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Symptom Control and Quality of Life in LUX-Lung 3: A Phase III Study of Afatinib or Cisplatin/Pemetrexed in Patients With Advanced Lung Adenocarcinoma With *EGFR* Mutations

James Chih-Hsin Yang, Vera Hirsh, Martin Schuler, Nobuyuki Yamamoto, Kenneth J. O'Byrne, Tony S.K. Mok, Victoria Zazulina, Mehdi Shahidi, Juliane Lungershausen, Dan Massey, Michael Palmer, and Lecia V. Sequist

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James Chih-Hsin Yang, National Taiwan University Hospital, Taipei, Taiwan; Vera Hirsh, McGill University, Montreal, Quebec, Canada; Martin Schuler, West German Cancer Center, University Duisburg-Essen, Essen; Juliane Lungershausen, Boehringer Ingelheim GmbH, Ingelheim, Germany; Nobuyuki Yamamoto, Shizuoka Cancer Center, Shizuoka, Japan; Kenneth J. O'Byrne, St James' Hospital, Dublin, Ireland; Tony S.K. Mok, State Key Laboratory of Southern China, Hong Kong Cancer Institute, The Chinese University of Hong Kong, Hong Kong; Victoria Zazulina, Mehdi Shahidi, and Dan Massey, Boehringer Ingelheim Limited, Bracknell; Michael Palmer, Keele University, Keele, United Kingdom; and Lecia V. Sequist, Massachusetts General Hospital and Harvard Medical School, Boston, MA.

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Corresponding author: James Chih-Hsin Yang, MD, PhD, National Taiwan University, Graduate Institute of Oncology, 7 Chung-Shan South Rd, Taipei, Taiwan; e-mail: chihyang@ntu.edu.tw.

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ABSTRACT

Purpose
Patient-reported symptoms and health-related quality of life (QoL) benefits were investigated in a randomized, phase III trial of afatinib or cisplatin/pemetrexed.

Patients and Methods
Three hundred forty-five patients with advanced epidermal growth factor receptor (*EGFR*) mutation–positive lung adenocarcinoma were randomly assigned 2:1 to afatinib 40 mg per day or up to six cycles of cisplatin/pemetrexed. Lung cancer symptoms and health-related QoL were assessed every 21 days until progression using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and Lung Cancer-13 questionnaires. Analyses of cough, dyspnea, and pain were preplanned, including percentage of patients who improved on therapy, time to deterioration of symptoms, and change in symptoms over time.

Results
Questionnaire compliance was high. Compared with chemotherapy, afatinib significantly delayed the time to deterioration for cough (hazard ratio [HR], 0.60; 95% CI, 0.41 to 0.87; $P = .007$) and dyspnea (HR, 0.68; 95% CI, 0.50 to 0.93; $P = .015$), but not pain (HR, 0.83; 95% CI, 0.62 to 1.10; $P = .19$). More patients on afatinib (64%) versus chemotherapy (50%) experienced improvements in dyspnea scores ($P = .010$). Differences in mean scores over time significantly favored afatinib over chemotherapy for cough ($P < .001$) and dyspnea ($P < .001$). Afatinib showed significantly better mean scores over time in global health status/QoL ($P = .015$) and physical ($P < .001$), role ($P = .004$), and cognitive ($P = .007$) functioning compared with chemotherapy. Fatigue and nausea were worse with chemotherapy, whereas diarrhea, dysphagia, and sore mouth were worse with afatinib (all $P < .01$).

Conclusion
In patients with lung adenocarcinoma with *EGFR* mutations, first-line afatinib was associated with better control of cough and dyspnea compared with chemotherapy, although diarrhea, dysphagia, and sore mouth were worse. Global health status/QoL was also improved over time with afatinib compared with chemotherapy.

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INTRODUCTION

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are effective in patients with non–small-cell lung cancer (NSCLC) with *EGFR* mutations. In five randomized studies examining patients with advanced *EGFR* mutation–positive NSCLC, progression-free survival (PFS) with first-line gefitinib or erlotinib was significantly longer than with platinum-containing combination chemotherapy.[1-5] However, there were no differences in overall survival between EGFR TKIs and chemotherapy in these studies,[1-5] most likely because of the high proportion of cross over from chemotherapy to EGFR TKIs observed after study completion and the strong response to EGFR TKIs in the salvage setting.[6]

Patient-reported outcomes (PROs) are clinically relevant treatment outcomes that are directly assessed by patients and reflect their symptoms, functional activities, and health-related quality of

life (QoL). Given the lack of survival benefit from first-line EGFR TKIs compared with chemotherapy, it is vital to document PRO improvements during disease control to further substantiate the clinical meaningfulness of PFS prolongation, a commonly used primary efficacy end point in trials of targeted cancer therapy.[7]

Afatinib is an irreversible ErbB family blocker[8,9] that was compared in a phase III randomized trial with cisplatin/pemetrexed among previously untreated patients with advanced *EGFR* mutation–positive NSCLC (LUX-Lung 3). LUX-Lung 3 met its primary end point, demonstrating a significant PFS advantage for afatinib over chemotherapy.[8] Because cisplatin/pemetrexed is a relatively well-tolerated chemotherapy regimen,[10] both arms had acceptable safety profiles. Full details of the primary study outcomes are reported in the accompanying article.[11] This article reports detailed analysis of PROs from LUX-Lung 3.

PATIENTS AND METHODS

Study Design

The LUX-Lung 3 trial randomly assigned (2:1) eligible patients with stage IIIB or IV lung adenocarcinoma with *EGFR* mutations to oral afatinib 40 mg once daily or intravenous cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 every 21 days[10] for up to six cycles. The primary end point was PFS, and secondary end points included objective tumor response, overall survival, adverse events (AEs), pharmacokinetics, and PROs.

PRO Assessments

Patient-reported symptom and health-related QoL benefits were assessed using the self-administered cancer-specific European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30)[12,13] and its lung cancer–specific module QLQ-LC13.[14,15] QLQ-C30 comprises 30 questions of both multi-item and single-item measures. The QLQ-LC13 comprises 13 questions and was designed for use in patients with lung cancer undergoing chemotherapy or radiotherapy.

PROs were assessed at random assignment and every 21 days until disease progression. For chemotherapy patients, this was on day 1 of each cycle and was delayed if the chemotherapy was delayed. Patients completed questionnaires in the clinic using an electronic portable data capture tool in validated translations for their native language at each time point, before they were provided with any test results to avoid influencing responses. Concomitant medications prescribed for cough, dyspnea, and pain were documented to enable analysis of their potential impact on reported symptoms.

Statistical Considerations

For all analyses, all randomly assigned patients with data were included. Scoring of EORTC questionnaires followed published algorithms.[12] For each scale or item, a linear transformation was applied to standardize the raw score to a range from 0 to 100 (high scores represent a high/healthy level of functioning or high/severe level of symptomatology).[12] A 10-point change in an item or domain is accepted as the threshold for being clinically meaningful.[16]

For each PRO assessed by the EORTC instruments, three analyses were prespecified comparing treatment arms in terms of the distribution of patients who were improved, stable, or worsened; the time to deterioration of the symptom; and the mean difference in symptom scores over time (longitudinal analysis). Prespecified PRO measures of interest were cough (assessed by QLQ-LC13 question 1), dyspnea (composite of QLQ-LC13 questions 3 to 5), and pain (composite of QLQ-C30 questions 9 and 19).[13,14] For the composite items (dyspnea and pain), additional analyses were performed using alternative measures for dyspnea (QLQ-C30 question 8) and pain (composite of QLQ-LC13 questions 10 to 12).

Symptom improvement was defined as a $\geq$ 10-point decrease from baseline at any time during the trial. If a patient had not improved, symptom worsening was defined as a $\geq$ 10-point increase in score at any time during the trial. Otherwise, a patient was considered to be stable. The distribution of those with improved, stable, or worsened symptoms was summarized by treatment arm. A multivariable logistic regression model, controlling for *EGFR* mutation type (Del 19, L858R, and other) and race (Asian and non-Asian), was used to compare the distribution of patients improved versus not improved (stable or worsened).

Time to deterioration in PROs was measured in months from random assignment to the first instance of symptom worsening (10 points from baseline).[12,16,17] Patients without worsening, including those with disease progression, were censored at the last available PRO assessment; those lacking postbaseline assessments were censored at random assignment. Patients who died without documented worsening were considered to have deteriorated at the time of death. Times to deterioration were summarized as Kaplan-Meier plots, and the treatment groups were compared using a Cox proportional hazards regression model stratified by *EGFR* mutation type and race.

Changes in PRO scores over time were assessed using mixed-effects growth curve models.[18] The average longitudinal profile for each end point was described by a piecewise linear model adjusted for the fixed effects of *EGFR* mutation type and race. The models allowed the slope to change at 3, 6, 12, and 18 weeks. The area under the estimated growth curve (AUC) up to the median time to last PRO assessment (39 weeks) was calculated for each treatment arm; AUC divided by time to last assessment was interpreted as the mean score over time. Treatment effect was estimated as the difference between the treatment arm mean scores.

Analyses were repeated in the subgroups defined by Eastern Cooperative Oncology Group[19] performance status (ECOG PS; 0 *v* 1) and baseline symptoms (present *v* absent). Compliance with PRO assessments was calculated per study visit as the number of completed instruments divided by the number of patients having not yet experienced progression or started new anticancer therapy.

Missing PRO data as a result of withdrawal were assessed in terms of the percentage of patients in each treatment group who completed EORTC questionnaires at baseline and at the start of each treatment course. For patients remaining on treatment, correlations between missing data at each visit, treatment group, and several covariates were assessed using Kendall's τ statistic, and sensitivity analyses were conducted exemplarily for cough and dyspnea to assess the potential impact of missing data.

Testing for durability of improvement, an additional analysis required 10-point changes over at least two PRO assessments. For longitudinal analyses, joint models that extended the mixed-effects model by including nonrandom dropout mechanisms were used.[20] Two dropout mechanisms were chosen—time to study completion and time to last PRO assessment.

The trial sponsor collected and analyzed the data; the lead investigators had full access to the data. All analyses were carried out using a two-sided 5% significance level with no adjustments for multiplicity.

RESULTS

PFS

The full results of the clinical study are published in the accompanying article.[11] In total, 345 patients with *EGFR* mutations were randomly assigned (230 to afatinib and 115 to cisplatin/pemetrexed; Fig 1). The median PFS times were 11.1 months for afatinib and 6.9 months for chemotherapy (hazard ratio[HR], 0.58; 95% CI, 0.43 to 0.78; $P < .001$) in all patients and 13.6 months for afatinib and 6.9 months for chemotherapy (HR, 0.47; 95% CI, 0.34 to 0.65; $P < .001$) in patients with common *EGFR* mutations (Del 19/L858R).

Baseline PRO Data

Baseline symptom burden was low overall and well balanced between treatment arms. Mean baseline symptom scores among the afatinib arm were 35 (standard deviation [SD], 26) for cough, 23 (SD, 19) for dyspnea, and 26 (SD, 24) for pain; in the chemotherapy arm, mean baseline scores were 33 (SD, 25) for cough, 25 (SD, 24) for dyspnea, and 24 (SD, 26) for pain. Baseline PRO questionnaires were

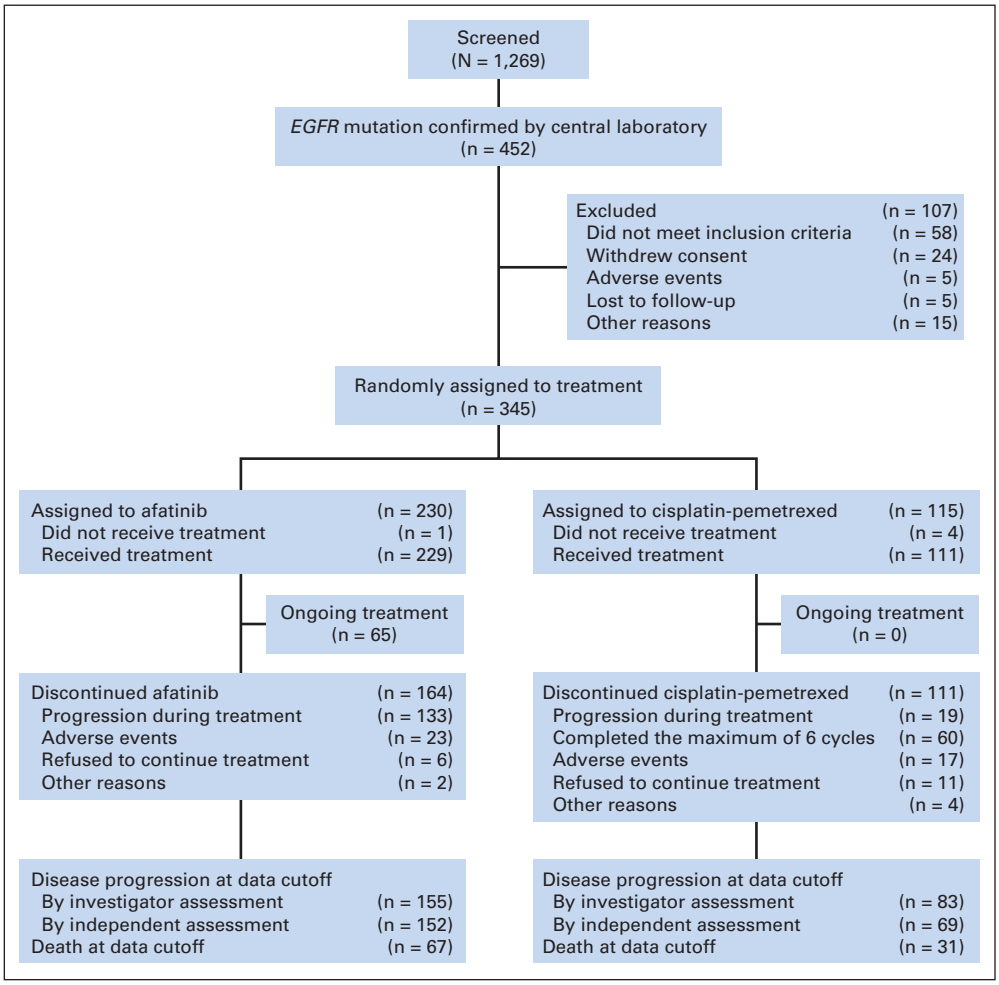

Fig 1. CONSORT diagram.

completed by 97% of patients, and compliance remained high before progression (Fig 2).

Prespecified PRO Measures of Interest

More patients on afatinib experienced clinically meaningful improvements in dyspnea (64% on afatinib *v* 50% on chemotherapy; $P = .010$; Fig 3A). An alternate measure for dyspnea (shortness of breath) similarly favored afatinib (57% *v* 36% for chemotherapy; $P < .001$). The proportion of patients with improvements in pain was higher for afatinib, approaching significance ($P = .051$), and improvements in cough with afatinib were not significant ($P = .244$). Compared with chemotherapy, afatinib significantly delayed the time to deterioration of cough (HR, 0.60; 95% CI, 0.41 to 0.87; $P = .007$), dyspnea (HR, 0.68; 95% CI, 0.50 to 0.93; $P = .015$; Figs 4A and 4B), and individual items of dyspnea (Fig 4D). The delayed deterioration time for pain did not reach statistical significance (HR, 0.83; 95% CI, 0.62 to 1.10; $P = .19$; Fig 4C), although afatinib did significantly delay worsening of the individual item of pain in the chest (Fig 4D). Differences in mean symptom scores over time significantly favored afatinib for cough (-5.73; $P < .001$) and dyspnea (-5.77; $P < .001$; Fig 5), with the extent of benefit for individual patients being much greater (Appendix Fig A1, online only). No significant differences were observed in pain (Fig 5).

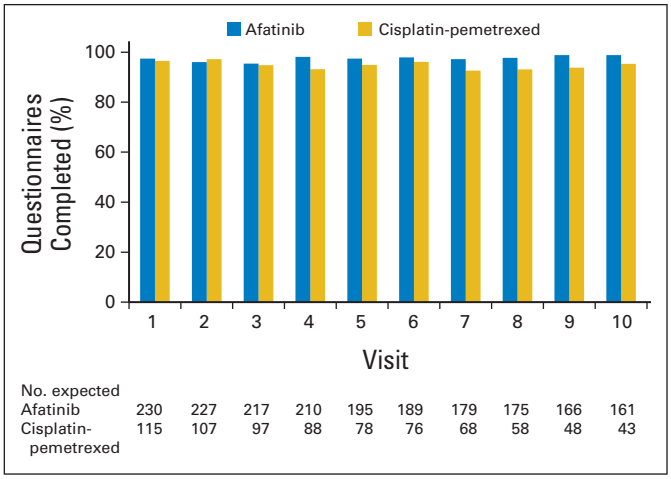

Fig 2. Compliance with European Organisation for Research and Treatment of Cancer questionnaires.

Subgroup analyses demonstrated that the symptom-relieving effect of afatinib compared with chemotherapy was more pronounced in those with baseline symptoms than in asymptomatic patients. Both treatments had comparable symptom efficacy for ECOG PS 0 and 1 patients. PRO analyses in patients with common *EGFR* mutations (n = 308) showed that the larger improvement in PFS in this group was coupled with more pronounced symptom improvement and

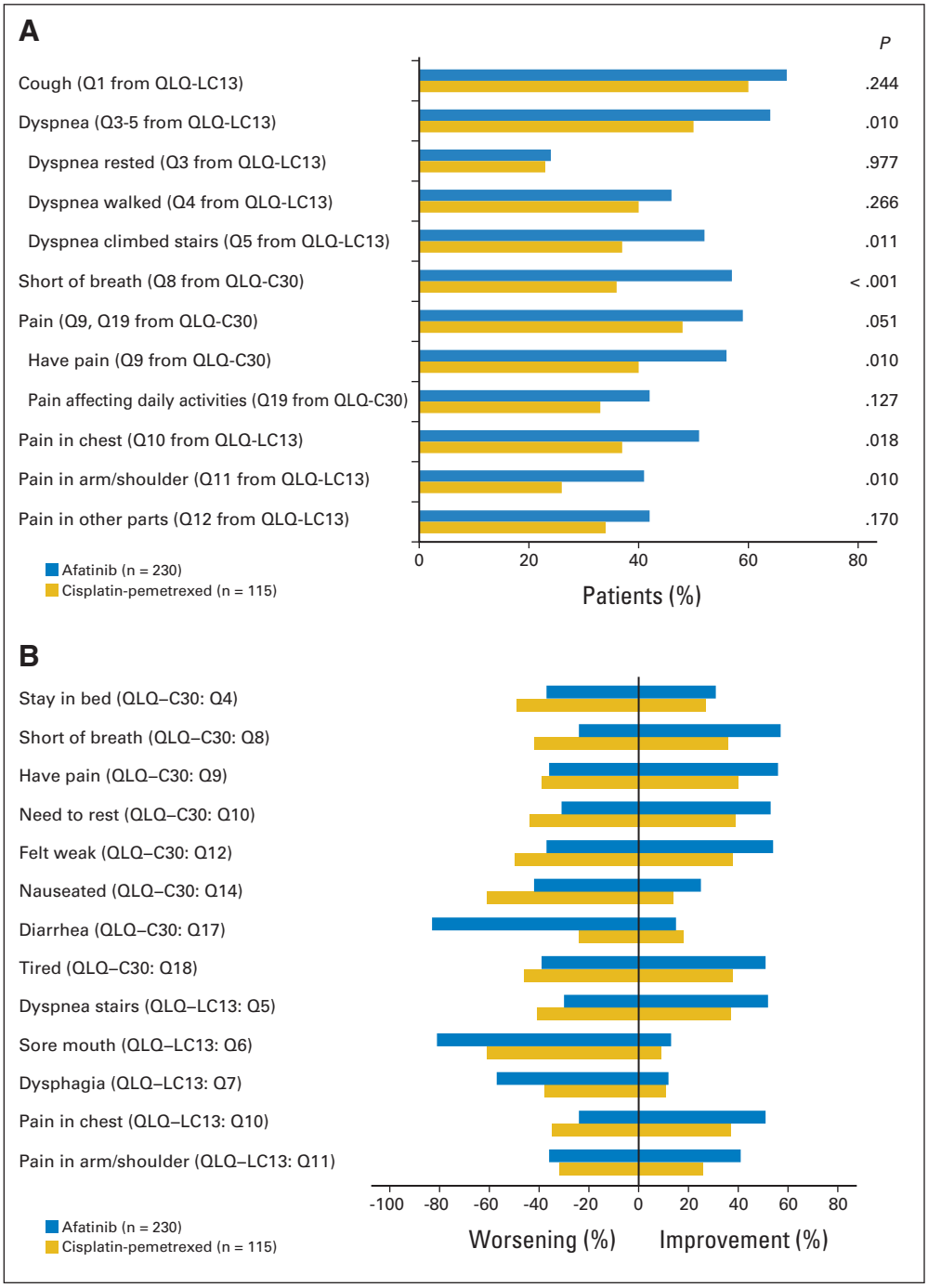

Fig 3. (A) Proportion of patients with improvement in the three prespecified patient-reported outcomes of interest—cough, dyspnea, and pain. (B) Individual items from the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) and its lung cancer–specific module QLQ-LC13 with a more than 10% difference in the percentage of patients experiencing an improvement or worsening of symptoms.

control compared with the overall population (Appendix Fig A2, online only). There were no significant differences in the prescription of concomitant medications for cough (10.4% for afatinib *v* 13.9% for chemotherapy), dyspnea (2.2% for afatinib *v* 3.5% for chemotherapy), and pain (61.3% for afatinib *v* 53.9% for chemotherapy) between treatment arms.

Analyses of Individual PRO Items and Scales

Compared with afatinib, a greater percentage of chemotherapy-treated patients had worsening of fatigue (25% *v* 39%, respectively) and nausea (42% *v* 61%, respectively), whereas more patients on afatinib had worsening of diarrhea (83% *v* 24%, respectively), sore mouth (81% *v* 61%, respectively), and dysphagia (57% *v* 38%, respectively; Fig 3B). Consistent findings were reported in the time-to-deterioration analysis (shorter time to deterioration of fatigue, nausea, and vomiting with chemotherapy and shorter time to deterioration of diarrhea and sore mouth with afatinib; Table 1). Longitudinal analysis results were also consistent (worse scores for fatigue, nausea, appetite, and constipation with chemotherapy and worse scores for diarrhea, dysphagia, and sore mouth with afatinib; all $P < .001$). In addition,

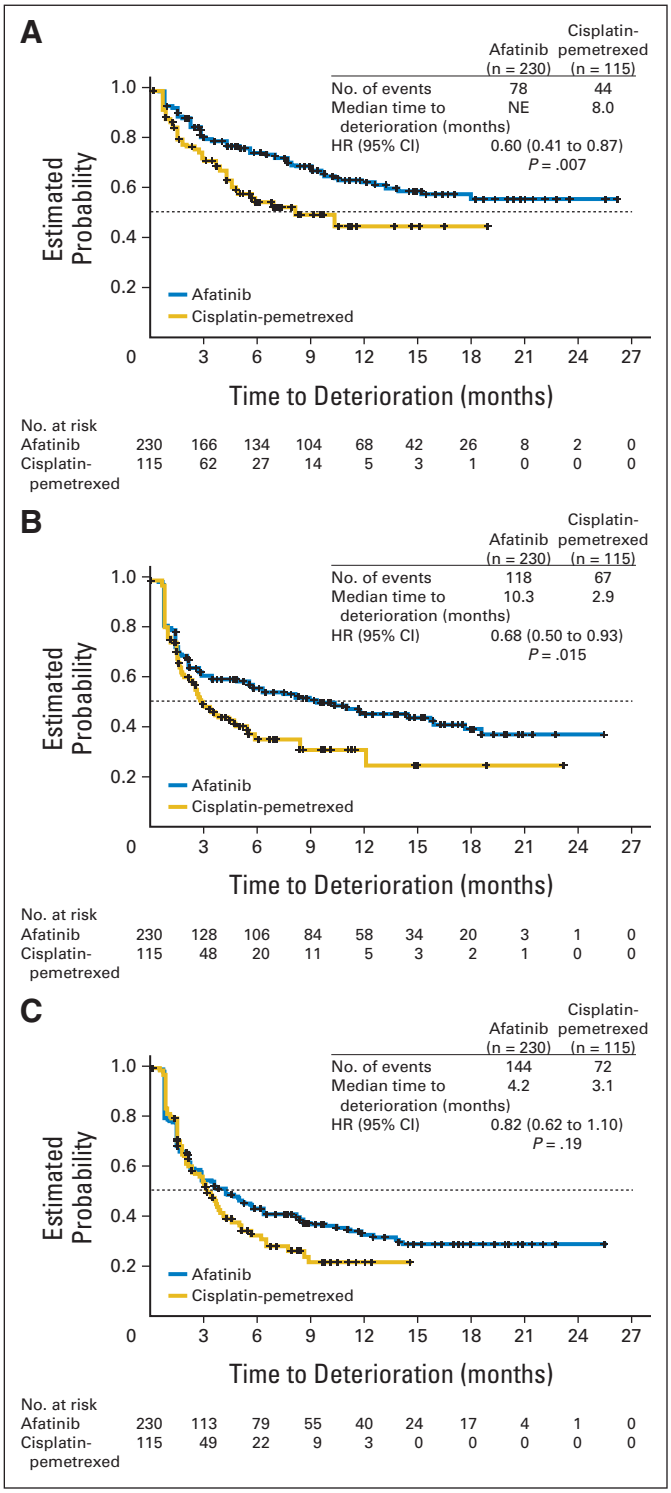

Fig 4. Time to deterioration in (A) cough, (B) dyspnea, and (C) pain and (D) time to deterioration in cough-, dyspnea-, and pain-related items. HR, hazard ratio; Q, question; QLQ-C30, Quality of Life Questionnaire C30; QLQ-LC13, Quality of Life Questionnaire lung cancer module.

significant improvements were observed for afatinib in the longitudinal analysis of individual items related to exercise and activity, such as strenuous activity (-5.69, $P < .001$), long walk (-7.22, $P < .001$), short walk (-4.17, $P = .008$), and leisure activities (-6.52, $P < .001$).

No significant difference between treatment arms was observed for the improvement proportions or time-to-deterioration analyses of global health status/QoL and functional scales. However, in the corresponding longitudinal analysis, patients on afatinib had significantly better mean EORTC scores over time for global health status/QoL, physical role, and cognitive functioning (Fig 6). Improvements were maintained over the course of treatment (Appendix Fig A3, online only).

Sensitivity Analyses

The proportion of patients with durable improvement (ie, over two assessments) confirmed robustness of the primary symptom improvement analysis. For the longitudinal analysis, several separate analyses of cough (calculating AUC up to 18 weeks and up to 57 weeks) were performed; all showed similar results to the primary analysis (with cutoff at 39 weeks; Appendix Fig A4, online only), further confirming robustness of the results.

Correlation analyses showed low or no association between missing data for PRO assessments and patient characteristics (age, race, ECOG PS, *EGFR* mutation status, and sex), being symptomatic at baseline, or treatment, respectively (Appendix Tables A1, A2, and A3, online only). There were no systematic differences between correlations in each treatment group and at each assessment. No correlation was found between symptom level at the prior assessment and missing data at the subsequent assessment (Appendix Table A4, online only). Of 150 correlation coefficients, only 10 were statistically significant ($P < .05$), a result that is consistent with chance alone.

Sensitivity analyses using joint models consistently gave slightly bigger estimates of differences favoring afatinib for cough (Appendix Fig A5, online only) and dyspnea scores, indicating that the results of the longitudinal analyses, which assume data are missing at random, were possibly conservative.

DISCUSSION

In clinical trials for patients with advanced, incurable cancer, the validity of PFS as a clinically meaningful end point depends on the rigorous and objective assessment of progression events as well as the demonstration of a parallel benefit in PROs.[7] The LUX-Lung 3 study demonstrated that afatinib as first-line therapy significantly prolongs PFS compared with chemotherapy in patients with *EGFR* mutation–positive NSCLC.[11] Here we report that genotype-directed therapy with afatinib in the LUX-Lung 3 study was also associated with significantly better control of two of the three prespecified lung cancer–related symptoms and longitudinal global health status/QoL compared with cisplatin/pemetrexed, the standard chemotherapy doublet for patients with nonsquamous NSCLC.

These symptom improvements were most pronounced among those with higher baseline symptom burden, although like most first-line cohorts, our study population was dominated by relatively asymptomatic patients at baseline. When considering the optimal first-line treatment of *EGFR* mutation–positive patients, the PRO data presented here are paramount. Because EGFR inhibition is associated with a high response rate in the salvage setting,[21,22] prior randomized trials with gefitinib and erlotinib have not shown a survival advantage for the genotype-directed strategy.[3,5,23,24] The LUX-Lung 3 survival data are not yet mature, but interim data do not show a survival

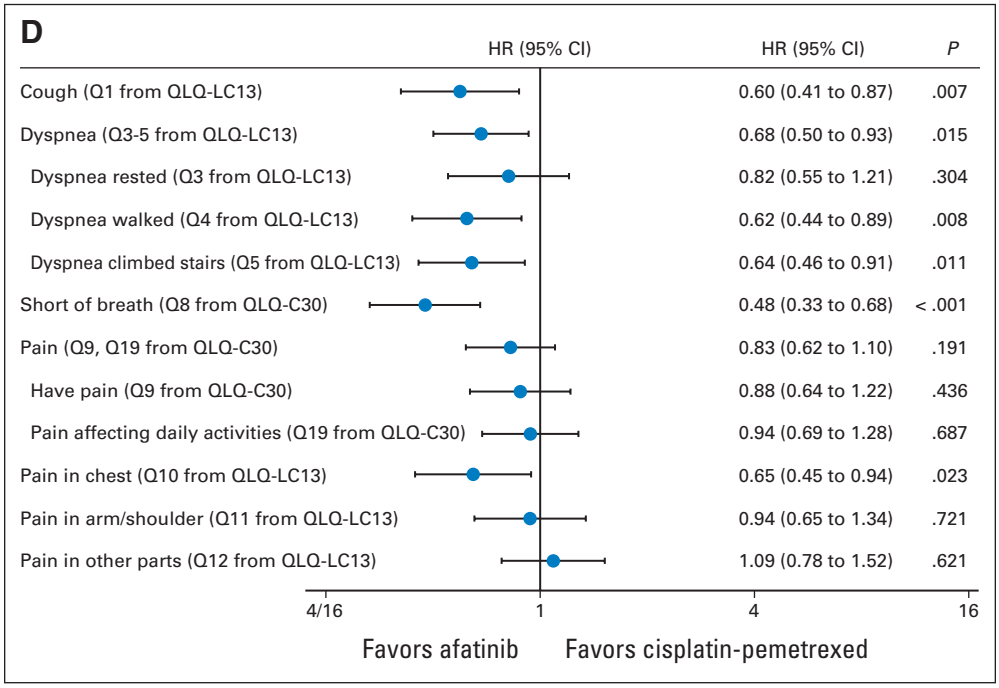

Fig 4. Continued.

advantage for afatinib.[11] However, it may be considered meaningful for patients to receive a therapy that can significantly delay progression of disease and offer better control of common lung cancer symptoms, such as cough and dyspnea.[7]

Cisplatin/pemetrexed chemotherapy is widely favored among oncologists for patients with lung adenocarcinoma because of its strong efficacy and its improved AE profile compared with other commonly used chemotherapies for lung cancer.[10,25] Thus, it is notable that over time, overall QoL with afatinib improved even in relation to this relatively well-tolerated chemotherapy regimen. The most common treatment-related AEs reported in LUX-Lung 3 were diarrhea, rash/acne, and stomatitis with afatinib and nausea, fatigue, and decreased appetite with chemotherapy.[11] These AE profiles were reflected in the PRO symptom analyses, with worse scores for nausea, vomiting, and fatigue on chemotherapy and worse scores for diarrhea, dysphagia, and sore mouth on afatinib. The longitudinal analysis of global

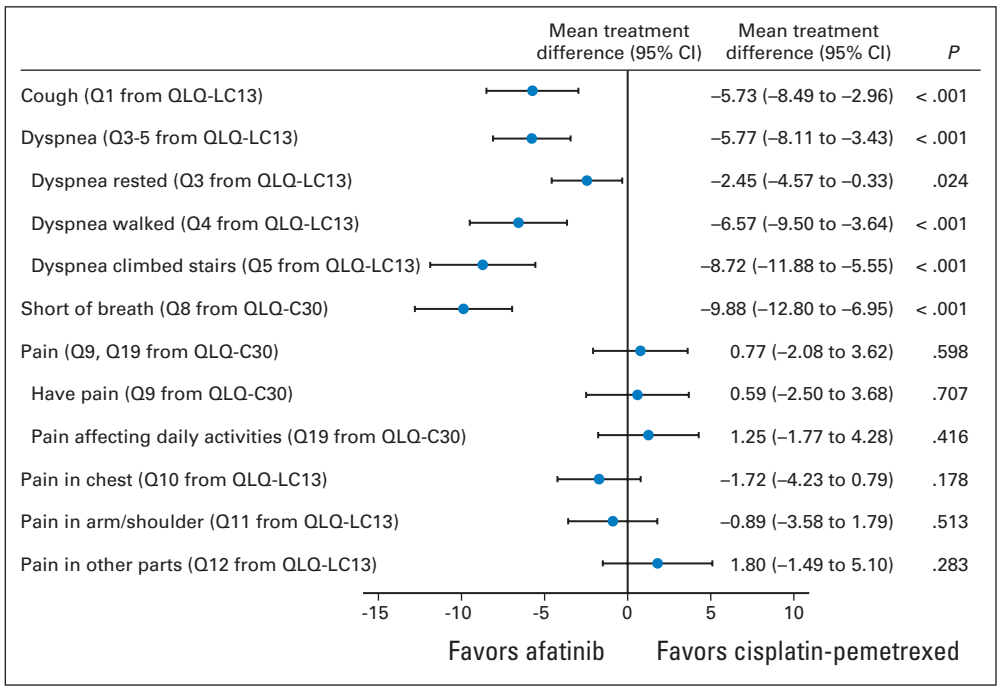

Fig 5. Longitudinal analysis for the three prespecified patient-reported outcomes symptoms of interest—cough, dyspnea, and pain. Q, question; QLQ-C30, Quality of Life Questionnaire C30; QLQ-LC13, Quality of Life Questionnaire lung cancer module.

Table 1. Time to Deterioration in Individual EORTC QLQ-C30 and QLQ-LC13 Items

Items	No. of Patients	HR*	95% CI	*P*
EORTC QLQ-C30				
Trouble strenuous activities (Q1)	345	0.90	0.66 to 1.22	.493
Trouble long walk (Q2)	345	0.77	0.57 to 1.05	.101
Trouble short walk (Q3)	345	0.89	0.64 to 1.25	.505
Stay in bed (Q4)	345	0.53	0.38 to 0.74	< .001
Trouble eat dress (Q5)	345	0.93	0.61 to 1.43	.746
Trouble daily activities (Q6)	345	0.97	0.71 to 1.33	.864
Trouble leisure activities (Q7)	345	0.77	0.57 to 1.05	.094
Short of breath (Q8)	345	0.48	0.33 to 0.68	< .001
Have pain (Q9)	345	0.88	0.64 to 1.22	.436
Need to rest (Q10)	345	0.61	0.44 to 0.84	.003
Insomnia (Q11)	345	1.00	0.70 to 1.43	.993
Felt weak (Q12)	345	0.64	0.47 to 0.88	.005
Appetite loss (Q13)	345	0.84	0.62 to 1.13	.241
Nauseated (Q14)	345	0.55	0.40 to 0.74	< .001
Vomited (Q15)	345	0.66	0.45 to 0.96	.031
Constipation (Q16)	345	0.73	0.51 to 1.04	.077
Diarrea (Q17)	345	7.74	5.15 to 11.63	< .001
Tired (Q18)	345	0.78	0.56 to 1.07	.124
Pain daily activities (Q19)	345	0.94	0.69 to 1.28	.687
Trouble concentrating (Q20)	345	1.04	0.74 to 1.46	.823
Felt tense (Q21)	345	1.06	0.73 to 1.55	.752
Worried (Q22)	345	1.12	0.77 to 1.64	.559
Irritable (Q23)	345	0.96	0.69 to 1.34	.807
Depressed (Q24)	345	0.89	0.63 to 1.26	.517
Trouble remembering (Q25)	345	0.77	0.54 to 1.09	.143
Family life affected (Q26)	345	0.94	0.68 to 1.32	.733
Social life affected (Q27)	345	0.81	0.58 to 1.12	.206
Financial difficulties (Q28)	345	0.76	0.52 to 1.11	.158
Overall health rate (Q29)	345	1.05	0.79 to 1.40	.746
Quality-of-life rate (Q30)	345	1.00	0.75 to 1.33	.998
EORTC QLQ-LC13†				
Coughing (Q1)	345	0.60	0.41 to 0.87	.007
Hemoptysis (Q2)	345	1.75	0.89 to 3.43	.101
Dyspnea rested (Q3)	345	0.82	0.55 to 1.21	.304
Dyspnea walked (Q4)	345	0.62	0.44 to 0.89	.008
Dyspnea stairs (Q5)	345	0.64	0.46 to 0.91	.011
Sore mouth (Q6)	345	2.47	1.86 to 3.28	< .001
Dysphagia (Q7)	345	1.85	1.31 to 2.61	< .001
Peripheral neuropathy (Q8)	345	1.24	0.92 to 1.67	.156
Alopecia (Q9)	345	0.61	0.46 to 0.81	< .001
Pain in chest (Q10)	345	0.65	0.45 to 0.94	.023
Pain in arm/shoulder (Q11)	345	0.94	0.65 to 1.34	.721
Pain in other parts (Q12)	345	1.09	0.78 to 1.52	0.621

NOTE. Symptom worsening defined as worsening by 10 points from baseline on a 0 to 100 scale.
Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio; Q, question; QLQ-C30, Quality of Life Questionnaire C30; QLQ-LC13, Quality of Life Questionnaire lung cancer module.
*HR < 1 favors afatinib, whereas HR > 1 favors chemotherapy.
†Question 13 data of QLQ-LC13 were not analyzed because this is an optional question concerning concomitant medication.

health status/QoL captures patients' perception of treatment that likely accounts for changes in both disease symptoms and treatment-related AEs during the study period. Although two of the three analyses of global health status/QoL (comparing the distribution of patients who were improved, stable, or worsened and the time to deterioration) did not significantly favor afatinib, the longitudinal analysis demonstrated statistically significant improvements for afatinib, suggesting that global health status/QoL while receiving continuous afatinib is at least as good as, and potentially better than, that among patients receiving cisplatin/pemetrexed, which is a regimen known for its relatively mild AE profile and ease of administration.[10] This is particularly important, because average treatment duration with afatinib was significantly longer than with cisplatin/pemetrexed, potentially introducing bias against afatinib because prolonged observation increases the likelihood of adverse symptoms/assessment.

The study protocol was rigorous in the design of the PRO end points. It specified three approaches for the analysis of PROs in each of the key lung cancer symptoms of interest—cough, dyspnea, and pain. Analyses included comparison of the proportion of patients with clinically meaningful improvement in each symptom; analysis of time

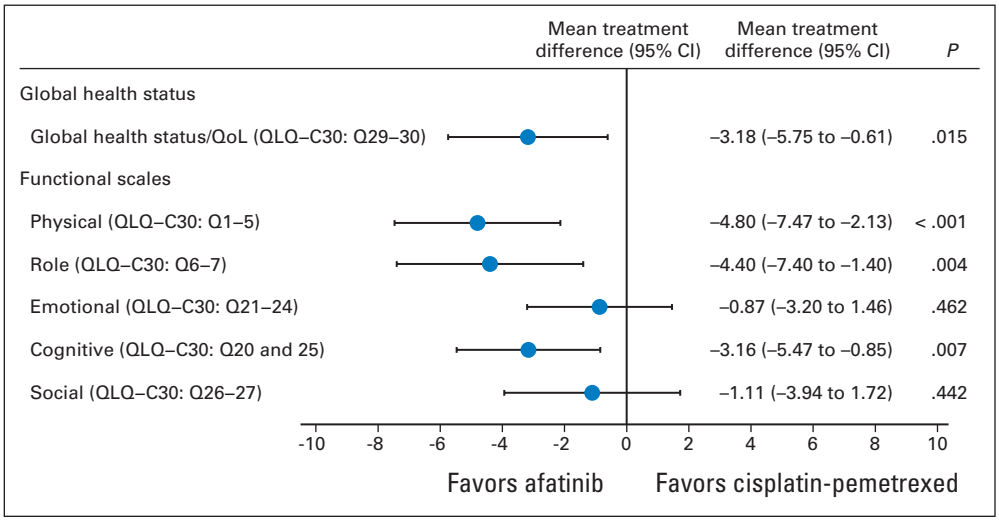

Fig 6. Results from the longitudinal analysis of global health status/quality of life (QoL) and functional scale domains. QLQ-C30, Quality of Life Questionnaire C30.

to deterioration of symptoms; and analysis of symptoms over time. Although each of these methods has individual strengths and limitations, this tripronged approach collectively broadens the perspective of the results, thereby enhancing their interpretation. However, the increase in the number of analyses also increases the chances of observing type I errors. The general consistency of the results across multiple instruments and methods of analysis suggest that compared with chemotherapy afatinib leads to better control and improvement of some lung cancer–related symptoms.

Similarly, minimizing the occurrence of missing data and properly accounting for its presence and pattern (which is often not missing at random) is an important factor in PRO studies.[26] High compliance rates for questionnaire completion partially ameliorate this concern; however, patient attrition, which was unbalanced in this study, remains an issue. To evaluate the potential bias caused by missing data, correlation and sensitivity analyses were carried out on cough and dyspnea scores; almost all correlations were close to zero or very small, whereas sensitivity analyses confirmed the primary analyses.

The EORTC QLQ-C30 and QLQ-LC13 instruments used in this study have been well validated and can accurately assess PROs. Three other phase III studies of similar design to LUX-Lung 3 have compared first-line gefitinib and erlotinib with chemotherapy in *EGFR* mutation–positive patients (North East Japan Study Group 002 [NEJSG002] and OPTIMAL [CTONG-0802]) or clinically selected patients (Iressa Pan-Asia Study [IPASS]) and incorporated PRO assessments.[4,27,28] Although these studies used different instruments than reported here (OPTIMAL and IPASS used the Functional Assessment of Cancer Therapy–Lung, and NEJSG002 used the Care Notebook), they demonstrated improvement of lung cancer–related symptoms and prolongation of time to deterioration of symptoms in *EGFR* mutation–positive patients treated with genotype-directed therapy.[4,27,28]

Several limitations should be considered that are inherent to assessing PROs. The PRO assessments were discontinued at progression, and time-to-deterioration analysis was censored at the last completed PRO assessment. Hence, major symptom deterioration after disease progression may not be captured by these data, and PRO benefits may be overestimated. However, interpretation of data collected beyond progression would have been difficult because of heterogeneous subsequent treatments. Similarly, patients who were not feeling well may have been less inclined to complete questionnaires, hence limiting information about symptomatic patients. As mentioned, differences in compliance between treatment arms have the potential to introduce bias. High compliance rates in both arms suggest that compliance was not a substantial problem in our study. The joint model used in sensitivity analyses account for missing data under various assumptions about the missing data mechanism, and the results show similar treatment benefits for afatinib compared with chemotherapy as other analyses; hence, differences in compliance are unlikely to have biased findings.

In conclusion, compared with cisplatin/pemetrexed, first-line afatinib significantly improved dyspnea and prolonged the time to deterioration of cough and dyspnea symptoms in patients with *EGFR* mutation–positive NSCLC. Results for pain seem to be at least comparable between treatments. The AE profiles of both treatments were reflected in the PRO analysis, with worsening nausea, vomiting, and fatigue on the chemotherapy arm and worsening diarrhea, dysphagia, and sore mouth on afatinib. These data will be useful in the consideration of first-line therapy with afatinib for patients with *EGFR* mutation–positive NSCLC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: James Chih-Hsin Yang, Vera Hirsh, Kenneth J. O'Byrne, Tony S.K. Mok, Mehdi Shahidi, Dan Massey, Lecia V. Sequist
Provision of study materials or patients: James Chih-Hsin Yang, Vera Hirsh, Martin Schuler, Kenneth J. O'Byrne
Collection and assembly of data: James Chih-Hsin Yang, Vera Hirsh, Martin Schuler, Nobuyuki Yamamoto, Kenneth J. O'Byrne, Victoria Zazulina, Dan Massey, Lecia V. Sequist
Data analysis and interpretation: All authors
Manuscript writing: All authors
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Appendix

Table A1. Correlation Between Patient Characteristics and Missingness of HRQoL Assessments

	Randomly Assigned Treatment			
	Afatinib		Cisplatin/Pemetrexed	
Characteristic and Visit No.	Kendall's τ	*P*	Kendall's τ	*P*
Age				
1	−0.03	.636	0.02	.801
2	0.01	.802	0.05	.565
3	0.00	.947	−0.25	.003
4	−0.10	.091	0.01	.881
5	0.01	.910	0.13	.185
6	0.02	.785	0.00	.968
Race				
1	0.04	.537	−0.09	.316
2	−0.03	.703	−0.02	.837
3	−0.02	.811	−0.06	.535
4	−0.08	.275	−0.13	.227
5	0.10	.185	−0.36	.002
6	−0.00	.995	−0.18	.125
ECOG status				
1	0.02	.736	0.04	.643
2	0.12	.071	0.13	.194
3	0.13	.047	−0.01	.891
4	0.04	.537	0.02	.874
5	0.14	.059	0.05	.643
6	0.05	.518	0.15	.193
EGFR mutation type				
1	0.01	.834	−0.12	.224
2	0.03	.662	−0.09	.397
3	−0.07	.316	−0.09	.400
4	−0.09	.225	−0.03	.768
5	−0.02	.824	0.20	.097
6	−0.02	.810	0.07	.594
Sex				
1	0.01	.887	0.03	.729
2	0.10	.123	0.12	.223
3	0.02	.780	0.06	.558
4	0.10	.150	0.10	.354
5	0.11	.114	0.16	.161
6	0.10	.164	−0.00	.987

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HRQoL, health-related quality of life.

Table A2. Correlation Between Cough at Baseline and Missingness of HRQoL Assessments

	Randomly Assigned Treatment			
	Afatinib		Cisplatin/Pemetrexed	
Visit No.	Kendall's τ	*P*	Kendall's τ	*P*
2	0.11	.073	0.02	.826
3	0.05	.440	−0.11	.263
4	0.06	.366	−0.22	.032
5	0.10	.129	−0.04	.695
6	0.07	.343	−0.06	.581
7	0.07	.354	0.30	.012
8	−0.00	.974	0.15	.251

Abbreviation: HRQoL, health-related quality of life.

Table A3. Correlation Between Randomly Assigned Treatment and Missingness of HRQoL Assessments

Visit No.	Kendall's τ	*P*
1	0.02	.650
2	−0.03	.595
3	0.01	.834
4	0.12	.032
5	0.06	.285
6	0.05	.401
7	0.10	.105
8	0.11	.095

Abbreviation: HRQoL, health-related quality of life.

Table A4. Correlation Between Cough at Previous Assessment and Missingness of Cough Assessments

	Randomly Assigned Treatment			
	Afatinib		Cisplatin/Pemetrexed	
Visit No.	Kendall's τ	*P*	Kendall's τ	*P*
2	0.11	.073	0.02	.826
3	0.07	.313	−0.01	.933
4	−0.01	.940	−0.00	.975
5	−0.05	.514	0.10	.388
6	−0.10	.146	0.13	.266
7	−0.10	.175	0.19	.119
8	0.15	.052	−0.13	.329

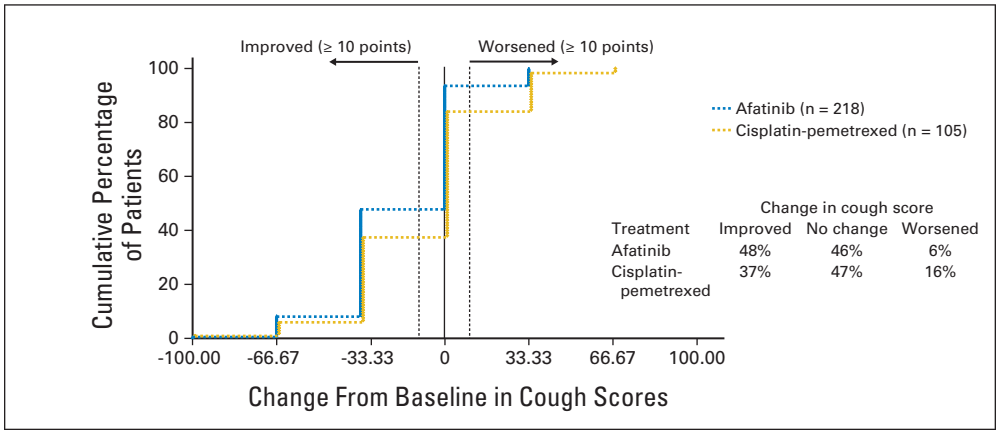

Fig A1. Change in cough scores from baseline at week 18.

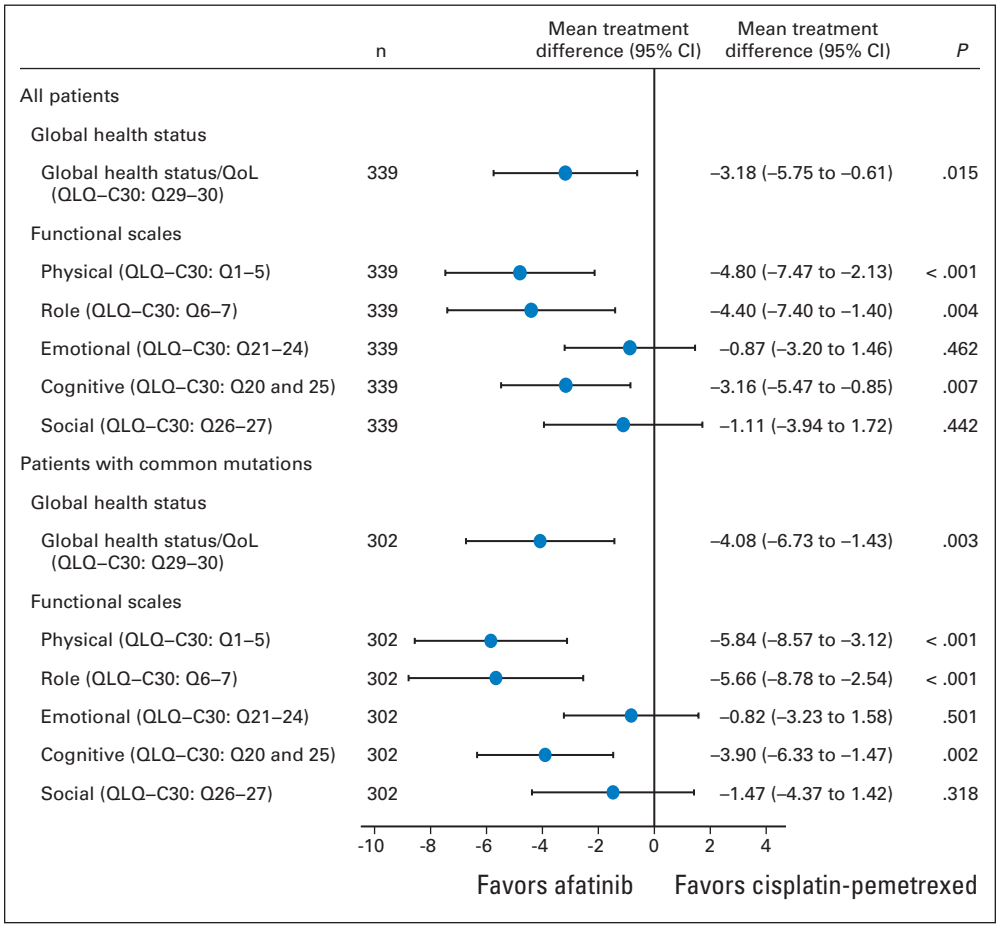

Fig A2. Results from the longitudinal analysis of global health status/quality of life (QoL) and functional scale domains in all patients and patients with common mutations. Q, question; QLQ-C30, Quality of Life Questionnaire C30.

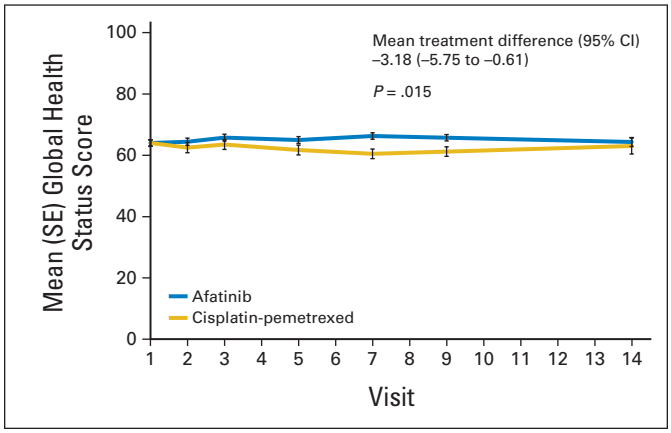

Fig A3. Mean change in global health status/quality of life scores over treatment (longitudinal analysis).

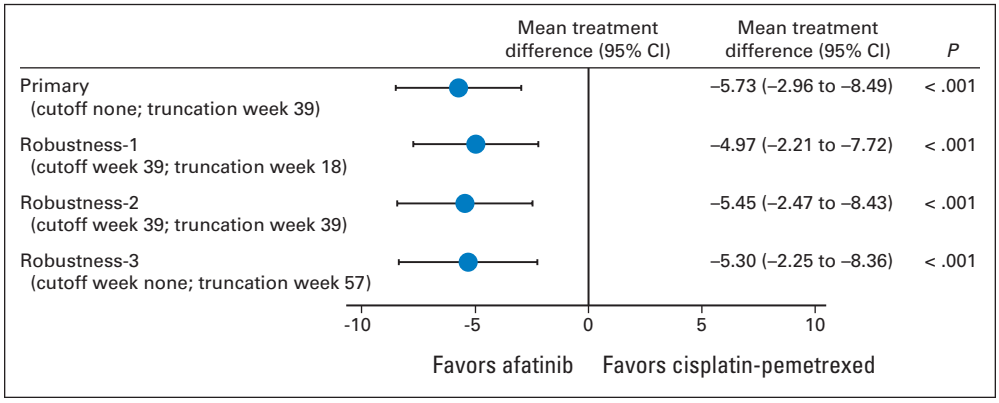

Fig A4. Longitudinal analysis for the symptoms of cough; mean difference in scores for robustness analysis.

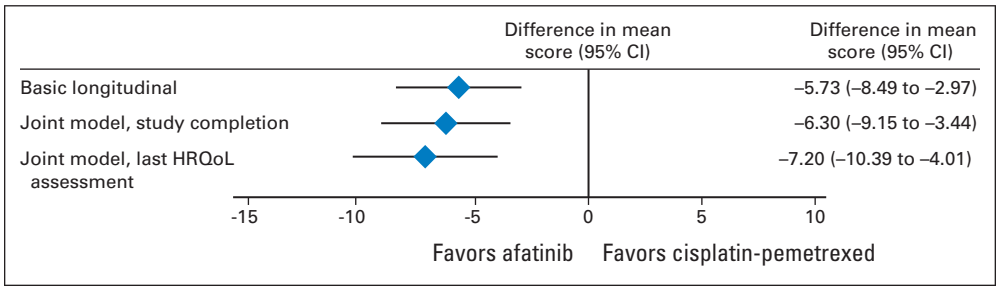

Fig A5. Sensitivity analyses using joint models for the symptom of cough. HRQoL, health-related quality of life.