Original Study

Symptom and Quality of Life Improvement in LUX-Lung 8, an Open-Label Phase III Study of Second-Line Afatinib Versus Erlotinib in Patients With Advanced Squamous Cell Carcinoma of the Lung After First-Line Platinum-Based Chemotherapy

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Abstract

The effect of treatment on health-related quality of life (HRQoL) is an important consideration for patients. In the LUX-Lung 8 trial, second-line afatinib improved survival outcomes versus erlotinib in patients with squamous cell carcinoma of the lung. In this report, afatinib was also associated with improvements in disease-related symptoms and HRQoL versus erlotinib, contributing to the overall clinical benefit of afatinib.

Introduction: In the phase III LUX-Lung 8 trial, afatinib significantly improved progression-free survival (PFS) and overall survival (OS) versus erlotinib in patients with squamous cell carcinoma (SCC) of the lung progressing during or after platinum-based chemotherapy. Patient-reported outcomes (PROs) and health-related quality of life (QoL) in these patients are presented. **Patients and Methods:** Patients (n = 795) were randomized 1:1 to oral afatinib (40 mg/d) or erlotinib (150 mg/d). PROs were collected (baseline, every 28 days until progression, 28 days after discontinuation) using the European Organization for Research and Treatment of Cancer QoL questionnaire and lung cancer-specific module. The percentage of patients improved during therapy, time to deterioration (TTD), and changes over time were analyzed for prespecified lung cancer-related symptoms and global health status (GHS)/QoL. **Results:** Questionnaire compliance was 77.3% to 99.0% and 68.7% to 99.0% with afatinib and erlotinib, respectively. Significantly more patients who received afatinib versus erlotinib experienced improved scores for GHS/QoL (36% vs. 28%; $P = .041$) and cough (43% vs. 35%; $P = .029$). Afatinib significantly delayed TTD in dyspnea ($P = .008$) versus erlotinib, but not cough ($P = .256$) or pain ($P = .869$). Changes in mean scores favored afatinib for cough ($P = .0022$), dyspnea

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($P = .0007$), pain ($P = .0224$), GHS/QoL ($P = .0320$), and all functional scales. Differences in adverse events between afatinib and erlotinib, specifically diarrhea, did not affect GHS/QoL. **Conclusion:** In patients with SCC of the lung, second-line afatinib was associated with improved prespecified disease-related symptoms and GHS/QoL versus erlotinib, complementing PFS and OS benefits with afatinib.

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Keywords: Cough, Diarrhea, Dyspnea, EGFR, Pain

Introduction

Until recently, approved treatment options for patients with squamous cell carcinoma (SCC) of the lung have represented a significant unmet medical need, with only the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) erlotinib, and docetaxel, approved in the second-line setting.[1] In the past few years, several new therapies have been approved in this setting, including immune checkpoint inhibitors (ie, programmed death 1 inhibitors [nivolumab, pembrolizumab] and programmed death ligand 1 [PD-L1] inhibitor [atezolizumab]), antivascular endothelial growth factor receptor-2 antibody therapy (ramucirumab, combined with docetaxel), and the ErbB family blocker afatinib.[2-4] This rapid expansion of treatment options raises a question among clinicians of which new therapy would provide optimal clinical benefit for patients with relapsed/refractory disease after progression during or after chemotherapy.

Afatinib is an irreversible ErbB family blocker.[5] In the phase III LUX-Lung 8 trial, which compared afatinib with erlotinib in patients with SCC of the lung after treatment failure during or after platinum-based chemotherapy,[6] afatinib improved progression-free survival (PFS; median 2.6 vs. 1.9 months; hazard ratio [HR], 0.81; $P = .0103$), overall survival (OS; median 7.9 vs. 6.8 months; HR, 0.81; $P = .0077$), and disease control rate (DCR; 50.5% vs. 39.5%; $P = .0020$) versus erlotinib. The adverse event (AE) profile in both treatment arms was consistent with previous experience. Treatment-related Grade 3 diarrhea was more frequent with afatinib (9.9%) than erlotinib (2.3%) and treatment-related Grade 3 rash/acne was more frequent with erlotinib (10.4%) than afatinib (5.9%); otherwise, AE profiles were comparable. The rate of dose reduction because of AEs was higher for afatinib compared with erlotinib (26.5% vs. 14.2%); however, discontinuation rates because of AEs were similar between the 2 treatment arms (20.2% and 17.0% with afatinib and erlotinib, respectively).[6] On the basis of the results of LUX-Lung 8, afatinib was approved by the US Food and Drug Administration for the treatment of patients with metastatic squamous non–small-cell lung cancer (NSCLC) progressing after platinum-based chemotherapy, and by the European Medicines Agency for the treatment of locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy.[7,8]

With the emergence of several new treatment options for SCC of the lung,[9,10] a key consideration when choosing the most appropriate treatment option is the effect on patients' health-related quality of life (HRQoL). In patients with NSCLC, disease-related symptoms, including cough, dyspnea, and pain, are known to have a profound effect on HRQoL and interfere with daily life activities.[11] Up to 68% of patients, when questioned, said they would prefer a therapy that improved disease-related symptoms without prolonging life, as opposed to a therapy that improved survival without symptom benefit.[12] On the basis of the importance of HRQoL, all phase III trials of afatinib in NSCLC have included fully integrated, comprehensive patient-reported outcome (PRO) evaluation.[13-15]

In the LUX-Lung 3 and LUX-Lung 6 studies, first-line afatinib significantly improved global health status/quality of life (GHS/QoL) and prespecified lung cancer-related symptoms (cough, dyspnea, and pain) versus platinum-based chemotherapy in patients with NSCLC and activating EGFR mutations.[13,15] Symptom and QoL benefit with afatinib has also been shown in patients with relapsed/refractory NSCLC[16] and SCC of the head and neck.[17] Furthermore, several studies have shown that tumor progression in afatinib-treated NSCLC patients is associated with deterioration in HRQoL, indicating that PROs are a patient-relevant end point.[13,18]

In this article we report on the effect of afatinib on prespecified PROs and disease-related symptoms compared with erlotinib in LUX-Lung 8. In addition, because class-related gastrointestinal AEs associated with TKI therapy are known to have a negative effect on patients' QoL, and that diarrhea is frequently observed in afatinib-treated patients,[19] we also report on results from an exploratory patient substudy of LUX-Lung 8 that assessed the occurrence and management of diarrhea in individual patients.

Patients and Methods

Study Design and Patients

Details of the LUX-Lung 8 (NCT01523587) study design and patient eligibility criteria have been published previously.[6] Briefly, this was an open-label, phase III, global, randomized study. Eligible patients were aged 18 years or older with a diagnosis of advanced-stage NSCLC of squamous histology, had received at least 4 cycles of platinum-based doublet chemotherapy as first-line treatment of stage IIIB/IV NSCLC, with subsequent disease progression, and had to be eligible for second-line treatment. Patients were randomized 1:1 to receive either afatinib 40 mg or erlotinib 150 mg orally once daily. The primary end point was PFS according to a central independent radiology review (Response Evaluation Criteria In Solid Tumors version 1.1). The key secondary end point was OS. Other secondary end points were objective response rate, DCR, tumor shrinkage, and PROs. The study protocol—designed in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guideline for Good Clinical Practice, and applicable region-specific regulatory requirements—was

approved by independent ethics committees at each center. All patients provided written informed consent for trial participation.

Assessment of PROs

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) is comprised of 30 questions and incorporates multi-item scales as well as single-item measures.[20] These include: 1 GHS/QoL scale; 5 functional scales; 3 symptoms scales; and 6 single items to assess dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. Each of the multi-item scales includes a different set of items, and no item occurs in more than 1 scale.[21] The lung cancer-specific module, Quality of Life Questionnaire Lung Cancer-13 (QLQ-LC13), is comprised of 13 questions and incorporates 1 multi-item scale to assess dyspnea, as well as a series of single items to assess pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis.[21,22]

Patient-reported outcomes were assessed at the first visit of each treatment course, at the end of treatment, and 28 days after treatment discontinuation. The respective questionnaires were completed by the patients at the site before they saw the investigator—before clinical assessment, before any treatment at the clinic, and before the patients were provided with any new information about their disease status—to avoid influencing the questionnaire responses. Information on the usage of cough, dyspnea, and pain medication was also collected.

An exploratory substudy was undertaken to assess the occurrence and management of diarrhea at centers that agreed to participate. Individual patients from these centers who volunteered to participate were included. Patients were asked to complete a detailed daily diary on the occurrence of diarrhea and interventions taken. The objective of the diarrhea substudy was to compare afatinib and erlotinib in terms of intensity and duration of diarrhea in the first 12 weeks of treatment. No formal hypothesis was tested; all analyses from the substudy are descriptive in nature.

Statistical Analyses

Patient-reported outcome responses were converted to a 0 to 100 scale and analyzed in line with EORTC scoring algorithms.[20] The HRQoL analyses focused on prespecified symptoms relevant to lung cancer, specifically cough (question [Q]1 from QLQ-LC13), dyspnea (Q3-Q5 from QLQ-LC13), and pain (Q9 and Q19 from QLQ-C30). GHS/QoL (Q29 and Q30 from QLQ-C30) was also analyzed.

For each of the summary scales and items that measured cough, dyspnea, and pain, the 2 treatment arms were compared in terms of 3 analyses. First, the proportion of patients who were improved, defined as an improvement of at least 10 points from baseline score at any time during the study, was compared. All randomized patients were included in the denominator. Second, the time to deterioration (TTD), defined as the time to a 10-point worsening from the baseline score, was evaluated. Patients who died before deterioration were analyzed as having deteriorated at the time of death. Patients with disease progression but without scale deterioration were censored at the time of the last scale measurement. Patients with no HRQoL assessments were censored at the day of randomization. Third, cough, dyspnea, and pain scores over time were assessed using a mixed-effects growth curve model with the average profile over time for each end point described by a piecewise linear model adjusted for the fixed effect race. In addition, all single items and subscales (functional and symptom) from the EORTC QLQ-C30 and QLQ-LC13 questionnaires were analyzed to summarize the effect of therapy on the time profile of the measures, and to examine the consistency of component items with the composite measures.

For functioning scales, a higher score represents a 'better' level of functioning, and deterioration in scales or items related to functioning was defined as a decrease of at least 10 points from baseline. Because some missing PRO data is inevitable, correlation analyses were conducted to determine whether missing data because of patient dropout was associated with patient characteristics or other factors. Robustness of the primary PRO results from the longitudinal model were assessed by varying data cutoff times and model truncation times, and sensitivity analyses were carried out using joint and pattern-mixture models.

Results

Patients

A total of 795 patients were randomized to receive afatinib (n = 398) or erlotinib (n = 397). Baseline characteristics were generally similar between the 2 arms and have been reported previously.[6] Briefly, the median age was 64 years, 666 (83.8%) patients were male, 172 (21.6%) were Eastern Asian, and 728 (91.6%) were ever smokers.

Baseline Scores and Compliance

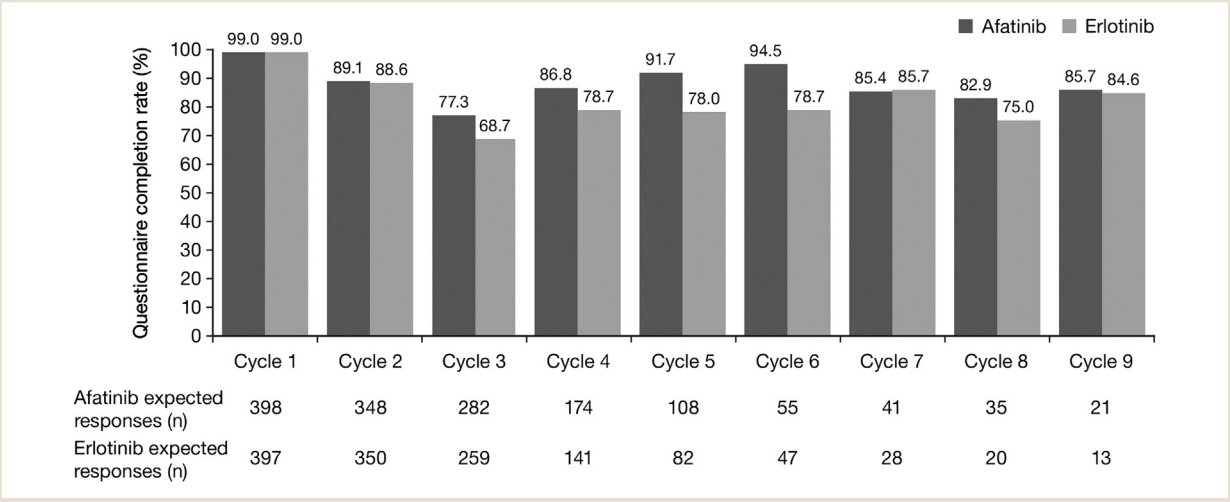
Baseline PRO questionnaires were completed by 95.5% of afatinib-treated patients and 95.0% of erlotinib-treated patients. Baseline symptom scores for cough, dyspnea, and pain were low and balanced between treatment arms (Table 1). The mean (SD) baseline score for GHS/QoL was 60.8 (21.0) for the afatinib arm and 60.2 (21.6) for the erlotinib arm; higher scores reflect better GHS/QoL. Questionnaire completion rates according to treatment cycle ranged from 77.3% to 99.0% in the afatinib arm and from 68.7% to 99.0% in the erlotinib arm (Figure 1). A similar proportion of patients in both arms completed at least 1 PRO

Table 1 Symptom Burden at Baseline

Scale	Mean Symptom Score (SD)	
	Afatinib	Erlotinib
Cough (Q1 from QLQ-LC13)	39.7 (29.5)	37.8 (26.3)
Dyspnea (Q3-Q5 from QLQ-LC13)	28.8 (23.5)	29.7 (23.5)
Pain (Q9, Q19 from QLQ-C30)	26.9 (29.2)	29.7 (28.5)

Abbreviations: Q = question; QLQ-C30 = Quality of Life Questionnaire C30; QLQ-LC13 = Quality of Life Questionnaire Lung Cancer-13.

Figure 1 Questionnaire Completion Rate[a]



[a]On the basis of completion of any item in the questionnaire. Cycle 1 is the baseline assessment since questionnaires were completed by patients before seeing the investigator and before any clinical assessment/treatment.

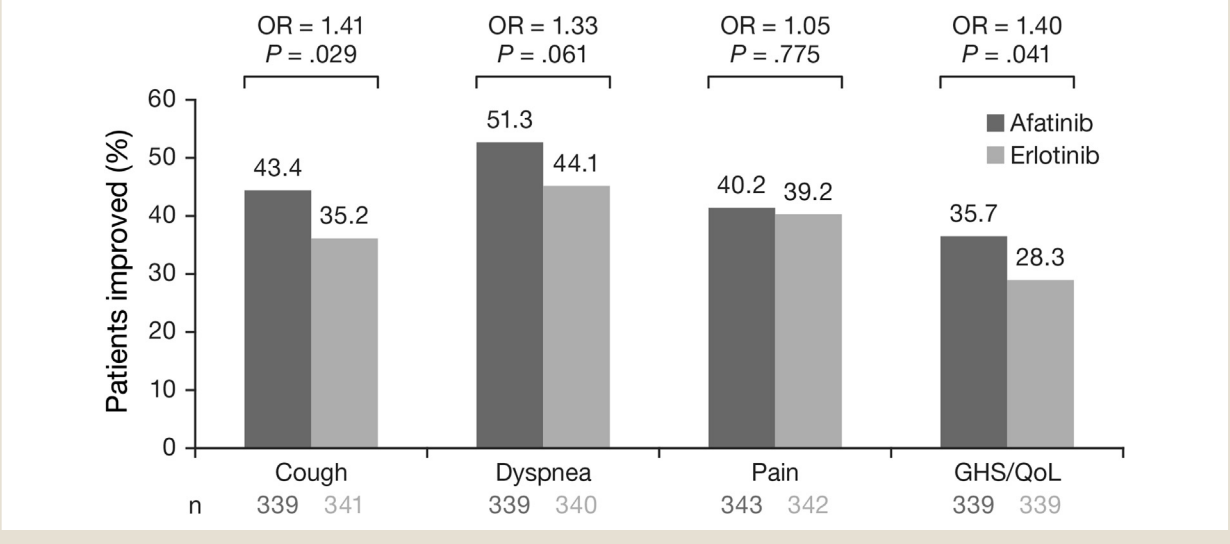
questionnaire after baseline (87.7% of afatinib-treated patients and 89.2% of erlotinib-treated patients). Most patients for whom HRQoL was not measured after the start of treatment either died or had disease progression before the second scheduled post-baseline PRO assessment at day 56.

Patient-Reported Outcomes

Proportion of Patients With Improvements

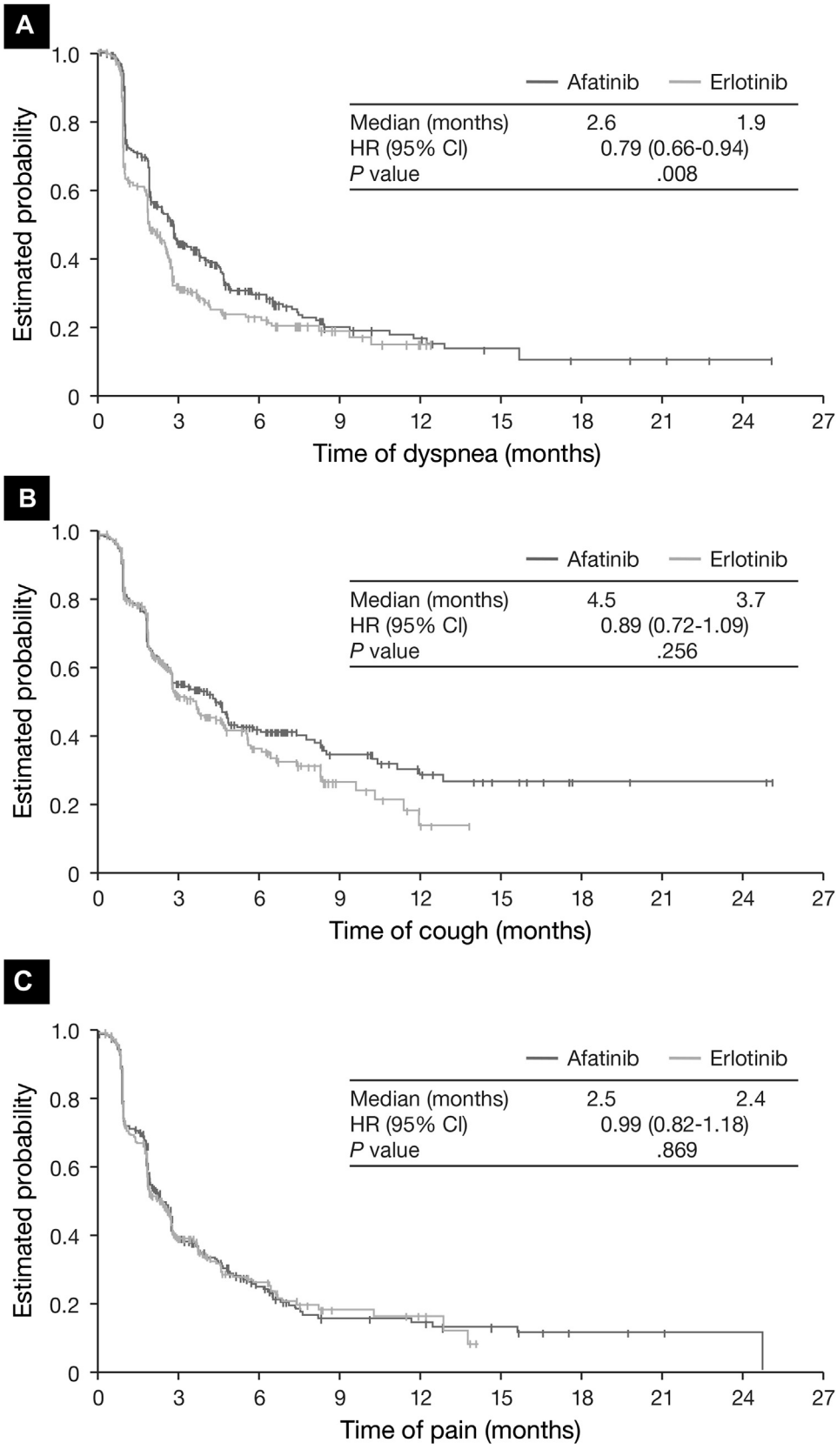
The percentage of patients reporting improved scores for GHS/QoL (35.7% vs. 28.3%; $P = .041$) and cough (43.4% vs. 35.2%; $P = .029$) was significantly higher with afatinib than erlotinib (Figure 2). There was no significant difference in the proportion of patients with improved dyspnea (51.3% vs. 44.1%; $P = .061$), or pain (40.2% vs. 39.2%; $P = .775$) between treatment arms (Figure 2). Improvements in individual dyspnea- and pain-related items, as well as in functional scales of QLQ-C30, are shown in Supplemental Table 1 in the online version. Afatinib was associated with a significant improvement in 'dyspnea walked' (34.6% vs. 26.5%; $P = .022$) but did not significantly improve any other individual symptom items, or functional scales of QLQ-C30, versus erlotinib.

Figure 2 Proportion of Patients With Improvements in Symptoms



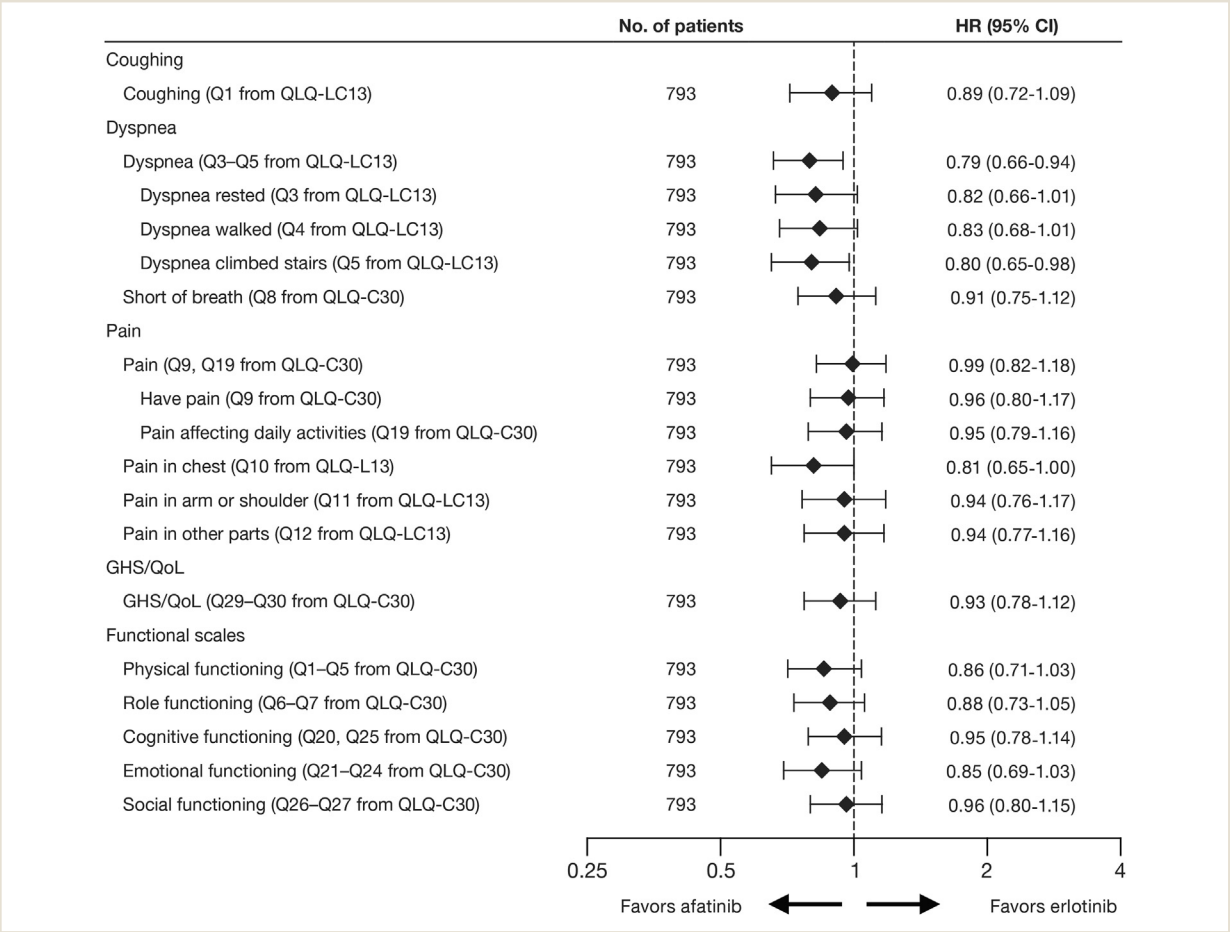
Abbreviations: GHS = global health status; OR = odds ratio (afatinib vs. erlotinib); QoL = quality of life.

Figure 3 Time to Deterioration of (A) Dyspnea, (B) Cough, (C) Pain



Abbreviation: HR = hazard ratio.

Figure 4 Time to Deterioration of Symptoms



Abbreviations: GHS = global health status; HR = hazard ratio; Q = question; QLQ-C30 = Quality of Life Questionnaire C30; QLQ-LC13 = Quality of Life Questionnaire Lung Cancer-13; QoL = quality of life.

Time to Deterioration

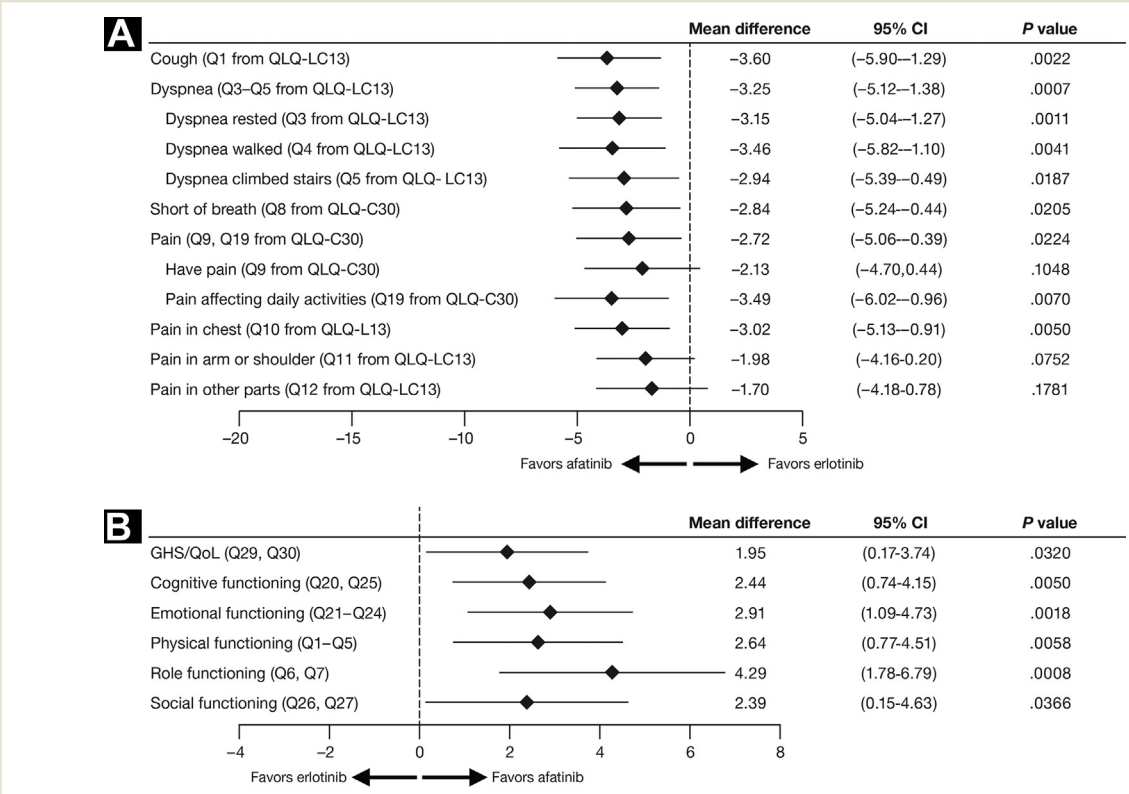
Afatinib significantly delayed TTD of dyspnea versus erlotinib (median 2.6 vs. 1.9 months; $P = .008$; Figure 3A), with a consistent pattern of improvement across dyspnea subcategories (Figure 4). There was no significant difference in TTD of cough (4.5 vs. 3.7 months; $P = .256$; Figure 3B) or pain (2.5 vs. 2.4 months; $P = .869$; Figure 3C) between treatment groups. TTD was also similar for GHS/QoL and functional scales with afatinib versus erlotinib (Figure 4).

Scores Over Time

Scores over time significantly favored afatinib over erlotinib for cough (mean difference = −3.60; $P = .0022$), dyspnea (mean difference = −3.25; $P = .0007$), and pain (mean difference = −2.72; $P = .0224$; Figure 5); significant improvements over time were also observed for all individual items with the exception of 'have pain,' 'pain in arm or shoulder,' and 'pain in other parts.' Significant differences in favor of afatinib were observed for GHS/QoL (mean difference = 1.95; $P = .0320$) and all functioning scales over time (Figure 5).

Correlation analyses between missing data, and patient characteristics and treatment, showed a weak positive correlation over the first few weeks of treatment with a baseline Eastern Cooperative Oncology Group performance status of 1 (see Supplemental Table 2 in the online version), as well as a weak positive correlation with erlotinib treatment at weeks 12 and 36, indicating that more erlotinib-treated patients dropped out at these time points relative to afatinib-treated patients (see Supplemental Table 3 in the online version). In each treatment arm, weak positive correlations, particularly during the early weeks of the trial, were associated with severity of dyspnea and pain symptoms at baseline but not with severity of cough; worse GHS/QoL score at baseline was also associated with missing data because of patient dropout (see Supplemental Table 4 in the online version). When GHS/QoL and symptoms were examined with respect to the last known assessment for each measure, the correlations were stronger than those found versus the baseline assessment, suggesting that the patterns of missing data for the parameters described do depend on the observed data (data on file).

Figure 5 Difference in Mean Scores Over Time for Cough, Dyspnea and Pain (A) and GHS and Functional Scales (B)



Abbreviations: GHS = global health status; Q = question; QLQ-C30 = Quality of Life Questionnaire C30; QLQ-LC13 = Quality of Life Questionnaire Lung Cancer-13; QoL = quality of life.

Differences in mean scores for cough, dyspnea, and GHS/QoL did not vary when different data cutoffs and truncation points were used (see Supplemental Figure 1 in the online version), suggesting the results of the primary PRO analysis were robust. Sensitivity analyses were conducted using 3 joint models on the basis of time to treatment termination (censored at time of database lock), and time to last assessment (either uncensored or censored at time of database lock) as the time to dropout event. The estimates of treatment effect consistently favored afatinib over erlotinib for each end point, supporting the primary PRO analysis conclusions (see Supplemental Table 5 in the online version). Further, results of sensitivity analyses on the basis of pattern-mixture models generally reflected the primary PRO analysis (see Supplemental Table 6 in the online version). Compared with the primary PRO analysis, a stronger between-treatment difference in favor of afatinib was observed for cough, suggesting that, at least for this measure, the results of the primary PRO analysis might be conservative.

Analyses of Individual PRO Items

Status changes (improved, stable, or worsened) in individual items of QLQ-C30 and QLQ-LC13 are shown in Supplemental Table 7 in the online version. Afatinib treatment was associated with a greater percentage of patients with improvements in overall health rate versus erlotinib (Q29 from QLQ-C30; 43.4% vs. 35.8%; $P = .045$). There were also trends toward a greater percentage of patients with improvements in QoL rate (Q30 from QLQ-C30; 43.1% vs. 36.0%; $P = .060$) and 'felt weak' (Q12 from QLQ-C30; 31.2% vs. 24.6%; $P = .058$) with afatinib versus erlotinib. Compared with erlotinib, a greater percentage of patients receiving afatinib had worsening of diarrhea (Q17 from QLQ-C30; 77.2% vs. 54.0%; $P = .146$) and sore mouth (Q6 from QLQ-LC13; 60.7% vs. 37.5%; $P = .113$; see Supplemental Table 7 in the online version), but the differences were not statistically significant.

Differences in TTD and mean scores over time between treatment arms for individual items of the QLQ-C30 and QLQ-LC13 are shown in Supplemental Figures 2 and 3, respectively, in the online version. Overall, most individual items tended to favor afatinib for TTD as well as changes over time. However, as expected because of the observed AE profiles of afatinib and erlotinib in LUX-Lung 8, the individual items of diarrhea and sore mouth favored erlotinib.

Patients' Perspectives on the Effect of Diarrhea

In LUX-Lung 8, the frequency of treatment-related Grade 3/4 diarrhea was higher with afatinib (9.9%/0.5%) than erlotinib (2.3%/0.3%), although discontinuations because of diarrhea were low for both treatment arms (4.1% with afatinib and 1.5% with erlotinib).[6] In a small substudy to assess the effect of diarrhea from a patient's perspective, a selected subset of 63 patients (afatinib

n = 36, erlotinib n = 27) consented to providing a detailed diary of the onset, intensity, and duration of diarrhea (any Grade) in the first 12 weeks of the study. The overall incidence of diarrhea was consistent with that in the main trial population, with 31 (86.1%) patients in the afatinib arm and 14 (51.8%) patients in the erlotinib arm reporting diarrhea (see Supplemental Table 8 in the online version). Seven patients experienced Grade 3 diarrhea in the afatinib group (median duration: 3 days [range, 2-10]). However, over the course of the whole 12-week substudy, cases of Grade 3 diarrhea were intermittent, being experienced on only 1.5% of the total number of patient-days of treatment. No patients in the substudy discontinued afatinib treatment because of diarrhea, although 7 patients in the afatinib arm had diarrhea-related dose reductions.

Medication Usage

A smaller proportion of patients in the afatinib group took pain medication (afatinib 52%; erlotinib 59%; odds ratio, 0.75; 95% confidence interval, 0.57-1.00; $P = .0508$), but the difference was not statistically significant. No differences were observed between treatment groups in the proportion of patients who took medication for cough or dyspnea.

Discussion

The recent phase III LUX-Lung 8 study showed significantly prolonged PFS and OS with afatinib versus erlotinib in patients with SCC of the lung after failure during or after platinum-based chemotherapy.[6] As with many oncology trials, PFS was chosen as the primary end point for LUX-Lung 8 because, unlike OS, it is not influenced by differences in subsequent therapies.[23] However, it is important to assess PROs/HRQoL alongside survival outcomes to validate the clinical meaningfulness of observed improvements in PFS and to ensure any extended lifespan attained during treatment is as comfortable as possible for patients.[24] Hence, comprehensive PRO/HRQoL assessments were prespecified in the LUX-Lung 8 trial to provide an essential component to analysis of the benefit/risk profile of treatment in conjunction with efficacy and safety assessments.[25]

We prespecified 3 key NSCLC-related symptoms that are reported to matter most to patients: dyspnea, cough, and pain.[26] These symptoms can have a profound effect on HRQoL and interfere with daily life activities in patients with NSCLC, although symptom burden at baseline was low and balanced between treatment arms in LUX-Lung 8. Three approaches for the analysis of the prespecified symptoms were stipulated in the protocol: proportion of patients with clinically meaningful improvements in each symptom, analysis of TTD of symptoms, and longitudinal analysis of symptoms over time. These approaches, also used in previous afatinib trials,[13,15] broadened the perspective of the results and enhanced their interpretation. Compared with erlotinib, afatinib treatment was associated with a significantly higher number of patients reporting improved GHS/QoL and cough, a significant delay in TTD of dyspnea, and significantly improved mean scores over time for cough, dyspnea, and pain. These data complement the consistent benefit observed with afatinib across all efficacy end points, including OS, PFS, and DCR, in patients with SCC of the lung who have disease progression during or after platinum-based chemotherapy. Overall, these findings are consistent with recent results in the second-line setting of recurrent and/or metastatic SCC of the head and neck, wherein the PFS benefit observed with afatinib over methotrexate was also associated with a significant improvement in PROs.[17]

The primary analysis of LUX-Lung 8 demonstrated that the overall tolerability profile was similar between treatment arms; 57.1% and 57.5% of patients experienced Grade $\geq$ 3 AEs with afatinib and erlotinib, respectively. Permanent treatment discontinuations were also comparable (occurring in 20.2% of afatinib-treated patients and 17.0% of erlotinib-treated patients), although dose reductions occurred more frequently with afatinib (26.5%) than erlotinib (14.2%).[6] Furthermore, AEs were consistent with the mechanism of action of afatinib, including characteristic class-related gastrointestinal (diarrhea, stomatitis) and cutaneous (rash/acne) events. As with all TKIs that target EGFR, afatinib is associated with diarrhea; the incidence of treatment-related Grade 3/4 diarrhea in LUX-Lung 8 was 9.9%/0.5% with afatinib, compared with 2.3%/0.3% in the erlotinib arm.[6] In the present study, the increased incidence of diarrhea with afatinib versus erlotinib was also reflected in patients' responses to the relevant individual items of QLQ-C30 and QLQ-LC13. A voluntary patient substudy, undertaken in $<$ 10% of the overall trial population, allowed further patient-level detail to be gathered on the occurrence and management of diarrhea. Although the frequency and duration of all-Grade diarrhea was greater with afatinib than erlotinib, median duration of Grade $\geq$ 3 diarrhea was 3 days. Overall, cases of Grade $\geq$ 3 diarrhea were intermittent, being experienced on 1.5% of the total number of patient-days of treatment. Furthermore, no patients in the substudy (compared with 4.1% of patients in the overall population) discontinued treatment with afatinib because of diarrhea, possibly as a result of the recommended afatinib dose-reduction scheme that is specified in the prescribing information and designed to manage such AEs.[8] Of note, post hoc analyses of LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 have shown that dose adjustment of afatinib does not affect efficacy.[27-29] Overall, although diarrhea is a frequent AE with afatinib, episodes generally appear to be transient and manageable with antidiarrheal medication and dose modification. Consequently, incidence of diarrhea does not affect overall GHS/QoL, which is improved with afatinib versus erlotinib.

Although several other phase III trials have evaluated the effect of reversible EGFR inhibitors (ie, erlotinib and gefitinib) on cancer-related symptoms and HRQoL in NSCLC patients, there is an overall lack of consensus in the findings, which might be related to the different assessment tools used to capture PROs. In the phase III BR.21 trial, which also used the well validated QLQ-C30 and QLQ-LC13 questionnaires, second- or third-line erlotinib significantly improved symptoms and delayed TTD for cough, dyspnea, and pain versus placebo, reinforcing the appropriateness of these instruments for detecting improvements in PROs in a second-line treatment setting.[30] However, in the phase III Tarceva in Treatment of Advanced NSCLC (TITAN) study, there was no significant difference in the TTD of symptoms with second-line erlotinib versus docetaxel or pemetrexed, on the basis of the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire.[31] Likewise, there is a lack of consensus regarding the effect of gefitinib on HRQoL in randomized studies. Some phase III trials have shown that significantly more patients attain sustained and clinically relevant

improvements in HRQoL with second-line gefitinib versus docetaxel on the basis of the FACT-L total score.[32,33] Conversely, the phase III IRESSA as Second-line Therapy in Advanced NSCLC - KoreA (ISTANA) trial showed no difference in HRQoL between gefitinib and docetaxel on the basis of FACT-L.[34] Although EGFR-TKIs have shown HRQoL improvements versus standard second-line chemotherapy in some studies, to our knowledge, the current study is the first randomized trial to compare PROs between 2 EGFR-targeted agents in patients with relapsed/refractory SCC. An analysis of HRQoL outcomes in the phase III CheckMate-017 trial was also recently reported, showing significant improvements from baseline in patient-reported health status over 48 weeks of treatment with nivolumab but not docetaxel, on the basis of the European Quality of Life-5 Dimensions questionnaire; outcomes for specific lung cancer-related symptoms have not been reported.[35] Similarly, pembrolizumab improved HRQoL and prolonged TTD of lung cancer symptoms compared with docetaxel in patients with previously treated PD-L1-positive, advanced NSCLC (KEYNOTE-010).[36]

A number of steps were taken to ensure the validity and robustness of the PRO results, and data collection was optimized to ensure their clinical relevance. To avoid bias, patients answered questions before meeting physicians and completed the questionnaires themselves, with data collected at the first visit of each treatment cycle. In addition, because of the importance of minimizing the occurrence of missing data in PRO analyses,[15,37] it is noteworthy that compliance with questionnaire completion ranged from 77% to 99% throughout the study for patients treated with afatinib. This high level of compliance was in line with that observed in LUX-Lung 3 (87%-99%) and LUX-Lung 6 (approximately 90%).[13,15] The EORTC QLQ-C30 and QLQ-LC13 instruments used in this study are well validated, and allow the accurate assessment of PROs.[20,22] However, PRO assessments are often discontinued at the time of disease progression, meaning that symptom deterioration beyond progression is not taken into account by the data, and PRO benefits might be overestimated. In LUX-Lung 8, this issue was avoided by scheduling a PRO assessment at the follow-up visit, 28 days after study drug discontinuation. Nevertheless, the collection of PRO data after disease progression also has an effect on data interpretation because of variations in postprogression treatments. In addition, patients might have been less inclined to complete questionnaires when feeling unwell, so the data might under-represent patients with more severe symptoms. Although differences in questionnaire compliance between treatment arms have the potential to introduce bias to the data, in the current study, sensitivity analyses conducted for individual disease-related symptoms (eg, cough, dyspnea) and GHS/QoL using additional data cutoffs and truncation points confirmed the robustness of the primary PRO analysis results.

Conclusion

In summary, second-line afatinib significantly improved symptoms of cough and GHS/QoL and significantly delayed TTD of dyspnea compared with erlotinib in patients with SCC of the lung. Mean scores over time also significantly favored afatinib over erlotinib for cough, dyspnea, pain, GHS/QoL, and all functional scales. Differences in AEs between afatinib and erlotinib were reflected in the PRO outcomes, with a greater proportion of patients in the afatinib arm experiencing worsening diarrhea and sore mouth compared with erlotinib, although these differences did not appear to affect overall GHS/QoL. These data, combined with significant improvements in PFS and OS with afatinib, should be taken into account when considering treatment options for patients with SCC of the lung after failure during or after platinum-based chemotherapy.

Clinical Practice Points

- Squamous cell carcinoma of the lung remains a disease with high unmet medical need, particularly for patients with relapsed/refractory disease after platinum-based chemotherapy. Among other emerging therapeutic options, afatinib was approved in this setting after showing significant improvements in PFS and OS versus erlotinib in the phase III LUX-Lung 8 trial. Because HRQoL is an important consideration for cancer patients, the effect of newer treatments, including afatinib, on PROs of disease-related symptoms and GHS might be a key factor in treatment choice.
- In LUX-Lung 8, second-line afatinib was associated with a significantly higher percentage of patients reporting improvements in cough and GHS/QoL, and significantly delayed TTD in dyspnea, versus erlotinib. Mean scores over time also significantly favored afatinib for cough, dyspnea, pain, GHS/QoL, and all functional scales. As expected, because of the observed AE profiles for each agent, PROs for worsening of diarrhea favored erlotinib over afatinib (nonsignificant difference). However, episodes of diarrhea were shown to be transient and manageable, and did not affect GHS/QoL.
- The improvements in disease-related symptoms and QoL observed with afatinib versus erlotinib in patients with SCC of the lung progressing on/after platinum-based chemotherapy contribute to the overall clinical benefit of afatinib. Combined with the significant improvements in PFS and OS observed with afatinib versus erlotinib in LUX-Lung 8, and a predictable and manageable safety profile, these findings suggest that afatinib is a favorable treatment option in this setting.

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Disclosure

Dr Felip has served on advisory boards for Eli Lilly, Pfizer, Boehringer Ingelheim, and Merck Sharp & Dohme, and has received lecture fees for a speaker's bureau with AstraZeneca,

Bristol-Myers Squibb, and Novartis. Dr Popat has received travel expenses from Boehringer Ingelheim. Dr Waller has received consultancy fees from Boehringer Ingelheim. Prof Soria has received consultancy fees from Boehringer Ingelheim and Roche. Dr Goss has served on an advisory board and received honoraria from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, and Pfizer. Drs Gordon, Wang, and Ehrnrooth are employees at Boehringer Ingelheim. Dr Palmer has received fees for statistical analysis from Boehringer Ingelheim and AstraZeneca. Dr Gadgeel has served on advisory boards for Boehringer Ingelheim and Genentech/Roche, and received personal fees from AstraZeneca, ARIAD, Bristol-Myers Squibb, and Pfizer. Profs Hirsh and Fülöp, and Drs Cobo, Dayen, Trigo, and Gregg have stated that they have no conflicts of interest.

Supplemental Data

Supplemental tables and figures accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clcc.2017.06.002.

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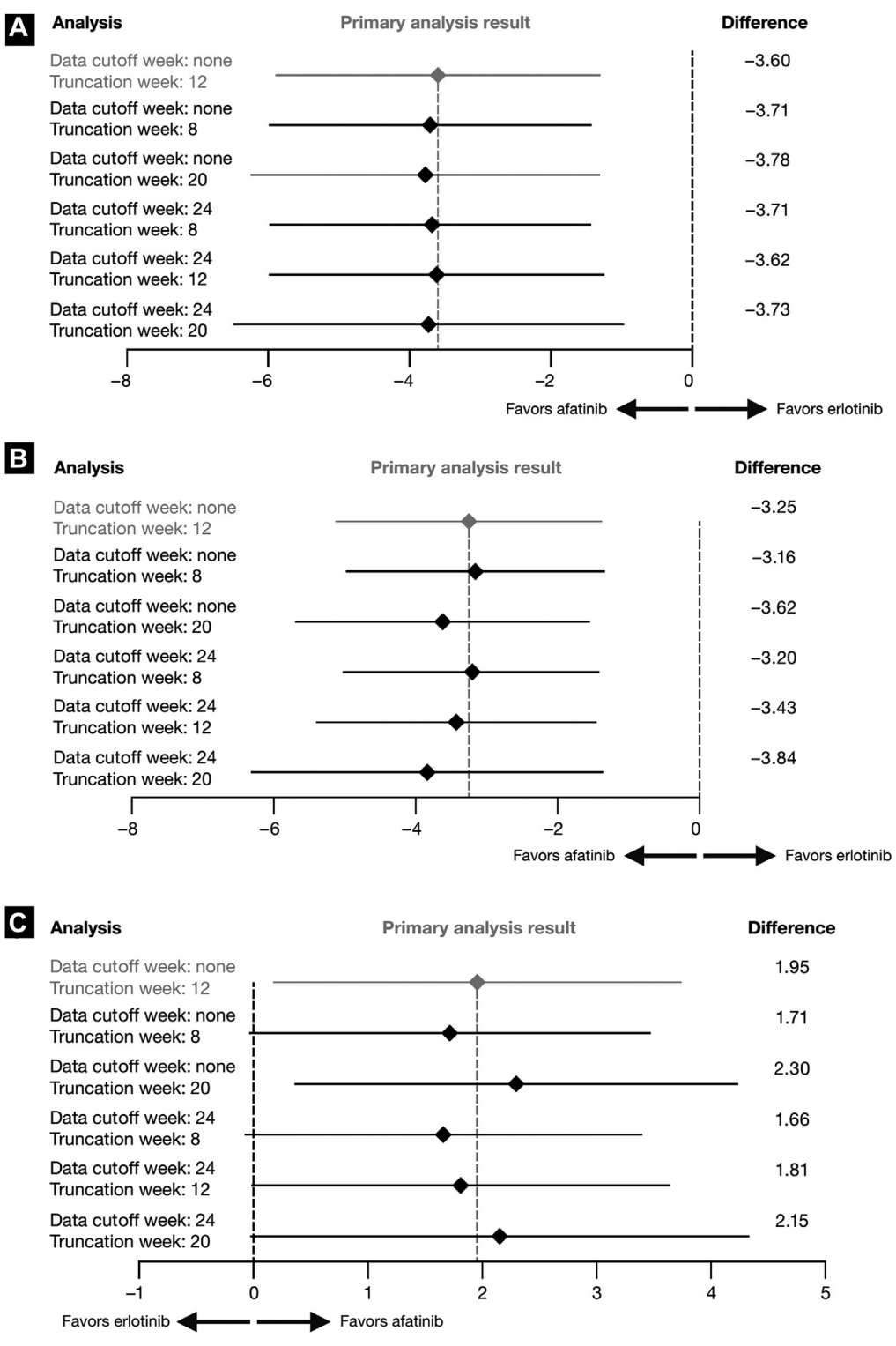
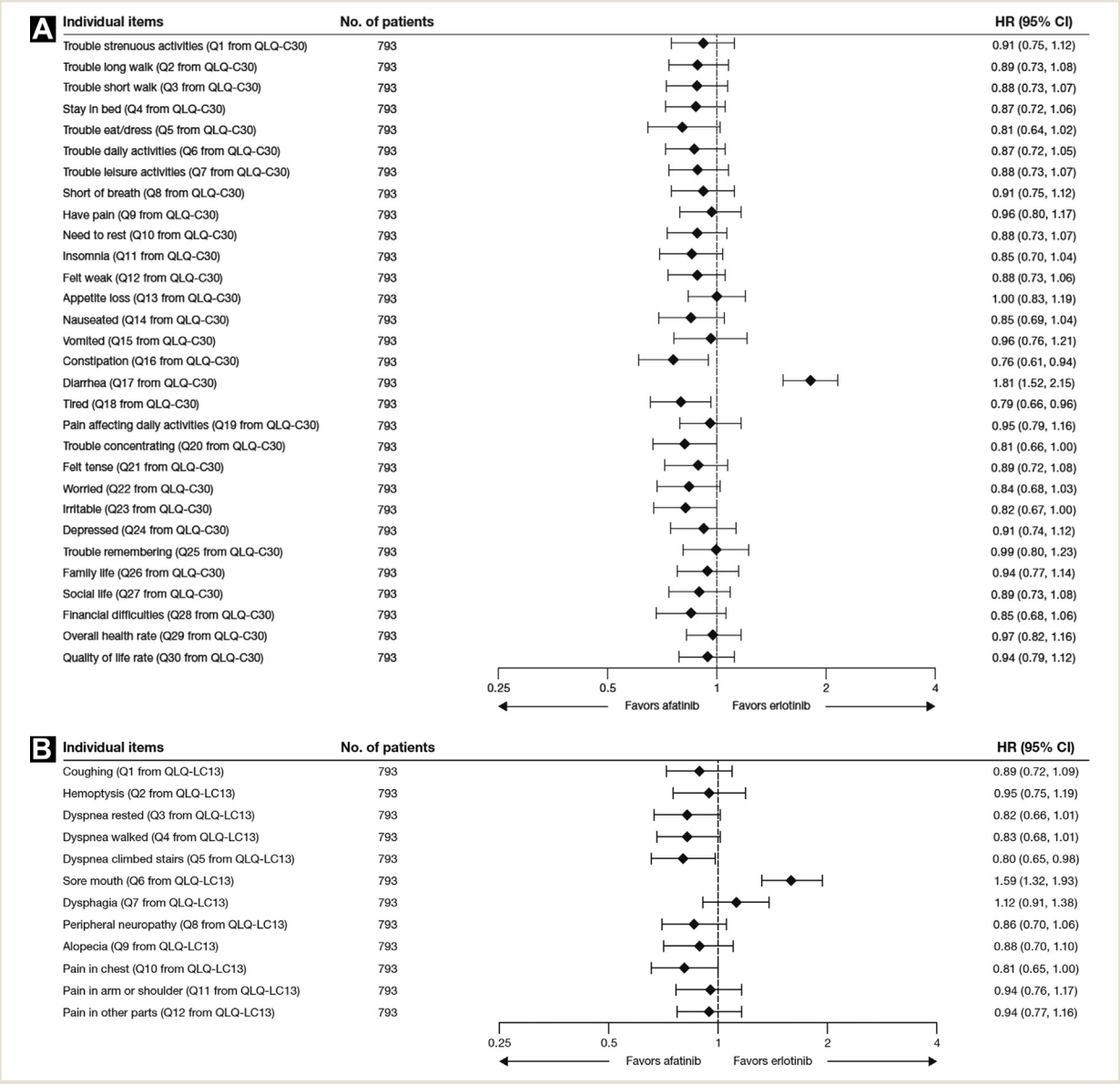
Supplemental Figure 1 **Differences in Mean Scores for (A) Coughing, (B) Dyspnea, and (C) GHS/QoL in the Primary Analysis and Using Additional Data Cutoffs and Truncation Points**



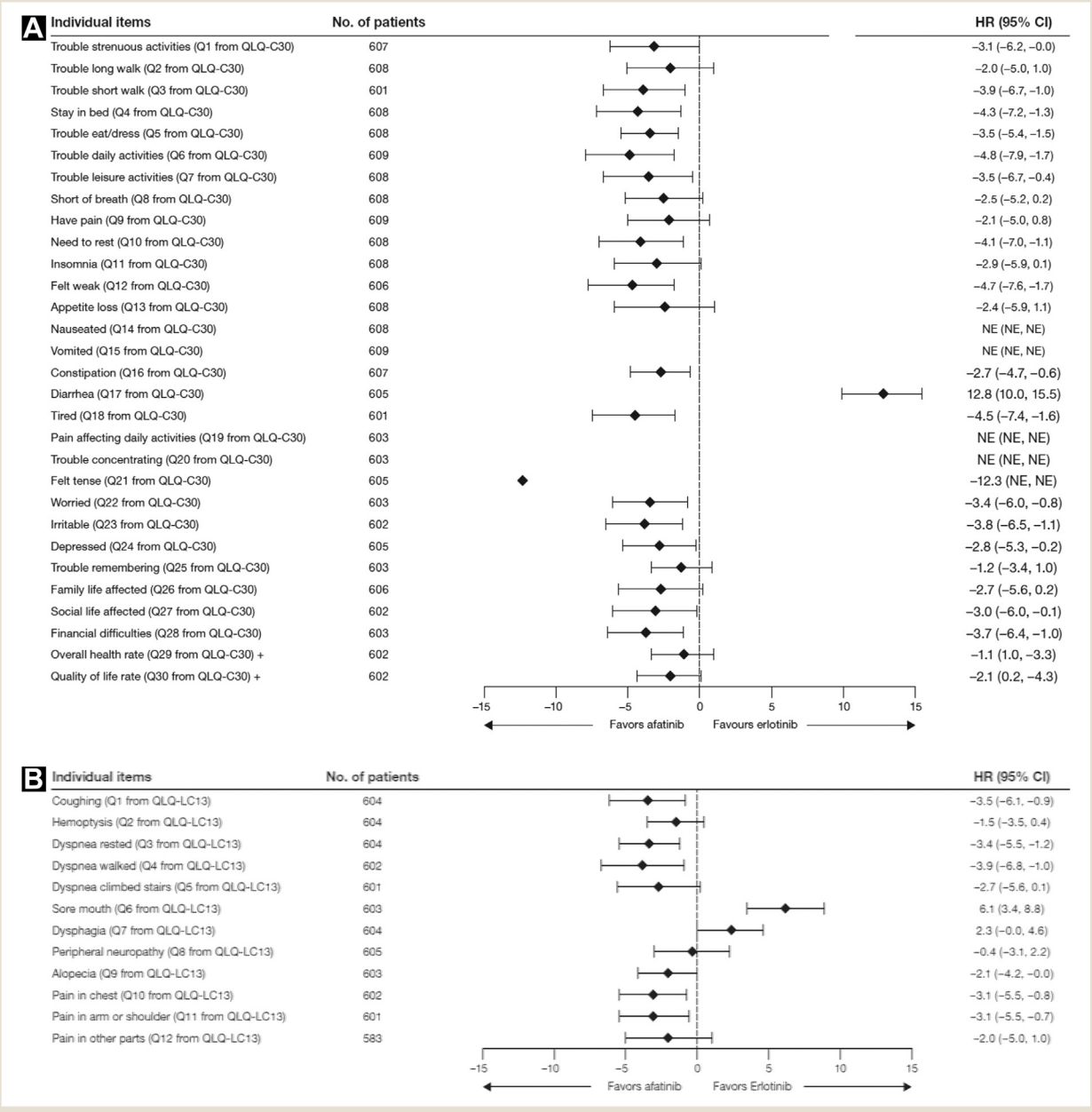
Abbreviations: GHS = global health status; QoL = quality of life.

Supplemental Figure 2 Time to Deterioration in Individual Items of (A) QLQ-C30 and (B) QLQ-LC13



Abbreviations: HR = hazard ratio; Q = question; QLQ-C30 = Quality of Life Questionnaire C30; QLQ-LC13 = Quality of Life Questionnaire Lung Cancer-13; QoL = quality of life.

Supplemental Figure 3 Difference in Mean Scores Over Time in Individual Items of (A) QLQ-C30 and (B) QLQ-LC13



Abbreviations: HR = hazard ratio; Q = question; QLQ-C30 = Quality of Life Questionnaire C30; QLQ-LC13 = Quality of Life Questionnaire Lung Cancer-13.

Supplemental Table 1 Improvement in GHS/QoL, Prespecified Symptoms, and Functional Scales of QLQ-C30 and QLQ-LC13

	Question	Afatinib				Erlotinib				OR	*P*
		n	Improved, %	Stable, %	Worsened, %	n	Improved, %	Stable, %	Worsened, %		
Global Health Status											
GHS/QoL	29, 30 QLQ-C30	339	35.7	20.6	43.7	339	28.3	20.9	50.7	1.40	.041
Prespecified Symptoms											
Cough	1 QLQ-LC13	339	43.4	25.4	31.3	341	35.2	29.3	35.5	1.41	.029
Dyspnea	3 to 5 QLQ-LC13	339	51.3	13.3	35.4	340	44.1	10.9	45.0	1.33	.061
Rested	3 QLQ-LC13	339	22.4	46.6	31.0	341	22.0	41.9	36.1	1.02	.897
Walked	4 QLQ-LC13	338	34.6	28.4	37.0	340	26.5	31.5	42.1	1.47	.022
Stairs	5 QLQ-LC13	337	34.7	30.6	34.7	338	33.1	28.7	38.2	1.07	.663
Shortness of breath	8 QLQ-C30	340	35.3	28.8	35.9	342	31.0	29.8	39.2	1.21	.234
Pain	9, 19 QLQ-C30	343	40.2	19.0	40.8	342	39.2	17.5	43.3	1.05	.775
Have pain	9 QLQ-C30	342	32.2	28.4	39.5	342	36.0	24.6	39.5	0.84	.297
Affecting daily activities	19 QLQ-C30	340	27.1	32.9	40.0	337	27.6	31.8	40.7	0.97	.880
Chest	10 QLQ-LC13	337	29.1	41.8	29.1	341	26.7	40.5	32.8	1.13	.489
Arm/shoulder	11 QLQ-LC13	337	25.2	43.9	30.9	339	32.2	39.8	28.0	0.71	.047
Other parts	12 QLQ-LC13	328	24.7	39.9	35.4	326	26.4	38.0	35.6	0.92	.621
Function Scales											
Physical	1 to 5 QLQ-C30	342	29.8	27.2	43.0	341	29.0	25.2	45.7	1.04	.819
Role	6, 7 QLQ-C30	342	33.3	21.9	44.7	342	29.2	21.3	49.4	1.21	.247
Cognitive	20, 25 QLQ-C30	342	29.5	30.4	40.1	339	30.4	26.5	43.1	0.96	.797
Emotional	21 to 24 QLQ-C30	342	30.1	34.2	35.7	340	26.5	32.4	41.2	1.20	.285
Social	26, 27 QLQ-C30	342	34.5	21.9	43.6	340	38.5	21.2	40.3	0.84	.274

Abbreviations: GHS = global health status; OR = odds ratio; QLQ-C30 = Quality of Life Questionnaire C30; QLQ-LC13 = Quality of Life Questionnaire Lung Cancer-13; QoL = quality of life.

Supplemental Table 2 Correlation Between Missing (Dropout) HRQoL Assessments and Patient Characteristics

Characteristic	Week of Assessment	Randomized Treatment					
		Afatinib			Erlotinib		
		n	Kendall Tau	*P*	n	Kendall Tau	*P*
Age, y	Baseline	391	0.06	.187	391	0.01	.741
	4	353	0.01	.747	354	−0.06	.212
	8	304	−0.06	.208	302	−0.02	.653
	12	236	0.01	.832	221	−0.02	.769
	20	145	0.00	.997	114	−0.08	.292
	28	93	−0.02	.788	71	−0.09	.349
	36	46	−0.04	.759	42	−0.26	.050
	44	39	−0.00	.973	24	−0.15	.386
	52	30	0.15	.335	18	−0.02	.928
ECOG Performance Status (0, 1)	Baseline	391	0.11	.025	391	0.14	.006
	4	353	0.10	.073	354	0.11	.037
	8	304	0.13	.019	302	0.04	.448
	12	236	0.06	.342	221	−0.03	.606
	20	145	0.07	.378	114	0.01	.931
	28	93	−0.10	.344	71	0.00	.989
	36	46	0.09	.539	42	−0.11	.468
	44	39	−0.04	.814	24	−0.20	.328
	52	30	−0.11	.554	18	0.24	.322
Race (Non-Eastern Asian/Eastern Asian)	Baseline	391	−0.11	.032	391	−0.02	.662
	4	353	0.01	.782	354	0.07	.200
	8	304	−0.01	.887	302	−0.05	.355
	12	236	0.00	.955	221	0.09	.167
	20	145	0.04	.631	114	0.00	.969
	28	93	−0.06	.578	71	0.13	.295
	36	46	0.05	.756	42	0.20	.209
	44	39	−0.01	.945	24	−0.17	.404
	52	30	−0.01	.977	18	0.08	.740
Sex (Male/Female)	Baseline	391	−0.02	.663	391	0.04	.391
	4	353	−0.08	.112	354	−0.01	.879
	8	304	0.05	.387	302	0.10	.088
	12	236	−0.04	.548	221	−0.00	.997
	20	145	0.00	.987	114	0.05	.593
	28	93	−0.06	.553	71	0.03	.815
	36	46	−0.06	.705	42	−0.17	.277
	44	39	−0.13	.432	24	−0.26	.216
	52	30	−0.16	.376	18	0.40	.103

Abbreviations: ECOG = Eastern Cooperative Oncology Group; HRQoL = health-related quality of life.

Supplemental Table 3 Correlation Between Missing (Dropout) HRQoL Assessments and Randomized Treatment

Week of Assessment	n	Kendall's Tau	*P*
0	782	−0.00	.903
4	707	0.01	.759
8	606	0.05	.203
12	457	0.10	.034
20	259	0.02	.759
28	164	−0.10	.219
36	88	0.31	.004
44	63	0.02	.863
52	48	−0.04	.765

Abbreviation: HRQoL = health-related quality of life.

Supplemental Table 4 Correlation Between Missing (Dropout) Assessments, and Baseline GHS/QoL and Symptom Assessments

	Afatinib			Erlotinib		
Week of Assessment	**n**	**Kendall's Tau**	***P***	**n**	**Kendall's Tau**	***P***
Correlation Between Baseline GHS/QoL Assessment and Missing (Dropout) GHS/QoL Assessments						
0	380	−0.17	<.001	376	−0.11	.018
4	339	−0.14	.004	339	−0.09	.065
8	294	−0.08	.135	287	−0.13	.012
12	229	0.15	.009	210	−0.12	.040
20	140	−0.13	.087	109	−0.18	.033
28	90	−0.01	.877	69	−0.06	.553
36	45	0.14	.281	41	−0.03	.811
44	38	−0.24	.092	23	0.08	.669
52	28	−0.39	.022	17	0.24	.274
Correlation Between Baseline Cough Assessment and Missing (Dropout) Cough Assessments						
0	380	−0.04	.360	377	0.01	.848
4	339	−0.02	.677	341	0.06	.236
8	295	−0.01	.858	287	0.04	.524
12	228	0.04	.546	210	0.04	.523
20	141	0.08	.338	111	0.15	.100
28	91	−0.02	.802	69	0.10	.376
36	46	0.07	.593	41	0.09	.571
44	39	0.18	.242	23	0.16	.431
52	29	−0.08	.646	17	0.07	.786
Correlation Between Baseline Dyspnea Assessment and Missing (Dropout) Dyspnea Assessments						
0	380	0.15	<.001	376	0.09	.036
4	339	0.02	.700	340	0.15	.001
8	296	0.02	.691	286	0.18	<.001
12	229	−0.07	.224	209	0.09	.128
20	141	0.11	.152	110	0.07	.400
28	92	−0.01	.914	69	0.11	.297
36	46	0.11	.389	41	−0.11	.425
44	39	−0.03	.857	23	0.12	.543
52	29	0.14	.404	17	0.10	.653
Correlation Between Baseline Pain Assessment and Missing (Dropout) Pain Assessments						
0	383	0.15	.001	378	0.09	.062
4	343	0.13	.007	342	0.11	.030
8	297	0.05	.334	290	0.14	.009
12	231	−0.05	.387	211	0.09	.149
20	143	0.18	.017	111	0.17	.044
28	92	0.02	.803	69	0.16	.159
36	46	−0.01	.935	41	0.01	.954
44	39	−0.15	.302	22	−0.29	.155
52	29	0.30	.080	17	0.02	.917

Abbreviations: GHS = global health status; QoL = quality of life.

Supplemental Table 5 Mean Score to Truncation Time for GHS/QoL and Symptoms From the Joint Model

	Afatinib		Erlotinib		Difference (Afatinib − Erlotinib)	
Dropout Event	Mean	SE	Mean	SE	Mean	SE
GHS/QoL						
None (primary analysis)	59.287	0.794	57.333	0.795	1.953	0.910
Treatment termination (censored[a])	58.573	0.808	56.657	0.808	1.916	0.914
Last assessment (uncensored)	58.767	0.810	56.829	0.810	1.937	0.921
Last assessment (censored[a])	58.770	0.810	56.802	0.810	1.968	0.921
Cough						
None (primary analysis)	35.410	1.030	39.007	1.031	−3.597	1.174
Treatment termination (censored[a])	35.715	1.032	39.298	1.034	−3.583	1.173
Last assessment (uncensored)	35.605	1.032	39.219	1.033	−3.614	1.175
Last assessment (censored[a])	35.605	1.032	39.238	1.034	−3.633	1.175
Dyspnea						
None (primary analysis)	27.697	0.870	30.947	0.872	−3.250	0.956
Treatment termination (censored[a])	28.242	0.880	31.469	0.881	−3.228	0.957
Last assessment (uncensored)	28.100	0.884	31.351	0.885	−3.251	0.964
Last assessment (censored[a])	28.088	0.882	31.366	0.884	−3.278	0.964
Pain						
None (primary analysis)	26.735	1.076	29.459	1.078	−2.724	1.192
Treatment termination (censored[a])	27.886	1.102	30.509	1.100	−2.623	1.206
Last assessment (uncensored)	27.617	1.108	30.241	1.105	−2.624	1.216
Last assessment (censored[a])	27.596	1.107	30.265	1.105	−2.668	1.216

Results from the longitudinal model (adjusting for race).
Abbreviations: GHS = global health status; QoL = quality of life; SE = standard error.
[a]Censored: at database lock date.

Supplemental Table 6 Mean Score to Truncation Time of 12 Weeks for GHS/QoL and Symptoms From the Pattern-Mixture Model

		Afatinib		Erlotinib		Difference (Afatinib − Erlotinib)	
Model	Extrapolation	Mean	SE	Mean	SE	Mean	SE
GHS/QoL							
Primary analysis	NA	59.287	0.794	57.333	0.795	1.953	0.910
Pattern mixture	LMCF	59.374	0.846	57.865	0.848	1.508	1.116
	Nearest neighbor	58.462	0.866	57.113	0.869	1.349	1.146
Cough							
Primary analysis	NA	35.410	1.030	39.007	1.031	−3.597	1.174
Pattern mixture	LMCF	34.638	1.137	39.946	1.140	−5.307	1.466
	Nearest neighbor	34.982	1.161	39.682	1.168	−4.700	1.505
Dyspnea							
Primary analysis	NA	27.697	0.870	30.947	0.872	−3.250	0.956
Pattern mixture	LMCF	27.298	0.907	30.193	0.910	−2.895	1.114
	Nearest neighbor	28.031	0.925	31.136	0.932	−3.105	1.144
Pain							
Primary analysis	NA	26.735	1.076	29.459	1.078	−2.724	1.192
Pattern mixture	LMCF	26.432	1.089	27.984	1.091	−1.552	1.367
	Nearest neighbor	27.081	1.114	29.074	1.118	−1.993	1.407

Results from the longitudinal model (adjusting for race).
Abbreviations: GHS/QoL = global health status/quality of life; LMCF = last mean carried forward; SE = standard error.

Supplemental Table 7 Improvement in Individual Items of QLQ-C30 and QLQ-LC13

	Question	Afatinib				Erlotinib				OR	*P*
		n	Improved (%)	Stable (%)	Worsened (%)	n	Improved (%)	Stable (%)	Worsened (%)		
Individual Items, QLQ-C30											
Trouble strenuous activities	1	340	37.1	24.1	38.8	340	35.3	25.6	39.1	1.08	.632
Trouble long walk	2	341	32.8	27.6	39.6	342	34.8	24.6	40.6	0.92	.595
Trouble short walk	3	336	18.8	38.7	42.6	338	20.4	33.4	46.2	0.9	.586
Stay in bed	4	342	21.3	37.4	41.2	341	26.1	30.2	43.7	0.77	.141
Trouble eat dress	5	341	4.4	70.4	25.2	341	5.6	66.3	28.2	0.78	.481
Trouble daily activities	6	341	29.3	28.7	41.9	341	24.6	26.4	49	1.27	.165
Trouble leisure activities	7	341	22.3	32.6	45.2	341	23.8	28.4	47.8	0.92	.651
Short of breath	8	340	35.3	28.8	35.9	342	31	29.8	39.2	1.21	.234
Have pain	9	342	32.2	28.4	39.5	342	36	24.6	39.5	0.84	.297
Need to rest	10	341	34	23.8	42.2	341	33.1	22.6	44.3	1.04	.806
Insomnia	11	341	30.8	31.1	38.1	342	28.1	31	40.9	1.14	.432
Felt weak	12	340	31.2	23.5	45.3	341	24.6	26.4	49	1.38	.058
Appetite loss	13	341	24.9	26.4	48.7	342	25.1	23.4	51.5	0.99	.947
Nauseated	14	342	17.3	48	34.8	341	14.4	47.2	38.4	1.24	.304
Vomited	15	342	6.7	70.2	23.1	342	7.6	68.1	24.3	0.88	.657
Constipation	16	341	27	48.4	24.6	342	31.9	40.9	27.2	0.79	.161
Diarrhea	17	342	8.5	14.3	77.2	339	5.6	40.4	54	1.56	.146
Tired	18	337	32.3	28.2	39.5	338	29.6	24.3	46.2	1.14	.436
Pain affecting daily activities	19	340	27.1	32.9	40	337	27.6	31.8	40.7	0.97	.88
Trouble concentrating	20	342	15.8	50.3	33.9	337	14.5	42.1	43.3	1.1	.651
Felt tense	21	341	28.2	35.5	36.4	339	24.5	35.7	39.8	1.21	.273
Worried	22	340	32.4	34.4	33.2	339	31	31.9	37.2	1.07	.684
Irritable	23	340	28.5	37.9	33.5	338	23.7	35.5	40.8	1.29	.149
Depressed	24	340	24.7	39.1	36.2	339	22.7	39.8	37.5	1.12	.54
Trouble remembering	25	339	23.9	45.4	30.7	339	25.7	40.4	33.9	0.9	.576
Family life affected	26	342	27.2	33.3	39.5	340	28.2	30.9	40.9	0.95	.758
Social life affected	27	340	25.6	31.2	43.2	338	27.8	29.9	42.3	0.89	.512
Financial difficulties	28	341	28.4	46.6	24.9	337	23.4	46	30.6	1.3	.139
Overall health rate	29	339	43.4	13	43.7	338	35.8	14.8	49.4	1.37	.045
Quality of life rate	30	339	43.1	12.1	44.8	339	36.0	13.9	50.1	1.34	.060

Supplemental Table 7 Continued

	Question	Afatinib				Erlotinib				OR	*P*
		n	Improved (%)	Stable (%)	Worsened (%)	n	Improved (%)	Stable (%)	Worsened (%)		
Individual Items, QLQ-LC13											
Coughing	1	339	43.4	25.4	31.3	341	35.2	29.3	35.5	1.41	.029
Hemoptysis	2	339	10	65.8	24.2	341	11.1	63.6	25.2	0.89	.628
Dyspnea rested	3	339	22.4	46.6	31	341	22	41.9	36.1	1.02	.897
Dyspnea walked	4	338	34.6	28.4	37	340	26.5	31.5	42.1	1.47	.022
Dyspnea climbed stairs	5	337	34.7	30.6	34.7	338	33.1	28.7	38.2	1.07	.663
Sore mouth	6	338	5.6	33.7	60.7	341	8.8	53.7	37.5	0.62	.113
Dysphagia	7	340	8.8	53.2	37.9	340	10	58.8	31.2	0.87	.598
Peripheral neuropathy	8	340	27.4	40.6	32.1	341	25.2	38.7	36.1	1.12	.528
Alopecia	9	339	18.9	54	27.1	339	22.4	51.6	26	0.8	.245
Pain in chest	10	337	29.1	41.8	29.1	341	26.7	40.5	32.8	1.13	.489
Pain in arm or shoulder	11	337	25.2	43.9	30.9	339	32.2	39.8	28	0.71	.047
Pain in other parts	12	328	24.7	39.9	35.4	326	26.4	38	35.6	0.92	.621

Abbreviations: OR = odds ratio; QLQ-C30 = Quality of Life Questionnaire C30; QLQ-LC13 = Quality of Life Questionnaire Lung Cancer-13.

Supplemental Table 8 Diarrhea Substudy

	Afatinib, n = 36	Erlotinib, n = 27
Incidence of Diarrhea, n (%)		
Any	31 (86.1)	14 (51.8)
CTCAE Grade ≥2	16 (44.4)	4 (14.8)
CTCAE Grade ≥3	7 (19.4)	0 (0.0)
CTCAE Grade ≥4	0 (0.0)	0 (0.0)
Median Duration of Diarrhea, d (Range)		
Any	23 (2-79)	5.5 (1-32)
CTCAE Grade ≥2	5.5 (1-28)	8.5 (1-24)
CTCAE Grade ≥3	3 (2-10)	–
Dose Reductions Because of Diarrhea, n (%)	7 (19.4)	1 (3.7)
Median Duration of Diarrhea After Dose Reduction, d (Range)	13 (3-43)	3 (3-3)
Treatment Discontinuations Because of Diarrhea, n (%)	0 (0.0)	0 (0.0)
Duration of First Episode of Diarrhea		
Median, d (range)	6 (1-74)	1 (1-27)
≤2 d, n (%)	11 (30.6)	10 (37.0)
3 to 5 d, n (%)	4 (11.1)	2 (7.4)
6 to 7 d, n (%)	3 (8.3)	0 (0.0)
≥7 d, n (%)	13 (36.1)	2 (7.4)

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.