates between treatments were compared using the χ^2 test.

Time to Deterioration in Pain in Chest, Dyspnea, or Cough

TTD was calculated as the time from randomization to the first 10-point or greater worsening from baseline in chest pain, dyspnea, or cough symptoms and was summarized using the Kaplan-Meier method. Patients were censored at the last time point that they completed the pain

in chest, dyspnea, and cough items, only if the symptoms had not "deteriorated" prior to this time point. The estimated Kaplan-Meier plots were provided for each symptom and the unstratified log-rank test used to compare the time to first deterioration between crizotinib and the subgroups of patients treated with pemetrexed or docetaxel. The Brookmeyer-Crowley method[16] was used to derive the median time. The Hochberg procedure was used to adjust for multiple comparisons.[17] A p value less than 0.05 was considered statistically significant.

Role of the Funding Source

The study sponsor, together with members of the PROFILE 1007 steering committee, was responsible for the study design. The sponsor collected the data and analyzed them in conjunction with the authors. All authors approved the final content of this report.

RESULTS

Patient Characteristics

The intent-to-treat population comprises 347 patients of whom 173 were randomized to crizotinib and 174 to chemotherapy. A total of 99 patients (57%) received pemetrexed and 72 patients (41%) received docetaxel. The PRO-evaluable population included 162 patients in the crizotinib arm and 151 patients in the chemotherapy arm (89 on pemetrexed and 62 on docetaxel). Patient baseline characteristics were generally comparable among the groups (Supplementary Table 1, Supplemental Digital Content, http://links.lww.com/JTO/A682). A numerically higher proportion of patients who received pemetrexed were older than 65 years and were Asian. The median duration of study treatment was longer in the crizotinib arm (31 weeks) compared with the chemotherapy arm (12 weeks; 18 and 9 weeks for pemetrexed and docetaxel, respectively).

Compliance

At baseline, 165 of 173 patients (97%) on crizotinib and 162 of 171 patients (95%) on chemotherapy (97% in the pemetrexed and 92% in the docetaxel subgroups, respectively) completed questionnaires. Compliance rate was defined for subsequent time points, as the percentage of eligible patients expected to complete QOL questionnaires at a time point (i.e., they had neither died nor discontinued study assigned treatment). The compliance rate ranged after baseline over the first 10 cycles from 96% to 100% for crizotinib, from 93% to 97% for pemetrexed, and from 83% to 85% for docetaxel.

Baseline Scores

Baseline scores were comparable among the groups for all domains and items of the EORTC-QLQ-C30 and LC-13 tools (Table 1). The mean (standard deviation; SD) scores at baseline were comparable between-treatment groups for the EQ-5D general health status and the EQ-5D utility index (Table 2). The proportion of patients reporting the presence of a problem at baseline for crizotinib and chemotherapy (pemetrexed and docetaxel), respectively, were mobility (31% and 32%), self-care (9% and 14%), usual activities (51% and 52%), pain (62% and 67%), and anxiety/depression (49% and 57%). Symptoms with the highest mean baseline scores were fatigue, cough, dyspnea, and pain. Compared with normative reference values for advanced lung cancer,[14] the mean scores at baseline were numerically higher for physical and role functioning (Table 1).

Impact on EQ-5D Health Utility Index and General Health Status Scores

The overall mean EQ-5D health utility index scores (95% CI) on treatment were significantly greater ($p < 0.05$) for crizotinib (0.82 [0.79−0.85]) than for chemotherapy (0.73 [0.70−0.77]; 0.74 [0.70−0.79] for pemetrexed and 0.66 [0.58−0.74] for docetaxel). Within groups, a significant overall improvement from baseline in general health status (EQ-5D VAS) was observed for crizotinib compared with a significant overall deterioration for chemotherapy. Significant overall deterioration from baseline was also observed for the pemetrexed and docetaxel subgroups. A greater overall improvement in general health status from baseline was observed in the crizotinib arm compared with either pemetrexed (estimated difference [95% CI]: 8.74 [4.47, 13]; $p < 0.001$) or docetaxel (estimated difference [95% CI]: 14.50 [7.82, 21.17]; $p < 0.001$) (Table 2).

Change from Baseline in Global QOL, Functioning, and Symptoms: Between-Treatment Comparison

Global QOL data demonstrated a greater improvement from baseline for crizotinib than for pemetrexed ($p < 0.05$) (Figure 1*A*) or docetaxel ($p < 0.001$) (Figure 1*B*). Compared with crizotinib, docetaxel was associated with worsening in all functional domains (physical, social, role, emotional, and cognitive). Although the same degree of deterioration in functioning was not demonstrated with pemetrexed, physical functioning was significantly improved on crizotinib when compared with pemetrexed ($p < 0.05$) (Figure 1*A*). Docetaxel was also associated with significantly greater worsening of alopecia, cough, dyspnea (QLQ C-30 and LC-13 domains), pain (all pain items), appetite loss, fatigue, insomnia, hemoptysis, peripheral neuropathy, dysphagia, and sore mouth compared with crizotinib (Figure 2*B*, *D*). Similarly, pemetrexed was associated with a significantly ($p < 0.05$) greater worsening of these symptoms compared with crizotinib, with the exception of alopecia, peripheral neuropathy, and dysphagia (Figure 2*A*, *C*). Concomitant use of analgesics was similar between the treatment arms (59.9% for crizotinib and 63.2% for chemotherapy). Higher antiemetic use was observed in the chemotherapy arm (67.3%) compared with crizotinib (20.3%). The only symptoms that deteriorated significantly ($p < 0.05$) from baseline on crizotinib were constipation (compared with pemetrexed) and diarrhea (compared with pemetrexed and docetaxel). No significant differences were observed between crizotinib and pemetrexed or docetaxel in overall change from baseline scores for nausea and vomiting.

TABLE 1. Baseline Scores: EORTC QLQ-C30 and LC-13 (PRO-Evaluable Population)

Domain	Crizotinib Mean ± SD	Chemotherapy Mean ± SD	Chemotherapy (Pemetrexed Subgroup) Mean ± SD	Chemotherapy (Docetaxel Subgroup) Mean ± SD	Normative Reference Values[a]
Global QOL (QLQ-C30)	57.6±21.4	59.2±22.4	59.5±22.6	58.9±22.2	54.7±23.8
Functioning (QLQ-C30)					
Physical	76.5±20.6	77.1±21.2	76.9±19.7	77.5±23.2	65.9±25.6
Social	68.5±27.5	67.7±29.1	67.8±29.0	67.5±29.5	69.8±30.3
Role	69.8±28.7	68.2±29.9	68.0±29.3	68.5±30.9	55.5±34.5
Cognitive	85.3±18.3	84.0±21.9	83.0±21.0	85.5±23.3	81.6±22.7
Emotional	74.8±21.2	74.0±20.7	75.1±20.8	72.4±20.7	67.3±24.1
Symptoms (QLQ-C30)					
Fatigue	38.2±24.5	34.6±25.1	35.8±25.2	32.8±25.0	44.2±27.5
Nausea and vomiting	8.2±14.2	11.7±18.2	11.8±19.8	11.6±15.9	10.8±19.1
Pain	23.6±24.8	27.6±27.2	29.4±26.7	25.0±27.8	34.7±32.3
Dyspnea	31.1±28.3	31.8±28.1	33.0±28.6	30.1±27.5	40.7±32.2
Insomnia	22.4±26.3	27.8±27.1	30.0±29.3	24.7±23.3	34.8±33.4
Appetite loss	23.7±28.2	22.1±28.3	21.3±28.1	23.1±28.7	31.1±34.6
Constipation	14.7±25.2	16.2±24.6	18.2±25.7	13.4±23.0	22.2±31.7
Diarrhea	9.5±18.7	7.8±15.6	9.5±17.5	5.4±12.4	7.3±18.1
Symptoms (QLQ-LC13)					
Dyspnea	27.0±21.8	26.9±24.1	30.0±25.2	22.4±21.6	31.5±24.6
Cough	37.9±27.0	40.9±30.9	43.8±33.2	36.6±27.0	38.4±26.6
Hemoptysis	2.5±9.5	3.8±12.5	4.1±14.1	3.3±10.0	7.7±17
Sore mouth	5.4±15.3	5.3±16.9	4.9±16.3	6.0±17.8	5.1±14.9
Dysphagia	6.6±14.8	8.0±19.9	9.4±20.1	6.0±19.7	6.8±17.8
Peripheral neuropathy	13.9±22.2	16.4±26.4	16.9±27.6	15.8±24.8	8.9±19.8
Alopecia	17.7±30.8	17.3±29.8	20.2±31.6	13.1±26.7	5.2±19.1
Pain in chest	19.2±22.9	23.6±27.8	29.1±28.2	15.8±25.5	20.8±26.6
Pain in arm or shoulder	16.6±24.2	19.0±27.7	20.6±28.2	16.7±27.1	22.4±30.1
Pain in other parts	22.5±27.1	31.7±30.8	32.2±30.8	31.0±31.1	23.8±30.9

[a]Normative reference values specific for advanced-stage lung cancer (stage III–IV).[14]

TABLE 2. Overall EQ-5D General Health Status and Utility Index Scores on Treatment and Overall Change from Baseline by Treatment Subgroup (PRO-Evaluable Population)

	Crizotinib (*N* = 160)	Chemotherapy (*N* = 150)	Pemetrexed (*N* = 88)	Docetaxel (*N* = 62)
EQ-5D General Health Status score at baseline, mean (SD)	64.49 (20.88)	67.49 (20.71)	68.45 (19.88)	66.15 (21.90)
EQ-5D Utility Index score at baseline, mean (SD)	0.73 (0.24)	0.70 (0.26)	0.73 (0.24)	0.67 (0.29)
Overall EQ-5D Utility Index score on treatment, mean (SE)	0.82 (0.01)	0.73 (0.02)	0.74 (0.02)	0.66 (0.04)
95% CI	0.79, 0.85	0.70, 0.77	0.70, 0.79	0.58, 0.74
p Value	NA	<0.001[a]	<0.05[a]	<0.001[a]
Overall EQ-5D General Health Status score on treatment, mean	73.75	63.01	65.17	58.51
95% CI	(71.3, 76.2)	(59.99, 66.05)	(61.61, 68.72)	(52.27, 64.74)
p Value		<0.001[a]	<0.001[a]	<0.001[a]
Overall EQ-5D General Health Status change from baseline, mean	4.68**	–6.06**	–4.09*	–9.46*
95% CI	(2.23, 7.12)	(–9.09, –3.03)	(–7.65, –0.54)	(–15.7, –3.23)
Difference between treatments (95% CI)		10.73 (6.85, 14.62)	8.74 (4.47, 13)	14.50 (7.82, 21.17)
p Value		<0.001[a]	<0.001[a]	<0.001[a]

[a]*p* Values are for between-treatment comparisons with crizotinib.
Within treatment change from baseline *$p < 0.05$, **$p < 0.001$.

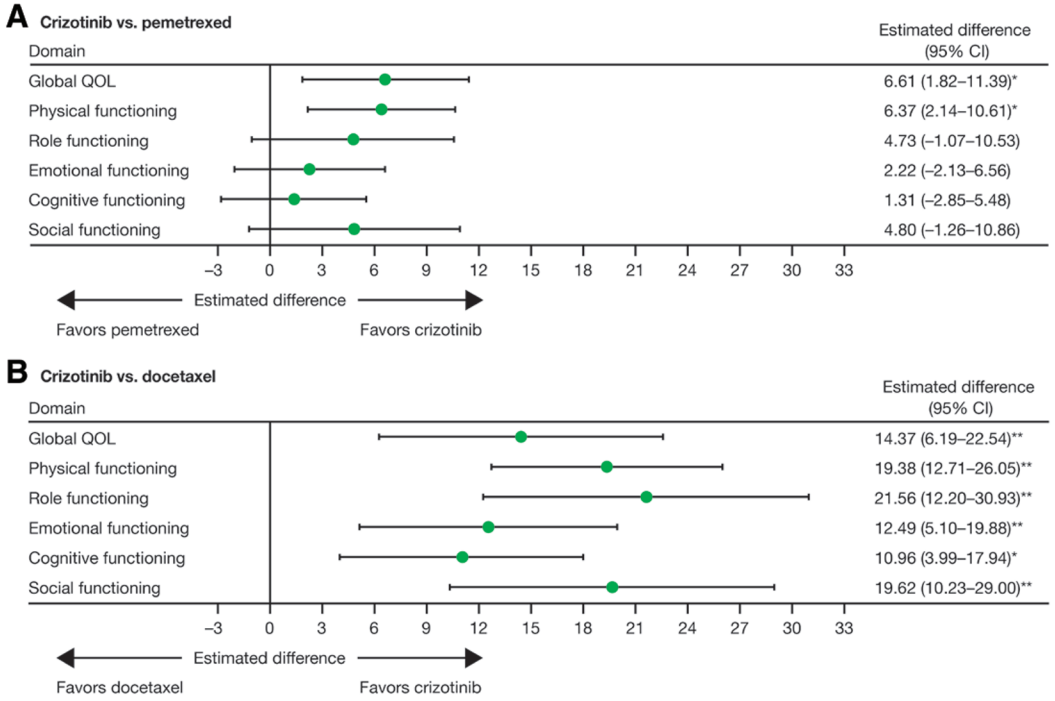

FIGURE 1. Differences between-treatment groups in overall change from baseline scores in patient-reported functioning and global QOL. *$p < 0.05$, **$p < 0.001$.

Proportion of Patients with Improved, Stable, or Worsened Outcome

Statistically significant ($p < 0.05$) differences were seen in global QOL improvement rates between crizotinib and the pemetrexed subgroup, with 42.6% versus 25.8% of patients improving, respectively (Figure 3*A*). Physical functioning (Figure 3*A*), fatigue, pain, appetite loss, cough, dyspnea, and pain in arm or shoulder (Figure 3*B*, *C*) were also improved in more patients on crizotinib than on pemetrexed. For example, for fatigue, improvement was observed in 46.3% versus 24.7% of patients and worsening in 16.7% versus 36% of patients on crizotinib versus pemetrexed, respectively. Similarly, for dyspnea (QLQ-C30) 40.7% versus 28.1% improved and 16.7% versus 30.3% worsened on crizotinib versus pemetrexed. The proportion of patients with worsening of constipation and diarrhea was statistically significantly lower on pemetrexed than on crizotinib (Figure 3*B*).

Similar results were obtained for crizotinib when compared with the docetaxel subgroup: global QOL improved in 42.6% versus 12.9% of patients and worsened in 21% versus 45% of patients, respectively. Physical, emotional, and social functioning also improved among more patients on crizotinib (Figure 3*A*), whereas physical, role, cognitive, and social functioning all worsened for significantly ($p < 0.05$) more patients on docetaxel. More patients on crizotinib than docetaxel experienced improvement (or less worsening) for fatigue, pain (all items), alopecia, insomnia, appetite loss, cough, dyspnea (QLQ-C30 and LC-13), peripheral neuropathy, and sore mouth (Figure 3*B*, *C*). No statistically significant differences were observed for nausea and vomiting, hemoptysis or dysphagia between crizotinib and either the pemetrexed or docetaxel subgroups (Figure 3*B*, *C*).

Time to Deterioration in Symptoms

The TTD event rate was observed to be 56% in the crizotinib arm, 67% in the pemetrexed subgroup, and 82% in the docetaxel subgroup. The median TTD for pain in chest, dyspnea (QLQ-LC13), or cough as a composite end point was 5.6 months (95% CI, 3.4–11.0 months) for the crizotinib arm compared with 1.9 months (95% CI, 1.4–3.0 months) for the pemetrexed subgroup, and 0.9 months (95% CI, 0.9–1.4 months) for the docetaxel subgroup. Treatment with crizotinib was associated with a longer TTD in symptoms of pain in chest, dyspnea, or cough compared with pemetrexed (HR, 0.664; 95% CI, 0.478–0.923; $p = 0.0253$) (Figure 4*A*) or with docetaxel (HR, 0.374; 95% CI, 0.262–0.536; $p < 0.001$) (Figure 4*B*). When each symptom was analyzed separately, crizotinib was associated with a greater delay in TTD for pain in chest (median 20.8 months; 95% CI, 18.7 months—not reached [NR]) compared with pemetrexed (median 15.4 months; 95% CI, 9.2 months—NR; HR, 0.468; $p = 0.0055$) and docetaxel (median 3.5 months; 95% CI, 1.5 months—NR; HR, 0.214; $p < 0.001$). Similarly, for dyspnea the median TTD for patients on crizotinib was 13.8 months (95% CI, 6.2–18.8 months) compared with a median of 3.0 months (95% CI, 1.8–5.7 months; HR, 0.613; $p = 0.0228$), for the pemetrexed subgroup and 2.2 months (95% CI, 1.2–4.2 months; HR, 0.455; $p < 0.001$) for the docetaxel subgroup. For cough, there was a longer TTD with crizotinib (median 18.8 months; 95% CI, 12.5–22.9; $p < 0.05$) than with docetaxel (median 8.3 months; 95% CI, 5.2–NR; HR, 0.528; $p = 0.0138$), whereas there was no difference for crizotinib compared with pemetrexed (HR, 0.886; $p = 0.619$).The longer TTD for individual symptoms with crizotinib is consistent with the finding that

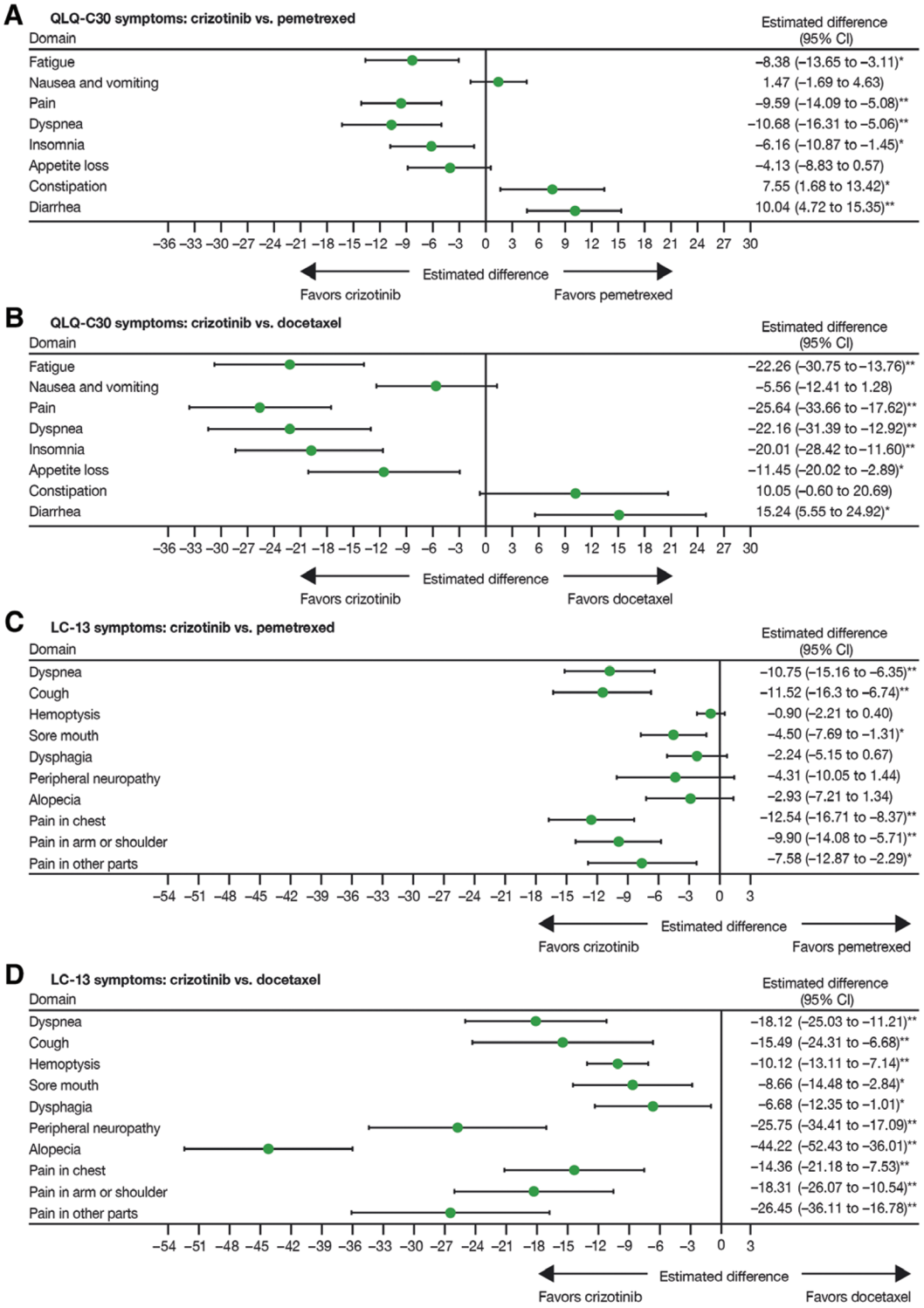

FIGURE 2. Differences between-treatment groups in overall change from baseline scores in patient-reported symptoms. *$p < 0.05$, **$p < 0.001$.

there is overall improvement from baseline in these symptoms with crizotinib. The individual symptom median TTD is the time at which 50% of the patients in a treatment arm have reported a 10-point or greater deterioration from baseline in that particular symptom. A 10-point deterioration on any one of the symptoms included in the composite end point (deterioration in one or more of cough, pain in chest, dyspnea) would be considered as an event for the TTD composite end point

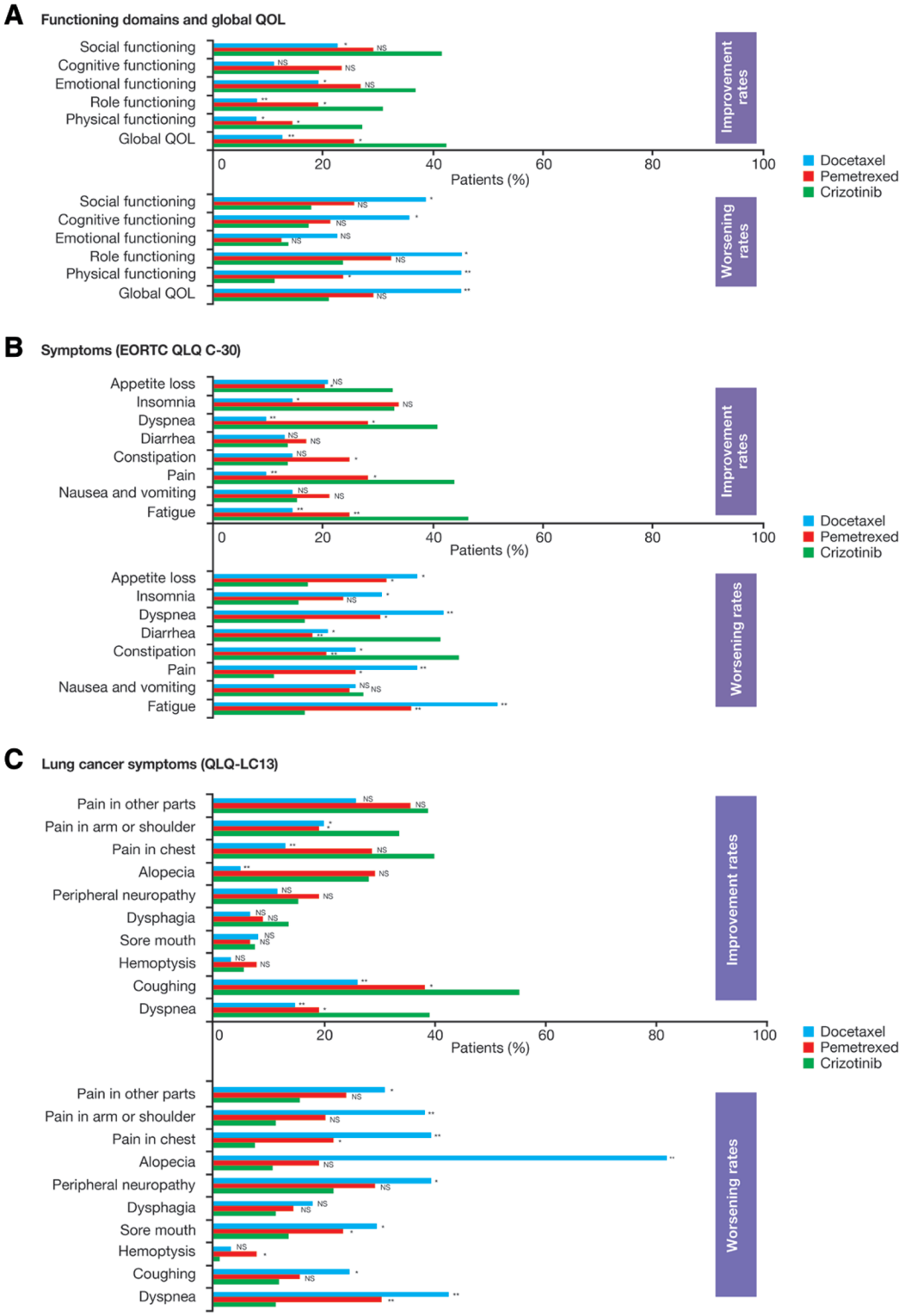

FIGURE 3. Proportion of patients showing improvement and worsening in functioning, global QOL, and symptoms by treatment subgroup. *A*, Functioning domains and global QOL. *B*, Symptoms (EORTC QLQ C-30). *C*, Lung cancer symptoms (QLQ-LC13). *$p < 0.05$, **$p < 0.001$; NS, not significant. All *p* values are for comparisons versus crizotinib.

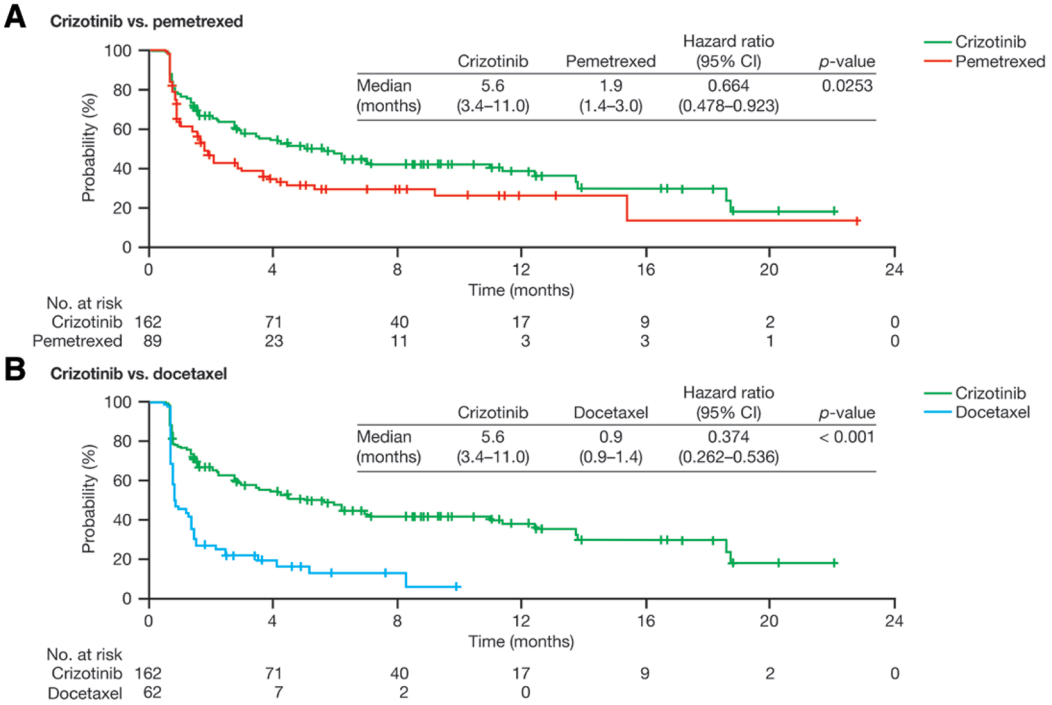

FIGURE 4. Time to deterioration in pain in chest, cough, or dyspnea.

and hence the probability of reaching the median sooner could increase than with each individual symptom.

DISCUSSION AND CONCLUSION

The major goals of treatment for advanced, incurable NSCLC are prolongation of survival, palliation of symptoms, and improvement in health-related QOL.[18] The primary analysis of results for the PROFILE 1007 trial demonstrated significantly better objective response rate, PFS, and PROs for crizotinib compared with chemotherapy (pemetrexed or docetaxel) in patients with *ALK*-positive NSCLC.[8] Here, previously unreported data are presented on general health status for crizotinib compared with chemotherapy, and post hoc subgroup analysis of PROs according to the type of chemotherapy received. The findings emphasize that the superiority of crizotinib for symptom control and QOL in the second-line treatment for *ALK*-positive NSCLC is maintained regardless of whether the chemotherapy comparator is pemetrexed or docetaxel.

The EQ-5D general health status is not specific for lung cancer and so gauges the generic benefit of an intervention. In this analysis, the baseline scores were higher (reflecting better status), consistent with trial eligibility, than those obtained for an observational study of over 1000 unselected advanced-stage NSCLC patients.[2] Nevertheless, crizotinib was associated with improvement in general health status in this study population. In subgroup analyses, overall general health status worsened on docetaxel on pemetrexed. These results provide striking confirmation of potential for a concurrent improvement in general health status alongside PFS on crizotinib, whereas the same is not demonstrable for either pemetrexed or docetaxel.

Within the chemotherapy comparator arm there was no randomization, and so this analysis was not designed to compare docetaxel to pemetrexed. The purpose was to assess a differential effect of crizotinib compared with either chemotherapy subgroup. In a randomized comparison, docetaxel and pemetrexed demonstrated similar response rates and survival, with no differences in symptom index scores, but differed with respect to toxicity.[9] Here, expected differences in alopecia and neuropathy were observed; in addition, the degree of difference demonstrated by the point estimates and CIs for change in baseline scores (shown in Figures 1 and 2*C*, *D*) suggest a greater difference for docetaxel versus crizotinib than for pemetrexed versus crizotinib. However, there is no symptom or functional domain where the direction of benefit differs according to chemotherapy subgroup. Among the physician-reported adverse events in the primary analysis,[8] there was more nausea on crizotinib compared with chemotherapy (55% versus 37%). Here, patient-reported nausea did not differ significantly for either crizotinib versus docetaxel or pemetrexed. This finding reinforces the value of patient-reported data for assessment of the impact of treatment side effects.

This is the first study to demonstrate improvement in lung cancer symptoms, QOL, and general health status of a targeted agent compared with second-line chemotherapy. Common symptoms of cough, dyspnea, and pain were improved by crizotinib more than by chemotherapy, consistent with the results of studies comparing epidermal growth factor receptor TKIs (EGFR-TKIs) with first-line chemotherapy[19–21] and EGFR-TKIs compared with best supportive care in the second or third line.[22,23] In contrast to studies of EGFR-TKIs, crizotinib also improved constitutional, nonrespiratory symptoms of fatigue (46%) and loss of appetite (33%). Effective

palliative treatments for fatigue are lacking despite this being as prevalent[24] and distressing a symptom as dyspnea and pain in patients with lung cancer.[2,25]

The symptom and QOL improvements reported here are highly clinically relevant. Although statistical significance does not automatically imply clinical significance, the EORTC tools used in this trial were previously validated to be clinically significant at a 10-point or greater change. The EQ-5D general health status is not oncology specific and is a relatively 'crude' measure which could be expected to lack sensitivity to detect a change in our population if the differential treatment effect is small. This reinforces the clinical relevance of the statistically significant improvement in general health status observed with this tool for crizotinib but not for either type of chemotherapy. PROs are arguably more representative of the patient perspective than physician-reported outcomes. In addition, adaptation to symptoms by patients can occur such that they are "downplayed."[26] The open-label trial design could be considered as a potential limitation of this study because patients could be biased in their self-reported assessments based on treatment expectations. Although open-label, the study had an active comparator; therefore, the potential for bias is relatively reduced compared with a placebo-controlled study. Different rates of attrition between-treatment groups, which is very common in oncology studies like the current one, could be considered another limitation as it influences the number of patients eligible to complete a questionnaire at the various time points.

PROs are required by physicians, payers, regulators, and patients for full assessment of the benefit-risk profile, particularly in the context of PFS.[27] In conclusion, using generic and oncology-specific measures, crizotinib demonstrates consistent improvement, compared with single-agent chemotherapy (docetaxel or pemetrexed), in key respiratory symptoms of cough, dyspnea, and pain; constitutional symptoms of fatigue and loss of appetite; and a positive impact on global QOL, functional domains, and general health status. Physician-reported adverse events such as nausea and patient-reported gastrointestinal symptoms that were worse on crizotinib than chemotherapy did not impact negatively on global QOL. Improvement in general health status was observed on crizotinib but not on either chemotherapy. These results reinforce the positive benefit-risk profile of crizotinib in previously treated patients with *ALK*-positive advanced NSCLC.

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