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Symptom and Quality of Life Improvement in LUX-Lung 6

An Open-Label Phase III Study of Afatinib Versus Cisplatin/Gemcitabine in Asian Patients With EGFR Mutation-Positive Advanced Non–small-cell Lung Cancer

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Introduction: In the phase III, LUX-Lung 6 trial, afatinib prolonged progression-free survival (PFS) versus cisplatin/gemcitabine in Asian patients with epidermal growth factor receptor (*EGFR*) mutation-positive non–small-cell lung cancer (NSCLC). This article provides detailed assessments of patient-reported outcomes (PROs), a LUX-Lung 6 secondary end point, and explores the relationship between PFS and health-related quality of life (QoL) in these patients.

Methods: Patients ($n = 364$) were randomized (2:1) to oral afatinib (40 mg/day) or up to six cycles of cisplatin/gemcitabine (21-day cycle; cisplatin 75 mg/m^2 [d1]; gemcitabine 1000 mg/m^2 [d1,8]). QoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire and its lung cancer-specific module. The relationship between PFS (investigator assessment and independent review) and QoL was evaluated using analysis of covariance and a longitudinal model.

Results: More patients treated with afatinib versus cisplatin/gemcitabine showed improvements in global health status/QoL ($p < 0.0001$) and physical ($p < 0.0001$), role ($p = 0.013$), and social ($p < 0.001$) functioning scales. Delayed symptom deterioration and better QoL over time was also observed with afatinib. QoL measured before tumor assessment was considerably poorer for patients with progression than those without progression, with significant differences in mean scores at multiple assessment time points. Results from the longitudinal analysis consistently demonstrated a significant negative impact of progression on QoL ($p < 0.0001$).

Conclusion: Afatinib improved PFS and PROs versus chemotherapy in *EGFR* mutation-positive NSCLC patients. Progression was associated with statistically significant worsening in QoL measured before tumor assessment, underscoring the value of PFS as a clinically relevant end point.

Key Words: Afatinib, Non–small-cell lung cancer, Progression-free survival, Patient-reported outcomes, Quality of life

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Therapeutic inhibition of epidermal growth factor receptor (EGFR) signaling is an effective treatment option in

patients with *EGFR* mutation-positive non–small-cell lung cancer (NSCLC).[1] Afatinib is an irreversible ErbB family blocker that inhibits signaling from all homodimers and heterodimers formed by ErbB family members (EGFR, human epidermal growth factor receptor 2 [HER2], ErbB3, and ErbB4).[2,3] In two seminal phase III studies in patients with *EGFR* mutation-positive advanced NSCLC (LUX-Lung 3, afatinib versus cisplatin/pemetrexed in patients recruited globally; LUX-Lung 6, afatinib versus cisplatin/gemcitabine in Asian patients), first-line afatinib monotherapy (40 mg/day, orally) significantly prolonged progression-free survival (PFS) compared with standard platinum-based chemotherapy regimens[4,5]; afatinib was consequently approved in this setting. In more recent analyses of these trials, afatinib was the first EGFR tyrosine kinase inhibitor to demonstrate an overall survival (OS) benefit over chemotherapy in patients with NSCLC harboring the *EGFR* Del19 mutation.[6] Furthermore, afatinib has demonstrated clinical efficacy after progression on reversible EGFR tyrosine kinase inhibitors, erlotinib and gefitinib.[7,8]

PFS offers practical advantages as a primary end point for clinical studies in patients with advanced cancers (e.g., faster trial completion and reporting of trial results, fewer patients, and lower costs).[9] However, the clinical benefit of prolonged PFS should be substantiated with patient-reported outcome (PRO) data that reflect health-related quality of life (QoL), symptoms, and functional activity.[9,10] Both LUX-Lung 3 and 6 fully integrated comprehensive PRO evaluation into outcome analyses, demonstrating improvements in lung cancer-related symptoms and QoL and a longer time to deterioration of these PROs.[4,5,11,12] In the primary report of LUX-Lung 6, afatinib provided improvements in prespecified PROs focused on lung cancer-related symptoms of coughing, dyspnea, and pain.[5] The current article expands on the previous report, providing additional data on prespecified lung cancer-related symptoms and evaluating whether improvements in disease-related symptoms are accompanied by an improvement in global health status (GHS)/QoL and functioning. Furthermore, although many state-of-the-art clinical studies in patients with NSCLC now include PRO measures,[13] the relationship between disease progression and QoL in these patients has rarely been analyzed. This analysis explores the relationship between PFS and QoL, evaluating the impact of tumor progression on QoL outcomes.

PATIENTS AND METHODS

Study Design and Patients

Details of the LUX-Lung 6 study design and patient eligibility criteria have been previously published.[5] Briefly, this was a randomized, open-label, phase III study conducted in China, Thailand, and South Korea. Patients were screened between April 2010 and November 2011. Eligible patients with *EGFR* mutation-positive stage IIIB (with pleural effusion) or stage IV lung adenocarcinoma were randomized (2:1) to oral afatinib 40 mg, once daily, or 1000 mg/m^2 gemcitabine followed by 75 mg/m^2 cisplatin on day 1 and 1000 mg/m^2 gemcitabine on day 8 of each 21-day treatment cycle. The primary end point was PFS by independent central review, with PFS by investigator assessment defined as the main sensitivity analysis. Key secondary end points included objective tumor response, OS, adverse events (AEs), pharmacokinetics, and PRO.

This study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization good clinical practice, local laws, and applicable regulatory requirements and was approved by the institutional review board or independent ethics committee of each center. All patients provided written, informed consent for participation in the study.

Patient-Reported Outcomes Assessments

Patient-reported symptoms and QoL benefits were assessed using the multidimensional, cancer-specific, self-administered European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and its lung cancer-specific module (QLQ-LC13).[14,15] The QLQ-C30 comprises 30 questions across five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea/vomiting), a GHS/QoL scale, and various single items (e.g., dyspnea, diarrhea). The QLQ-LC13 comprises 13 questions across one multi-item scale to assess dyspnea and various other single items (e.g., chest pain, cough, sore mouth). Each of these questionnaires has been used routinely in previous studies, and additional details regarding the composition and application of the questionnaires have been previously published.[5,11,16]

PROs were assessed at randomization and every 3 weeks until disease progression or start of new cancer treatment. For chemotherapy patients, assessments occurred on day 1 of each treatment cycle and were delayed if the scheduled chemotherapy was delayed. Patients completed the questionnaires at the clinic, before clinical assessment and treatment and before being provided with any test results. Compliance with PRO assessments was calculated per study visit as the number of completed questionnaires divided by the number of patients who had not yet progressed or started new cancer treatment.

Statistical Analyses

Questionnaire scales/items were scored according to EORTC published algorithms.[17] For each scale or item, a linear transformation was applied to standardize the raw score to a range of 0 to 100. A 10-point change in score was considered clinically meaningful and was used to determine the proportion of patients classified as improved (≥10-point increase for functioning scales; ≥10-point decrease for symptom scales/items), stable, or worsened (≥10-point increase for symptom scales/items; ≥10-point decrease for functioning scales).[18] Proportions of patients with improved, stable, or worsened scores were summarized by treatment group, and a logistic regression model stratified by *EGFR* mutation type (Del19, L858R, or other) was used to compare the treatment arms.

Time to deterioration of a score (in months) was defined as the time from randomization to the first appearance of a score ≥10 points worse than baseline (≥10-point increase for symptom scales/items; ≥10-point decrease for functioning scales).[18] Patients without post-baseline measurements

or without worsening were censored; those who died without documented worsening were considered to have deteriorated at the time of death. Time to deterioration was summarized as Kaplan–Meier plots, and a Cox proportional-hazards model (stratified by *EGFR* mutation type) was used to compare the treatment arms.

Changes in mean scores over time were assessed by longitudinal analysis with a mixed-effects growth curve model,[19,20] allowing for within-patient assessment of changes, as previously described.[11] Treatment effect was estimated as the average difference in mean scores between treatment arms. Analyses were repeated in subgroups defined by gender, age (<65 vs. ≥65 years), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1), *EGFR* mutation type (Del19/L585R/other), and baseline symptoms (present vs. absent). To document the methodological robustness of the longitudinal analysis, which was conducted using a truncation point of 36 weeks (i.e., the median follow-up point in both treatment arms) with no data cutoff, sensitivity analyses were conducted that included a data cutoff point of 36 weeks and/or shortening of the truncation point to 18 weeks. In addition, joint models that extended the mixed-effects model by including nonrandom dropout mechanisms were used. Two dropout mechanisms were chosen: time to study completion and time to last PRO assessment.

As previously described by Griebsch et al.[21] the relationship between tumor progression and QoL (based on the composite of QLQ-C30 questions 29 and 30) was evaluated in patients who completed a baseline QoL assessment and at least one measurement at the time of tumor progression (within a ±7-day interval). If a patient had more than one QoL assessment, the one closest to the actual tumor measurement date was used. Change from baseline in QoL score between patients with or without tumor progression was compared at each assessment time point (weeks 6, 12, 18, 24, 36, 42, and 48) using an analysis of covariance model, including covariates for baseline QoL score, progression, *EGFR* mutation type, and randomized treatment; adjusted mean changes from baseline in QoL measures at each assessment time are reported. The effects of tumor progression on QoL over time were assessed using a longitudinal mixed-effects growth curve model, including the two random effects of intercept and slope (the week variable), terms for week, covariates related to progression status (based on either investigator assessment or independent review), and baseline covariates used for stratification at randomization.[19–21] No data cutoff was applied, but QoL data after the start of subsequent anticancer treatment following discontinuation of study medication was excluded.

RESULTS

Patient Population

Three hundred and sixty-four patients were randomized to receive afatinib ($n = 242$) or cisplatin/gemcitabine ($n = 122$). Patient characteristics were generally well balanced between the treatment groups and have been previously reported.[5] Briefly, median age was 58 years (range, 27–79 years), 65% of patients were female, 76% had an ECOG performance status of 1, and 77% had never smoked. The total number of patients who completed a baseline QoL assessment and at least one post-baseline QoL measurement and the progression status of patients based on investigator assessment at each study time point are shown in Figure 1.

Summary of Primary Efficacy

Detailed primary efficacy and safety findings for this patient population have been previously published.[5] Median PFS based on independent review was significantly improved with afatinib (11.0 months) compared with cisplatin/gemcitabine (5.6 months; hazard ratio [HR] = 0.28, $p < 0.0001$). This improvement in PFS was consistent with that observed with afatinib versus cisplatin/pemetrexed in the LUX-Lung 3 study.[4]

Baseline Scores and Compliance

Mean (standard deviation; SD) baseline symptom scores in the afatinib arm were 37 (24) for cough, 25 (19) for dyspnea, and 24 (22) for pain; in the cisplatin/gemcitabine arm, mean (SD) baseline scores were 29 (26) for cough, 24 (21) for dyspnea, and 23 (23) for pain. Compliance rates for questionnaire completion on treatment were high for both the afatinib (96%) and cisplatin/gemcitabine (88%) arms. The most common reasons for noncompletion of PRO questionnaires were not related to health state.

Proportion of Patients with Improvements

Analysis of cough, dyspnea, and pain at the first occurrence of improvement or worsening from baseline was prespecified, and significant benefit of afatinib over cisplatin/gemcitabine has been previously reported.[5] A significantly greater percentage of patients treated with afatinib compared with cisplatin/gemcitabine also showed improvements in GHS/QoL ($p < 0.0001$) and physical ($p < 0.0001$), role ($p = 0.013$), and social ($p < 0.001$) functioning scales (Fig. 2), and the symptom of fatigue (77.2% vs. 52.5%; $p < 0.0001$).

Time to Deterioration

Longer time to deterioration was observed with afatinib compared with cisplatin/gemcitabine for the individual lung cancer-related symptoms of cough, dyspnea, and pain,[5] and for all functioning scales and the overall GHS/QoL score (Fig. 3).

Changes in Scores over Time

Improvements in mean scores were observed with afatinib compared with cisplatin/gemcitabine for the individual lung cancer-related symptoms of cough, dyspnea, and pain.[5] Patients treated with afatinib versus cisplatin/gemcitabine also demonstrated better mean scores over time for all functioning scales, and the overall GHS/QoL score (Fig. 4).

Subgroup Analyses

Findings from subgroup analyses were largely consistent with primary analysis results. Delay in time to deterioration with afatinib over cisplatin/gemcitabine was more

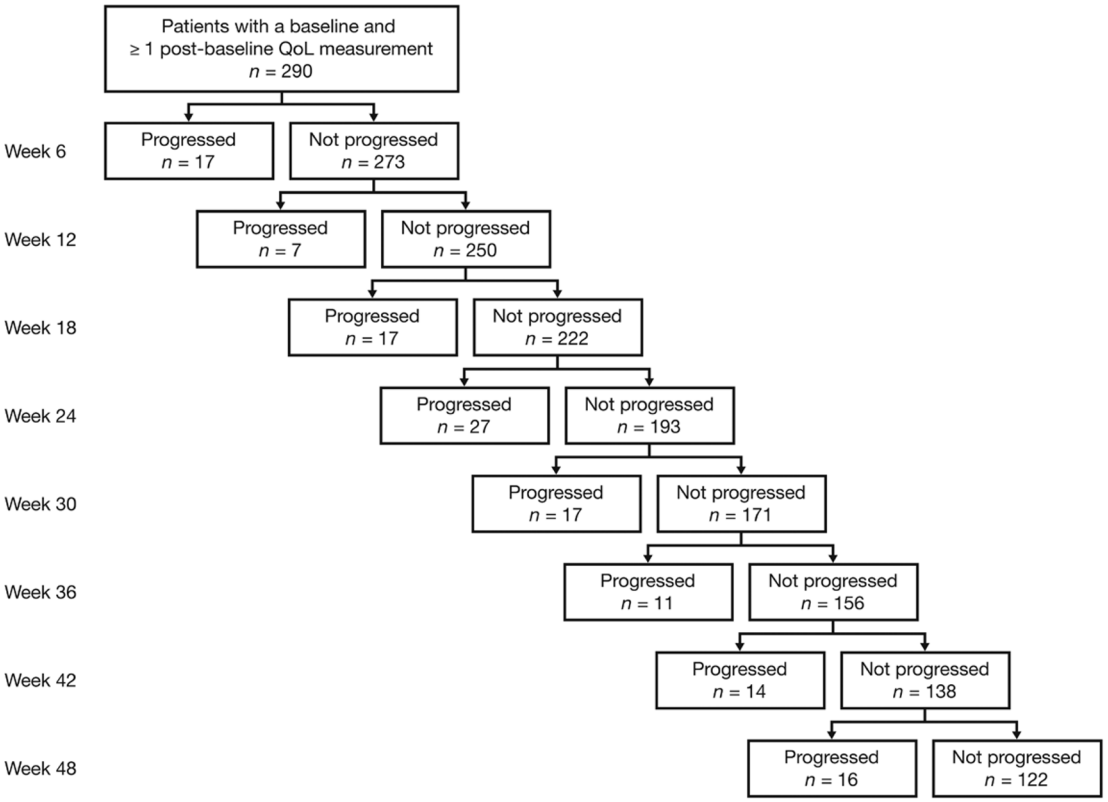

FIGURE 1. Flow chart of patients with disease progression based on investigator assessment at each study time point. At each assessment time point, patients who had died or were lost to follow-up since the previous assessment were excluded from the analysis. QoL, quality of life.

pronounced in patients experiencing baseline symptoms versus asymptomatic patients for lung cancer-related symptoms (QLQ-LC13) of cough (HR = 0.38 vs. 1.05), dyspnea while walking (HR = 0.38 vs. 0.62), and pain in chest (HR = 0.33 vs. 0.64), pain in arm/shoulder (HR = 0.27 vs. 0.77), and pain in other parts (HR = 0.47 vs. 1.17).

Sensitivity Analyses

For the analysis of differences in scores over time, several sensitivity analyses of cough (see Supplemental Fig. 1, Supplemental Digital Content 1, http://links.lww.com/JTO/A816, displaying sensitivity analyses for differences in mean scores for cough in the primary analysis and using additional data cut-offs and truncation points), dyspnea, and pain were conducted. For all three symptoms, differences in mean scores between afatinib and cisplatin/gemcitabine were similar to the primary analysis with all data cut-offs and truncation points analyzed, confirming robustness of the results. In addition, sensitivity analyses using joint models based on different patient dropout events consistently showed slightly larger estimates

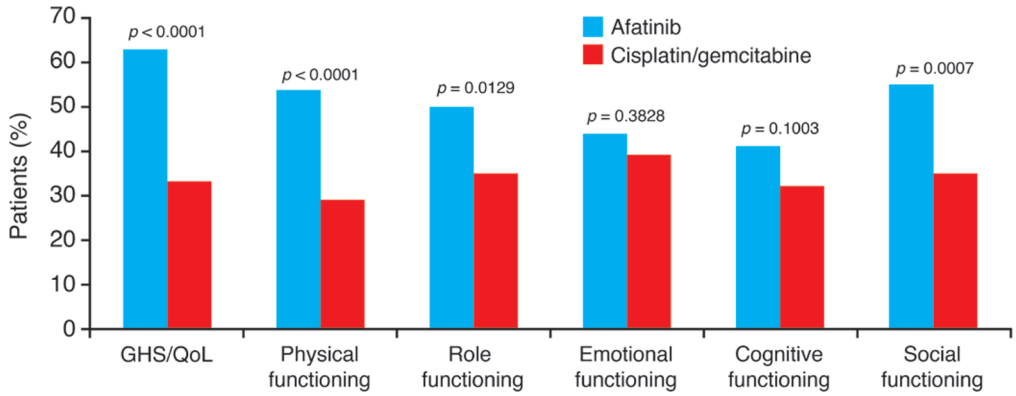

FIGURE 2. Percentage of patients with improvements in EORTC QLQ-C30 scores. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; GHS/QoL, global health status/quality of life.

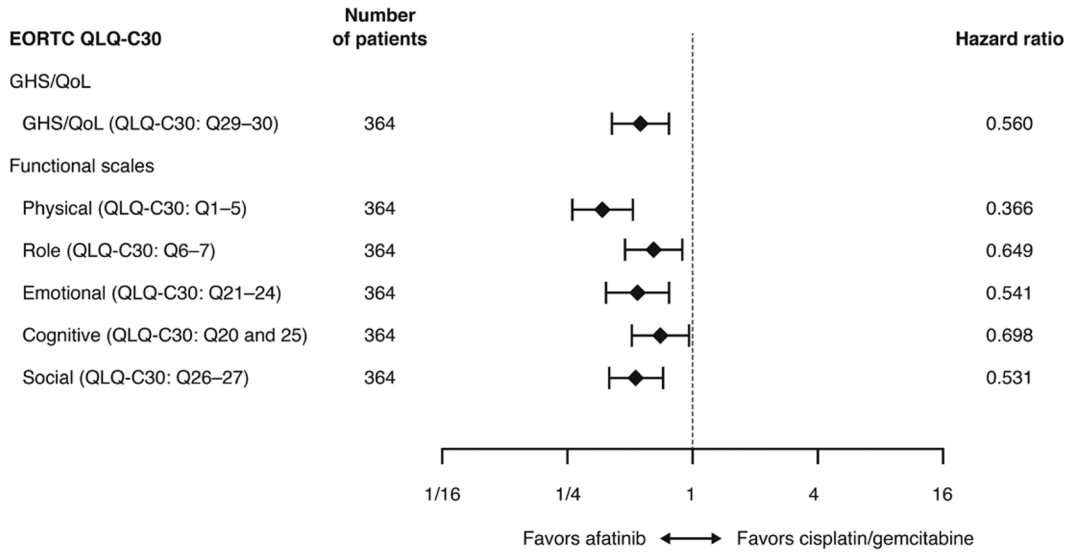

FIGURE 3. Time to deterioration in GHS/QoL and functioning scores. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; GHS/QoL, global health status/quality of life; Q, question.

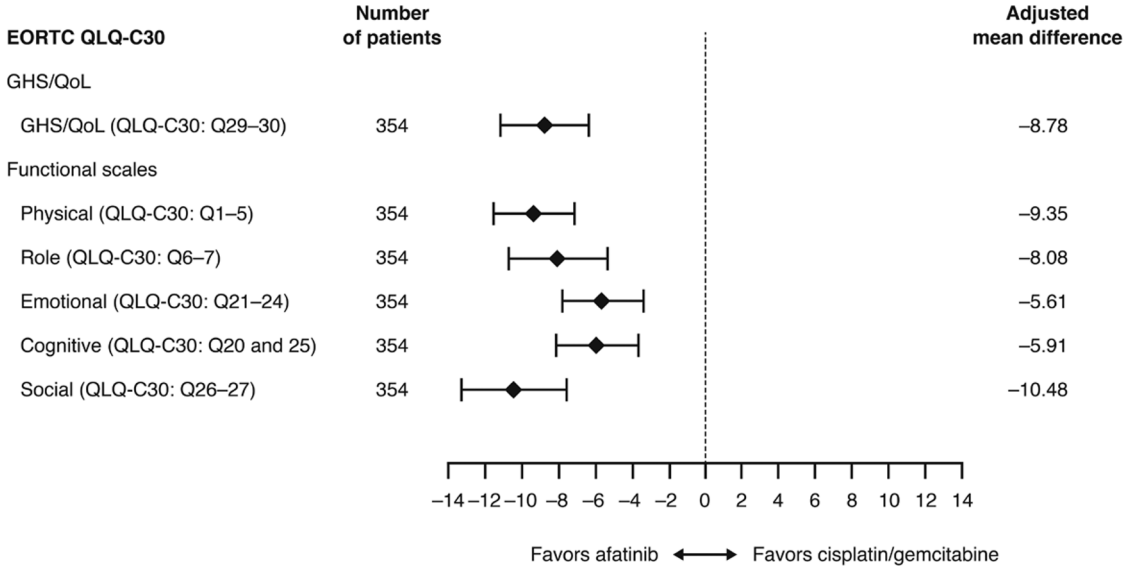

FIGURE 4. Differences in mean scores over time for GHS/QoL and functioning scores. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; GHS/QoL, global health status/quality of life; Q, question.

of differences in mean scores favoring afatinib compared with cisplatin/gemcitabine for all three symptoms, suggesting that the results of the primary analysis were conservative (see Supplemental Fig. 2, Supplemental Digital Content 2, http://links.lww.com/JTO/A817, displaying sensitivity analyses for differences in mean symptom scores for coughing, dyspnea, and pain in the primary analysis and based on different patient dropout events).

Relationship Between Tumor Progression and QoL

The effects of tumor progression on QoL over the 48-week assessment period, in terms of adjusted mean changes from baseline in GHS/QoL, in patients with and without progression are shown in Figure 5 (based on investigator assessment) and in Supplemental Figure 3 (Supplemental Digital Content 3, http://links.lww.com/JTO/A818, based on independent central review). Patients with tumor progression consistently experienced poorer QoL at the time of progression compared with patients without progression, with more pronounced differences from baseline in mean QoL scores for patients progressing more rapidly. Furthermore, results from the longitudinal analysis showed that progression had a significant negative impact on GHS/QoL score, with an effect size of –7.69 (95% confidence interval, –9.22 to –6.17; $p < 0.0001$), indicating a deterioration in QoL.

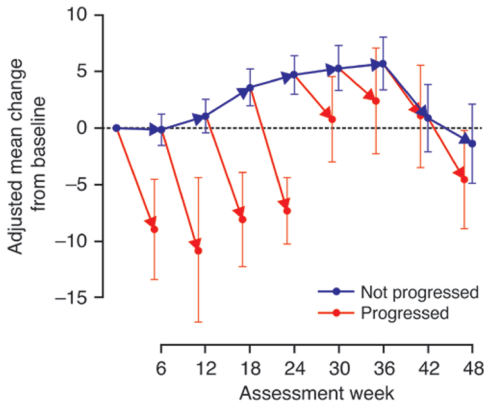

FIGURE 5. Adjusted mean changes from baseline in GHS/QoL scores by progression status (investigator assessment). Data points represent adjusted least squares mean change from baseline; error bars represent standard error. GHS/QoL, global health status/quality of life.

DISCUSSION

The overall clinical benefit of new therapies in the treatment of patients with advanced cancers, such as NSCLC, requires rigorous assessment of tumor progression and PROs.[9,22] Afatinib monotherapy has consistently provided similar improvements in PFS compared with standard chemotherapy regimens in clinical studies of patients with advanced NSCLC recruited globally and in Asia.[4,5] Importantly, afatinib treatment was associated with manageable AEs and low discontinuation rates because of treatment-related AEs.[4,5] Previously reported improvements in lung cancer-related symptoms and overall QoL with afatinib in patients with NSCLC further support the clinical benefit of afatinib treatment with respect to PROs.[4,5,11,12,16]

In this study, afatinib provided significant improvements compared with cisplatin/gemcitabine in GHS/QoL score, and physical, role, and social functioning scales, with a longer time to deterioration and better mean scores over time for all functioning and symptom scales. Afatinib also provided significant improvements in lung cancer-related symptoms of cough, dyspnea, and pain[5]; these improvements were most pronounced in patients experiencing baseline symptoms compared with asymptomatic patients. Overall, the improvements in PROs reported with afatinib in this study are consistent with those reported in the phase III LUX-Lung 3 study.[11]

In addition to the improvements in PROs, a relationship between tumor progression and QoL was demonstrated in patients treated in the study. Of note, PROs were collected before clinical assessment and before patients were provided with any test results (e.g., progression status). In this study, tumor progression was accompanied by a statistically significant worsening in QoL, which was more pronounced in those patients with rapidly progressing disease. Furthermore, the observed progression-related deterioration in QoL was considered to be clinically meaningful based on recently proposed thresholds for the interpretation of GHS/QoL scores.[23] A similar analysis of progression effects on QoL was recently conducted for the LUX-Lung 1 (afatinib vs. placebo in patients with advanced NSCLC after failure of erlotinib and/or gefitinib) and LUX-Lung 3 (afatinib vs. cisplatin/pemetrexed in patients with treatment-naive, *EGFR* mutation-positive, advanced NSCLC) trials.[21] The results presented here are consistent with the findings previously reported for these studies.

Overall, these results demonstrate the value of PFS as a clinically relevant end point associated with PROs in patients with advanced NSCLC. Furthermore, they provide support for the use of PRO measures in addition to PFS in the development of new treatments and as a consideration when choosing available treatment options for patients in the clinic. These combined measures are particularly relevant for new therapies in the absence of OS data and in combination with traditional chemotherapy regimens that are not associated with improvements in PROs.

In summary, this report expands on the robust analyses to date showing improved PROs and prolonged PFS with the ErbB family blocker afatinib in patients with advanced *EGFR* mutation-positive NSCLC. Furthermore, tumor progression was associated with a significant, clinically meaningful deterioration in PROs at the time of progression. These findings confirm those from previous analyses of afatinib and demonstrate the value of PFS as a clinically relevant primary end point associated with improved PROs in patients with advanced NSCLC.

REFERENCES

1. Hirsch FR, Jänne PA, Eberhardt WE, et al. Epidermal growth factor receptor inhibition in lung cancer: status 2012. *J Thorac Oncol* 2013;8:373–384.
2. Li D, Ambrogio L, Shimamura T, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *Oncogene* 2008;27:4702–4711.
3. Solca F, Dahl G, Zoephel A, et al. Target binding properties and cellular activity of afatinib (BIBW 2992), an irreversible ErbB family blocker. *J Pharmacol Exp Ther* 2012;343:342–350.
4. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013;31:3327–3334.
5. Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol* 2014;15:213–222.
6. Yang JC, Wu YL, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol* 2015;16:141–151.
7. Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol* 2012;13:528–538.
8. Katakami N, Atagi S, Goto K, et al. LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. *J Clin Oncol* 2013;31:3335–3341.
9. Fallowfield LJ, Fleissig A. The value of progression-free survival to patients with advanced-stage cancer. *Nat Rev Clin Oncol* 2012;9:41–47.
10. Gutman SI, Piper M, Grant MD, et al. *Progression-free survival: what does it mean for psychological well-being or quality of life?* Rockville (MD): Agency for Healthcare Research and Quality (US); 2013. Report No: 13-EHC074-EF.
11. Yang JC, Hirsh V, Schuler M, et al. 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. *J Clin Oncol* 2013;31:3342–3350.
12. Langer CJ. Epidermal growth factor receptor inhibition in mutation-positive non-small-cell lung cancer: is afatinib better or simply newer? *J Clin Oncol* 2013;31:3303–3306.

13. Claassens L, van Meerbeeck J, Coens C, et al. Health-related quality of life in non-small-cell lung cancer: an update of a systematic review on methodologic issues in randomized controlled trials. *J Clin Oncol* 2011;29:2104–2120.
14. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365–376.
15. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. *Eur J Cancer* 1994;30A:635–642.
16. Hirsh V, Cadranel J, Cong XJ, et al. 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). *J Thorac Oncol* 2013;8:229–237.
17. Fayers PM, Aaronson NK, Bjordal K, et al. *The EORTC QLQ-C30 scoring manual*. 2001. Available at: http://www.eortc.be/qol/files/SCManualQLQ-c30.pdf. Accessed February 26, 2014.
18. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998;16:139–144.
19. Fairclough DL. *Design and analysis of quality of life studies in clinical trials*. London: Chapman & Hall, 2010.
20. Diggle P, Heagerty P, Liang K-Y, et al. *Analysis of Longitudinal Data*. Oxford: Oxford University Press, 2002.
21. Griebsch I, Palmer M, Fayers PM, Ellis S. Is progression-free survival associated with a better health-related quality of life in patients with lung cancer? Evidence from two randomised trials with afatinib. *BMJ Open* 2014;4:e005762.
22. Damm K, Roeske N, Jacob C. Health-related quality of life questionnaires in lung cancer trials: a systematic literature review. *Health Econ Rev* 2013;3:15.
23. Cocks K, King MT, Velikova G, Martyn St-James M, Fayers PM, Brown JM. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *J Clin Oncol* 2011;29:89–96.

