

Symptom and Quality of Life Benefit of Afatinib in Advanced Non–Small-Cell Lung Cancer Patients Previously Treated with Erlotinib or Gefitinib

Results of a Randomized Phase IIb/III Trial (LUX-Lung 1)

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Background: Patient-reported symptom and health-related quality of life (HRQoL) benefit of afatinib, a novel, irreversible, ErbB Family Blocker, was investigated in a double-blind, randomized, phase IIb/III trial (LUX-Lung 1).

Methods: Five hundred and eighty-five patients with lung adenocarcinoma (stage IIb/IV), who had progressed after chemotherapy (1–2 lines) and at least 12 weeks of erlotinib or gefitinib, were randomized (2:1) to receive either afatinib plus best supportive care (BSC) or placebo plus BSC. Symptom and HRQoL benefit were measured using the lung cancer-specific European Organisation for Research and Treatment of Cancer (QLQ-C30/LC13) and EuroQol (EQ-5D) questionnaires. Non–small-cell lung cancer–related symptoms (cough, dyspnea, and pain) were prespecified using three preplanned analyses (percentage of patients improved/worsened/stable, change in scores over time, and time to deterioration of scores).

Results: Compared with patients on placebo, a significantly higher proportion of afatinib-treated patients showed an improvement in cough ($p < 0.0001$), dyspnea ($p = 0.006$), and pain ($p < 0.0001$). Afatinib also significantly improved the mean scores over time for cough ($p < 0.0001$), dyspnea ($p = 0.0161$), and pain ($p = 0.0056$);

significantly delayed the time to deterioration for cough ($p < 0.001$); and showed a trend in delaying dyspnea ($p = 0.170$) and pain ($p = 0.287$). Consistent with the adverse-event profile of afatinib, a significantly ($p < 0.05$) higher proportion of afatinib-treated patients showed worsening of diarrhea, sore mouth, dysphagia, and appetite scores. However, compared with placebo, afatinib significantly ($p < 0.05$) improved QoL assessed with the EQ-5D questionnaire and global health status/QoL, physical functioning, and fatigue, which were assessed with the European Organisation for Research and Treatment of Cancer questionnaires.

Conclusion: In the LUX-Lung 1 trial, the addition of afatinib to BSC significantly improved non–small-cell lung cancer–related symptoms (cough, dyspnea, and pain), fatigue, physical functioning, and HRQoL and significantly delayed time to deterioration of cough.

Key Words: Afatinib, Quality of life, Symptom benefit, Non–small-cell lung cancer, Phase IIb/III trial.

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Lung cancer remains a leading cause of cancer death worldwide, for both men and women.¹ Approximately 90% of patients with advanced non–small-cell lung cancer (NSCLC) experience two or more disease-related symptoms, which may result in psychological distress. Disease-related symptoms commonly include pulmonary symptoms such as cough, dyspnea, and the general symptoms of fatigue, pain, and anorexia.² These symptoms have a negative impact on a patient's health-related quality of life (HRQoL); dyspnea and fatigue have been shown to interfere with at least one daily life activity in the majority of patients, and pain interferes with one daily life activity in approximately 40% of patients.² High degrees of psychological distress experienced by lung cancer patients influence the emotional well-being in both patients and their families. Given the impact that disease-related symptoms have on patient HRQoL, it is not surprising that 68% of patients would prefer a therapy that improved disease-related symptoms without prolonging life, as opposed to one that marginally improved survival without symptom benefit.³

Therefore, patient-reported outcomes (PROs) of treatment (including symptom and HRQoL outcomes) are considered to be important, in addition to efficacy and safety endpoints, in patients with advanced NSCLC. Furthermore, PROs should be viewed as components of the total value of a treatment and, together with these other cancer endpoints, provide a comprehensive picture of the benefits and risks of anticancer therapies, as discussed during an American Society of Clinical Oncology/U.S. Food and Drug Administration workshop on endpoints for the approval of cancer drugs for lung cancer, in 2003. A similar position has been taken by the European Medicines Agency.^{4,5}

Afatinib is a novel, orally bioavailable, irreversible, small-molecule ErbB Family Blocker that inhibits epidermal growth factor receptor (EGFR, also known as ErbB1), human epidermal growth factor receptor (HER2) (ErbB2), and ErbB4 receptor kinases.^{6,7} Clinical studies have confirmed the efficacy of afatinib in EGFR-tyrosine kinase inhibitor (TKI)-naïve patients with activating EGFR mutations.^{8,9} Preclinically, the activity of afatinib extends beyond the common EGFR mutations to the T790M mutation, the main mechanism of acquired resistance to the reversible EGFR-TKIs, erlotinib and gefitinib.⁷ Therefore, afatinib offers a potential alternative for patients who have progressed after chemotherapy and EGFR-TKI therapy.

The efficacy and safety of afatinib in EGFR-TKI pretreated patients was investigated in a randomized, double-blind, multicenter phase IIb/III trial (LUX-Lung 1).¹⁰ The primary objective of this trial was to investigate the efficacy of afatinib monotherapy (plus best supportive care [BSC]) compared with placebo (plus BSC) in patients with progressive, advanced NSCLC in the refractory setting. One of the secondary objectives was to assess patient-reported symptom and HRQoL outcomes, which are presented here.

PATIENTS AND METHODS

Study Population

Adult patients with pathologically confirmed NSCLC stage IIb/IV adenocarcinoma (tumor, node, metastasis classification system by the International Union Against Cancer, 6th edition), who had progressed on one or two lines of cytotoxic chemotherapy (one of which was platinum based), and had progressive disease after at least 12 weeks of treatment with erlotinib or gefitinib, were eligible for inclusion.¹⁰

Study Design

Patients were randomized 2:1 to receive BSC plus either oral afatinib 50 mg once daily or placebo until disease progression, death, or withdrawal because of adverse events (AEs). The primary study endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), objective tumor response (Response Evaluation Criteria in Solid Tumors criteria), safety, and HRQoL.

Patient-Reported Outcomes Assessments

Patient-reported symptom and HRQoL benefits were assessed using the self-administered cancer-specific

European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-Core 30 (C30),¹¹ the lung cancer-specific EORTC QLQ-Lung Cancer 13 (LC13),¹² and the EuroQol (EQ-5D)¹³ questionnaire. The QLQ-C30 questionnaire incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea/vomiting), a global health status/QoL scale, and a number of single items (dyspnea, loss of appetite, sleep disturbance, constipation, diarrhea, and financial impact). The QLQ-LC13 questionnaire incorporates one multi-item scale to assess dyspnea, and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and use of pain medication.

For each scale/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 for functional scales, and highest burden of symptoms for symptom scales and symptom items. A 10-point change in an item or domain is perceived to be clinically meaningful.¹⁴ Therefore, the percentage of patients who were classified as improved (≥ 10 -point increase for functioning scales and ≥ 10 -point reduction for symptom domains or items from baseline score), stable or worsened (≥ 10 -point reduction for functioning scales and ≥ 10 -point increase for symptom scales or items from baseline score), with respect to each of the EORTC QLQ-C30 and QLQ-LC13 scales/items, was examined.¹⁴ In addition, time to deterioration of an item/domain score was defined as the time from randomization to the first appearance of a score that was 10 points or more lower or higher than the baseline score (≥ 10 -point reduction for functioning scales and ≥ 10 -point increase for symptom scales or items).

The EQ-5D is a disease-generic questionnaire that comprises the EQ-5D and EQ-visual analogue scale (VAS). The EQ-5D measures five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension comprises three levels (no problems, some/moderate problems, and extreme problems). Utility scores range from 0 to 1 and were calculated from the five EQ-5D item scores using the U.K. preference weights.¹⁵ The EQ-VAS records the patient's self-rated health status on a vertical, graduated (0–100) VAS.

Per protocol, the EORTC QLQ-C30, QLQ-LC13, and EQ-5D questionnaires were scheduled to be completed every 2 weeks during the first 2 months, every 4 weeks thereafter, at the end-of-treatment (EOT) visit, and during the first follow-up visit. Questionnaires were administered more frequently during the first 2 months to maximize data capture before patients discontinued treatment, especially in the placebo treatment arm. To assess symptoms and HRQoL related to afatinib and placebo treatment, questionnaires were only completed up to the first follow-up visit. To attribute any observed symptom or HRQoL benefit directly to afatinib or placebo, the use of concomitant medications was assessed in both the afatinib and placebo treatment arms at baseline and during the trial.

Statistical Methods and Analyses

The intention-to-treat data set was used for all EORTC QLQ-C30, QLQ-LC13, and EQ-5D analyses. The NSCLC-related symptoms of cough, dyspnea, and pain were prespecified because of the relevance of these symptoms and to avoid multiplicity.¹⁶ Cough (question 1 on the QLQ-LC13), dyspnea (composite of questions 3–5 on the QLQ-LC13), and pain scores (composite of questions 9 and 19 on the QLQ-C30) were assessed. All items and alternative measures for dyspnea and pain were examined descriptively for consistency and comparison.

Analyses included a comparison of the percentage of patients considered to have improved, become stable or worsened for each of the QLQ-C30 and QLQ-LC13 summary scales or single items in the two treatment arms (χ^2 square test). Time to deterioration was analyzed similar to OS and PFS (log-rank test stratified by baseline Eastern Cooperative Group [ECOG] performance score [PS; 0 or 1 versus 2] and sex). The Hochberg–Bonferroni procedure was applied to the group of comparisons comprising the three symptom scales or single items.¹⁷ Patients who died before deteriorating but within 4 weeks of treatment discontinuation were considered to have deteriorated at the time of death. Disease progression without scale deterioration was censored at the time of the last EORTC assessment; patients with no patient-reported outcomes assessments were censored at day 1. If a patient-reported outcome assessment was missed but followed by another assessment and deterioration occurring during that time period, the time to deterioration was defined as the midpoint between the two observed assessments. The longitudinal analysis in this study used a mixed-effects growth-curve model, with the average profile over time for each endpoint being described by a piecewise linear model that allowed the slope to change at predefined time points (2, 4, 8, and 12 weeks). QLQ-C30 and QLQ-LC13 summary scales or single items, EQ-5D utility scores, and EQ-VAS scores were analyzed using this model. All analyses were prespecified before unblinding the study data.

Terms in the model were randomized treatment, actual time since randomization, ECOG PS at baseline, and sex. For each treatment group, the area under the estimated growth curve (AUC) up to the median follow-up time for each EORTC/EQ-5D score was calculated. The AUC divided by the median follow-up time was interpreted as the mean EORTC/EQ-5D score, up to the median follow-up time. Between-treatment arm differences for the proportion of patients improved, the time to deterioration and longitudinal analysis when described as significant refer to statistical significance.

Sensitivity analyses were carried out for the proportion of patients improved and the longitudinal analysis. The durability of improvement was tested by requiring patients to have an improvement of 10 points or more over at least two assessments. Joint models were fitted using SAS NLMixed, extending the basic model described above to test the results of the longitudinal analyses for uncertainty associated with missing data. Of several candidates for the

time to event that is included in the joint model, time to randomized permanent discontinuation of last study medication and time to last EORTC/EQ-5D assessment were chosen.¹⁸

RESULTS

Patient Population

In total, 585 patients were randomized from May 2008 to September 2009 across 15 countries in North America, Europe, and Asia (390 patients received afatinib and 195 patients received placebo). The patient characteristics between the two treatment arms were well balanced. The study population comprised a highly selected population (histology: 98% adenocarcinoma, 58% East Asian, 60% women, 63% never-smokers, 25% ECOG PS of 0, 68% ECOG PS of 1; median age of 58 years) that was very sensitive to previous EGFR inhibition. Indeed, 45% of patients had achieved a partial or complete response on previous EGFR-TKI therapy, with a median treatment time of 43 weeks. Of 141 patients with tumor tissue available for optional testing, 68% were positive for EGFR mutation.¹⁰

Brief Summary of Other Clinical Outcomes

At the time of database lock, median OS was 10.8 months for the afatinib arm and 12 months for the placebo arm (HR 1.08, [95% confidence interval 0.86, 1.35], $p = 0.74$). Afatinib significantly improved PFS compared with placebo (median 3.3 versus 1.1 months, HR 0.38, [0.31, 0.48], $p < 0.0001$). In addition, patients in the afatinib arm had a disease-control (≥ 8 weeks) rate (partial response/stable disease) of 58%, compared with 18% in the placebo arm.¹⁰

Compliance with Patient-Reported Assessments

Compliance rates for each treatment arm are presented in Table 1. High compliance rates were observed (65%–100%) up to week 24/EOT and were comparable across both treatment arms. Lower compliance rates were observed during the first follow-up visit (45–46%), which occurred 28 days after the EOT visit. The main reason for missing EORTC and EQ-5D questionnaires was treatment discontinuation, particularly in the placebo treatment arm, justifying the usefulness of completing the EORTC questionnaires every 2 weeks during the first 2 months.

Concomitant Medication

At baseline, no difference between treatment arms was observed with regard to the proportion of patients receiving symptomatic treatment for dyspnea (3% versus 3%), cough (15% versus 15%), and pain (49% versus 48%) for afatinib versus placebo, respectively. During the treatment period, concomitant use of such medications was also similar between the two treatment groups: dyspnea (6% versus 4%), cough (23% versus 20%), and pain (60% versus 57%) for afatinib versus placebo, respectively.

TABLE 1. Patient Compliance Rates with EORTC and EQ-5D Questionnaires by Treatment Arm

| | Afatinib + BSC | | Placebo + BSC | |
|--------------|--------------------------|---|--------------------------|---|
| | Total No. of Patients, N | Patients Completing EORTC and EQ-5D Questionnaires, n (%) | Total No. of Patients, n | Patients Completing EORTC and EQ-5D Questionnaires, n (%) |
| Baseline | 390 | 367 (94.1) | 195 | 182 (93.3) |
| Week 2 | 389 | 346 (88.9) | 195 | 166 (85.1) |
| Week 4 | 369 | 302 (81.8) | 103 | 89 (86.4) |
| Week 6 | 302 | 247 (81.8) | 75 | 62 (82.7) |
| Week 8 | 287 | 231 (80.5) | 66 | 49 (74.2) |
| Week 12 | 221 | 158 (71.5) | 39 | 26 (66.7) |
| Week 16 | 174 | 149 (85.6) | 22 | 19 (86.4) |
| Week 20 | 158 | 103 (65.2) | 20 | 15 (75.0) |
| Week 24 | 105 | 85 (81.0) | 9 | 9 (100.0) |
| End of trial | 380 | 275 (72.4) | 194 | 149 (76.8) |
| FUV 1 | 326 | 148 (45.4) | 179 | 82 (45.8) |

BSC, best supportive care; EORTC, European Organisation for Research and Treatment of Cancer; FUV, follow-up visit.

TABLE 2. EORTC Questionnaire Scores at Baseline

| EORTC QLQ-C30 or LC13 Item or Domain | Afatinib + BSC | | Placebo + BSC | |
|---|-----------------|-----|-----------------|-----|
| | Mean Score (SD) | n | Mean Score (SD) | n |
| Cough (Q1 from QLQ-LC13) | 30.7 (26.2) | 361 | 28.9 (27.2) | 182 |
| Dyspnea (Q3–Q5 from QLQ-LC13) | 24.2 (21.2) | 361 | 24.0 (21.4) | 182 |
| Shortness of breath (Q8 from QLQ-C30) | 28.3 (27.7) | 362 | 25.6 (26.9) | 182 |
| Pain (Q9, Q19 from QLQ-C30) | 27.8 (27.0) | 365 | 26.8 (25.7) | 182 |
| Pain in chest (Q10 from QLQ-LC13) | 21.1 (24.5) | 361 | 18.3 (23.2) | 180 |
| Pain in arm or shoulder (Q11 from QLQ-LC13) | 22.1 (26.3) | 360 | 21.5 (26.5) | 181 |
| Pain in other parts (Q12 from QLQ-LC13) | 23.6 (27.5) | 346 | 24.2 (28.7) | 168 |

Lower scores indicate that patients experience fewer or no problems on a scale of 0–100.

EORTC, European Organisation for Research and Treatment of Cancer; BSC, best supportive care; SD, standard deviation.

Baseline Symptoms and HRQoL Scores

At baseline, mean EORTC scores for the three prespecified NSCLC related symptoms—cough, dyspnea, and pain—were generally low ranging from 24–31 (Table 2), suggesting that patients had low symptom levels. Similarly, the EQ-5D U.K. utility and EQ-VAS scores were found to be favorable (0.727 and 69.5, respectively). This finding was consistent with patients' good ECOG PS at baseline (PS 0, 25%; PS 1, 68%; PS 2, 8%). Common Terminology Criteria of Adverse Events (CTCAE) also demonstrate low rates of cough (30%), dyspnea (17%), and chest pain (12%) across both treatment arms at baseline.

Proportion of Patients with Improved Symptoms and HRQoL Scores

A significantly greater percentage of patients in the afatinib treatment arm showed improvements for the prespecified NSCLC-related symptoms of cough (46% versus 25%, $p < 0.0001$), dyspnea (51% versus 36%, $p = 0.0060$), and pain (50% versus 32%, $p < 0.0001$) as measured with the EORTC questionnaires, compared with the placebo treatment arm (Fig. 1). Significant benefits favoring patients

treated with afatinib were also observed for the single items of shortness of breath (40% versus 25%, $p = 0.0014$), pain in chest (40% versus 24%, $p = 0.0014$), pain in arm or shoulder (41% versus 27%, $p = 0.0044$), and pain in other parts (36% versus 26%, $p < 0.0037$). Conversely, a significant worsening of scores was observed for the symptoms of appetite loss (53% versus 40%, $p < 0.0001$), diarrhea (83% versus 17%, $p < 0.0001$), sore mouth (76% versus 17%, $p < 0.0001$), and dysphagia (46% versus 17%, $p < 0.0001$) for patients treated with afatinib compared with patients on placebo, respectively. Afatinib showed a significantly greater percentage of patients with improvement in fatigue symptom scores compared with placebo (53% versus 40%, $p < 0.0007$). Overall, improvements were observed for global health status/QoL (38% versus 29%, $p < 0.084$) for afatinib-treated patients compared with patients treated with placebo, respectively.

Time to Deterioration of Symptom and HRQoL Scores

Afatinib significantly delayed the time to deterioration for cough (HR 0.60, [0.44, 0.81]), and showed a trend in

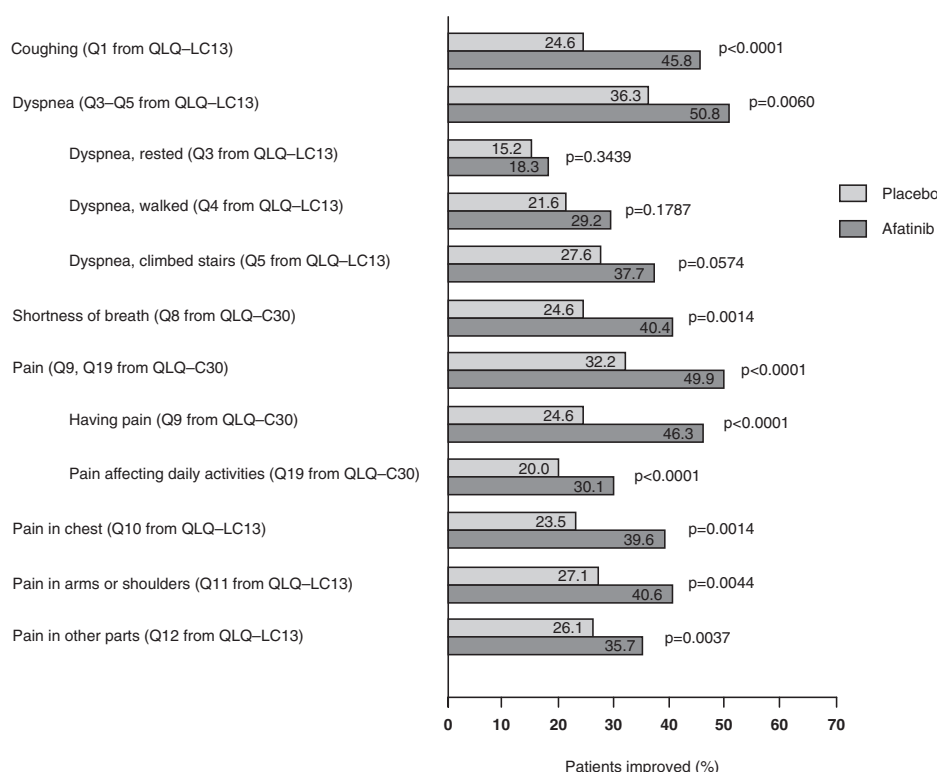


FIGURE 1. Percentage of patients with improvement in the three prespecified symptoms of cough, dyspnea, and pain. Improvement was defined as ≥ 10 -point increase for functioning scales and ≥ 10 -point reduction for symptom domains or items from baseline score. The number of patients included in the analysis of each of the listed items/domains was $n = 339$ – 359 (afatinib) and $n = 153$ – 171 (placebo).

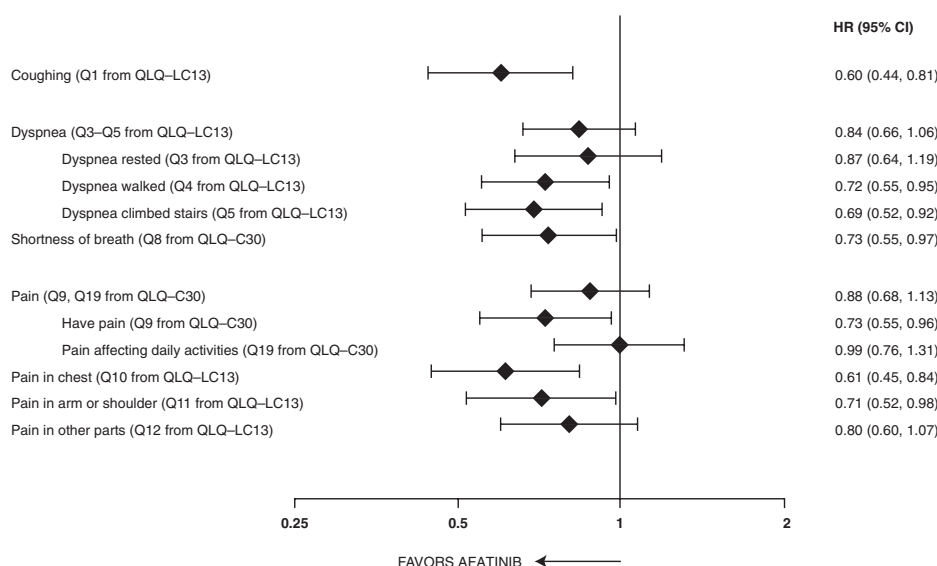


FIGURE 2. Time to deterioration analysis for the three prespecified symptoms of cough, dyspnea, and pain. Time to deterioration was analyzed using log-rank test stratified by baseline ECOG PS and sex. The time to deterioration analysis included all randomized patients, that is, $n = 390$ (afatinib) and $n = 195$ (placebo). Patients who did not complete any questionnaires were either censored on day 1 or considered deteriorated if they died within 4 weeks after randomization.

delaying dyspnea (HR 0.84, [0.66, 1.06]) and pain (HR 0.88, [0.68, 1.13]) (Fig. 2). For dyspnea, the potential benefit of afatinib compared with placebo was more apparent when items relating to physical exertion were assessed, such as dyspnea while walking (HR 0.72, [0.55, 0.95]), dyspnea while climbing stairs (HR 0.69, [0.52, 0.92]) and the single item of shortness of breath (HR 0.73, [0.55, 0.97]). Afatinib treatment was favored over placebo for time to deterioration for the item have pain 0.73, [0.55, 0.96]), pain

in chest (HR 0.61, [0.45, 0.84]), pain in arm or shoulder (HR 0.71, [0.52, 0.98]), constipation (HR 0.46, [0.34, 0.62]), hemoptysis (HR 0.89, [0.56, 1.41]), fatigue (HR 0.97, [0.78, 1.22]), and insomnia (HR 0.70, [0.53, 0.93]). Conversely, a significantly shorter time to deterioration was observed for afatinib for the EORTC questionnaire scores for appetite loss (HR 1.29, [1.00, 1.66]), dysphagia (HR 2.17, [1.54, 3.06]), sore mouth (HR 5.88, [4.21, 8.21]), and diarrhea (HR 7.88, [5.63, 11.02]).

Afatinib was found to delay the time to deterioration for global health status/QoL (HR 0.78, [0.62, 1.00]) and the functioning scales of emotional (HR 0.87, [0.65, 1.16]), physical (HR 0.81, [0.62, 1.05]), role (HR 0.81, [0.64, 1.03]), and social (HR 0.97, [0.75, 1.25]) functioning. No difference in time to deterioration was observed for the remaining items or scales.

Longitudinal Analysis of Symptom and HRQoL Scores

Afatinib-treated patients had significantly better mean symptom scores up to the median follow-up time (13 weeks) for the prespecified symptoms: cough (−6.99 [95% confidence interval: −9.71, −4.27]), dyspnea (−2.68 [−4.86, −0.49]), and pain (−4.02 [−6.87, −1.18]) (Fig. 3). Between-group differences in symptom scores favoring afatinib started at week 2 and generally lasted throughout the study period. Patients in the afatinib treatment arm, who assessed their experience of dyspnea during physical activity demonstrated the largest difference in scores compared with patients in the placebo arm. The difference in means was also more pronounced in favor of afatinib for the following items: have pain (−6.08 [−9.21, −2.96]), pain in chest (−5.60 [−8.03, −3.17]), pain in other parts (−4.04 [−7.37, −0.71]), pain in arm and shoulder (−6.26 [−8.91, −3.61]), and shortness of breath (−3.46 [−6.21, −0.71]).

Afatinib-treated patients also demonstrated significantly better EORTC scores for the items constipation (difference in means, −9.96 [−12.3, −7.63]) and insomnia (−6.73 [−9.69, −3.78]) compared with the patients in the placebo treatment arm. Furthermore, mean difference in scores for fatigue (−2.99 [−5.54, −0.45]), nausea and vomiting (−0.66 [−2.66, 1.35]), financial difficulties (−1.11 [−3.82, 1.60]), and alopecia (−0.92 [−3.59, 1.76]) favored the afatinib treatment arm. Conversely, the difference in mean scores for appetite loss (4.71 [1.51, 7.91]), dysphagia (4.54 [2.28, 6.79]), peripheral neuropathy (2.41 [−0.27, 5.08]), sore mouth (21.04 [18.24, 23.84]), and diarrhea (33.18 [30.13, 36.23]) favored

the placebo treatment arm. No difference in mean score for hemoptysis (0.11 [−1.08, 1.30]) was observed.

Patients treated with afatinib also demonstrated significantly better EORTC scores for global health status/QoL (difference in means, 3.29 [1.05, 5.53]) and physical functioning (3.49 [1.19, 5.79]) compared with patients in the placebo treatment arm. A positive trend favoring the afatinib treatment arm was also observed for the other functioning domains.

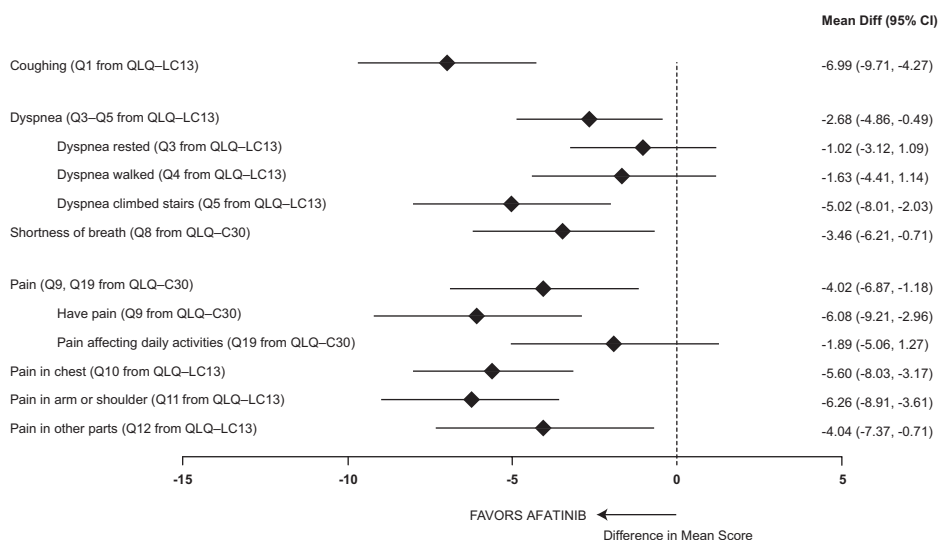
The longitudinal analysis was also performed for the EQ-5D utility score and EQ-VAS scores. HRQoL, when measured using those, was significantly better in the afatinib treatment arm compared with the placebo treatment arm. The mean EQ-5D utility score to median follow-up time was 0.71 versus 0.67 ($p = 0.006$) for the afatinib and placebo groups, respectively. For EQ-VAS, this was 67.4 versus 65.2 ($p = 0.0205$) for the afatinib and placebo groups, respectively.

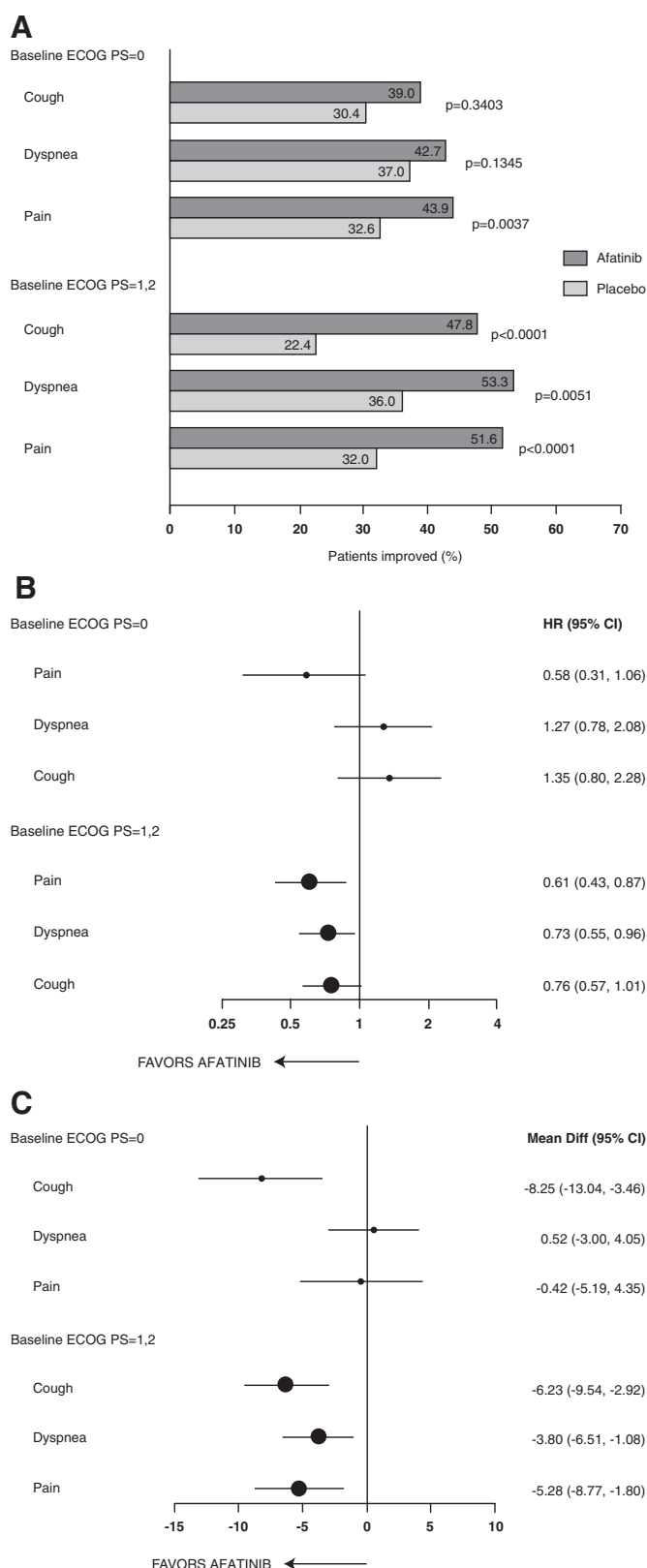
Sensitivity Analyses

For the proportion of patients who had improved, the durability of improvement was tested. Patients were required to have an improvement of 10 points or greater over at least two assessments. The magnitude in the differences between treatment arms remained more than 10% and statistical significance was maintained. Findings of this analysis were therefore found to be robust.

For the longitudinal analysis, two separate analyses (1 including data until week 4 and 1 including data until week 8) showed similar results. In addition, no notable differences in results were observed when data from the follow-up visit were removed. In addition, sensitivity analyses were carried out using a joint model,¹⁸ which is more general than a longitudinal model because it relaxes the missing data assumptions to *missing at random* that are conditional on the time to treatment termination or last EORTC/EQ-5D assessment. Results of these analyses were similar to those from the longitudinal model.

FIGURE 3. Results from the longitudinal analysis for the three prespecified symptoms of cough, dyspnea, and pain. The longitudinal analysis uses a mixed-effects growth curve model with the average profile over time for each endpoint described by a piecewise linear model adjusted for baseline ECOG PS and sex. The number of patients included in the analysis for each of the listed items/domains was $n = 385$ – 386 (afatinib) and $n = 191$ (placebo). ECOG PS, Eastern Cooperative Oncology Group performance status.





Subgroup Analyses

To determine the influence of patient PS on the outcomes of the EORTC scores, two subgroup analyses were performed (ECOG PS 0 patients versus ECOG PS 1, 2 patients). For each of the three analyses (proportion of patients improved, time to deterioration, and longitudinal analyses), the symptom benefit associated with afatinib therapy was larger for patients with ECOG PS 1 and 2 compared with patients with ECOG PS 0 (Fig. 4A–C).

Clinician-Reported Outcomes

Clinician-reported outcomes are derived from the reporting of AEs according to the CTCAE v3.0. Cough (any grade) was reported in 13% of afatinib-treated patients and 19% of placebo-treated patients. Any-grade dyspnea was reported in 15% of patients treated with afatinib, compared with 13% of placebo-treated patients. When exposure was corrected to take into consideration the longer treatment duration for patients in the afatinib treatment arm, time to onset of cough and dyspnea was delayed in the afatinib arm compared with the placebo arm. By day 84, 25% of placebo-treated patients had experienced cough compared with 8% of afatinib-treated patients (HR 0.41, $p < 0.0001$). By day 84, 13% of placebo-treated patients and 10% of afatinib-treated patients had experienced dyspnea (HR 0.80, $p = 0.354$). In general, the most frequent clinician-reported AEs (with a $> 10\%$ difference between treatment arms) were diarrhea, rash/acne, stomatitis, nail effect, and decreased appetite. Fewer patients in the placebo arm compared with the afatinib arm experienced diarrhea of any grade (9% versus 87%) and decreased appetite (11% versus 31%).

DISCUSSION

This large, phase IIb/III study comparing afatinib plus BSC with placebo plus BSC demonstrated that afatinib significantly improved the NSCLC-related symptoms of cough, dyspnea, and pain, while also significantly delaying deterioration of cough. An analysis of concomitant medication confirms that the benefit observed with afatinib is not the result

FIGURE 4. Subgroup analyses with patients with ECOG PS 0 versus ECOG PS 1, 2. **A**, Proportion of patients improved. The number of patients included in the analysis of the proportion of patients improved for each of the listed items/domains was for baseline ECOG = 0, $n = 82$ (afatinib) and $n = 46$ (placebo); for baseline ECOG = 1 or 2, $n = 274$ –277 (afatinib) and $n = 125$ (placebo). **B**, Time to deterioration. The time to deterioration analysis included all randomized patients: baseline ECOG = 0, $n = 92$ (afatinib), and $n = 53$ (placebo); for baseline ECOG = 1 or 2, $n = 298$ (afatinib), and $n = 142$ (placebo). Patients who did not complete any questionnaires were either censored on day 1 or considered deteriorated if they died within 4 weeks after randomization. **C**, Longitudinal analysis. The number of patients included in the longitudinal analysis of each of the listed items/domains was $n = 91$ (afatinib) and $n = 53$ (placebo) for ECOG PS 0, and $n = 294$ –295 (afatinib) and $n = 138$ (placebo) for ECOG PS 1–2. ECOG PS, Eastern Cooperative Oncology Group performance status.

of patients receiving additional symptomatic treatment compared with patients in the placebo arm.

Previous studies have shown that EGFR-TKIs are associated with the occurrence of diarrhea. The finding that afatinib treatment worsened the symptom of diarrhea correlates with the higher rate of diarrhea reported as an AE in the afatinib treatment arm. Although diarrhea worsened in the afatinib treatment arm, and was more frequently observed as an AE compared with the placebo treatment arm, improvements in overall global health status/QoL favored the afatinib treatment arm. In addition, few patient discontinuations were reported as being the result of the occurrence of diarrhea (3.6%), suggesting that the implementation of antidiarrheals and dose reductions were effective in allowing patients to continue afatinib treatment.

Patients enrolled in this trial had a good ECOG PS and relatively low symptom burden at baseline according to the CTCAE and EORTC scores for cough, pain, and dyspnea, in particular. Despite the low symptom burden at baseline, patients in the afatinib treatment arm were found to have significantly better EORTC scores for cough, dyspnea, and pain, compared with patients receiving placebo. However, the difference in EORTC scores seemed to be more pronounced in patients with a baseline ECOG PS of 1 or 2 compared with those with an ECOG PS of 0.

Although patient compliance with the EORTC and EQ-5D questionnaires was high in both treatment arms, a substantial amount of data was missing in the placebo treatment arm because of early patient discontinuation. Results of the three main analyses, as well as the sensitivity analyses, confirmed the positive effect of afatinib on symptoms and HRQoL compared with placebo. Completing the EORTC and EQ-5D questionnaires every 2 weeks during the first 2 months provided more frequent data points to inform each of the three main analyses and the sensitivity analyses. Collecting EORTC and EQ-5D data beyond the first follow-up visit postprogression may have alleviated the issue of missing data; however, this could have led to the occurrence of several potential challenges in this study: the inclusion of EORTC and EQ-5D data that showed results no longer attributable to afatinib and placebo because of the initiation of subsequent treatment regimens, compliance (completion of questionnaire and timing of completion), and difficulties administering questionnaires. Although no EORTC and EQ-5D data were collected beyond the first follow-up visit, removing data from the first follow-up visit from the sensitivity analysis showed no notable differences in results, indicating the robustness of the initial analyses.

Over recent years, HRQoL-based measures have been increasingly incorporated into oncology phase III clinical trials, mainly as secondary endpoints.^{19,20} A patient's own assessment of the benefit of anticancer therapy has been considered important from the perspective of a patient, physician, payer, and regulator and also in terms of the clinical measures of OS, PFS, and response. Most researchers and clinicians agree that measuring PROs, such as pain or physical function, is fundamental because of their impact on patient compliance and outcome. Furthermore, assessing symptom and HRQoL outcomes demonstrates how positive PFS outcomes can translate into additional patient benefit.

Previous studies have demonstrated symptom and HRQoL benefits of different magnitudes after treatment with EGFR-targeting therapy.^{21–24} One large, randomized, phase III study, BR.21, compared second- or third-line erlotinib treatment with placebo in patients with NSCLC and measured symptom and HRQoL outcomes using the EORTC questionnaires.²² Patients receiving erlotinib in BR.21 experienced significantly longer times to symptom deterioration and reported notable symptom improvements for cough, dyspnea, and pain compared with patients receiving placebo. Erlotinib was found to be associated with a significant worsening of diarrhea, sore mouth, hair loss, and significant improvements in emotional functioning, physical functioning, and global QoL. Patterns of symptom improvement and HRQoL were largely consistent with the findings from the LUX-Lung 1 study. In general, differences in NSCLC patient populations, compliance, selected HRQoL questionnaires, timing of assessments, HRQoL analyses, and whether the analyses and endpoints were prespecified require consideration when attempting to make cross-trial comparisons.

To conclude, the addition of afatinib to BSC improved not only PFS but also the NSCLC-related symptoms of cough, dyspnea, and pain, while also delaying deterioration of cough. Although afatinib treatment was associated with a worsening of diarrhea, overall HRQoL was found to be improved. Positive symptom and HRQoL data reported from this study, in addition to the previously reported efficacy data, support the use of afatinib in advanced NSCLC patients previously treated with an EGFR-TKI.

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