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ORIGINAL RESEARCH ARTICLE

Does EGFR Mutation Type Influence Patient-Reported Outcomes in Patients with Advanced EGFR Mutation-Positive Non-Small-Cell Lung Cancer? Analysis of Two Large, Phase III Studies Comparing Afatinib with Chemotherapy (LUX-Lung 3 and LUX-Lung 6)

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Abstract

Introduction In LUX-Lung 3 and LUX-Lung 6, afatinib significantly improved progression-free survival (PFS) versus chemotherapy in patients with tumors harboring common epidermal growth factor receptor (EGFR) mutations (Del19/L858R) and significantly improved overall survival (OS) in patients with tumors harboring Del19 mutations. Patient-reported outcomes stratified by EGFR mutation type are reported.

Patients and Methods Lung cancer symptoms and health-related quality of life (QoL) were assessed every 21 days until progression using the EORTC Quality of Life Core Questionnaire C30 and its lung cancer-specific module, LC13. Analyses of cough, dyspnea, and pain were pre-specified and included analysis of percentage of patients who improved on therapy, time to deterioration of symptoms, and change over time. Global health status (GHS)/QoL was also assessed. Analyses were conducted for all patients with tumors harboring Del19 or L858R mutations and were exploratory.

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Results Compared with chemotherapy, afatinib more commonly improved symptoms of, delayed time to deterioration for, and was associated with better mean scores over time for cough and dyspnea in patients with Del19 or L858R mutations. All three prespecified analyses of pain showed a trend favoring afatinib over chemotherapy. In both Del19 and L858R mutations, afatinib was also associated with improvements in GHS/QoL. Longitudinal analyses demonstrated statistically significant improvements in GHS/QoL for afatinib over chemotherapy for patients with tumors harboring Del19 mutations or L858R mutations.

Conclusions These exploratory analyses suggest first-line afatinib improved lung cancer-related symptoms and GHS/QoL compared with chemotherapy in patients with non-small-cell lung cancer with tumors harboring common EGFR mutations, with benefits in both Del19 and L858R patients. When considered with OS (Del19 patients only) and PFS benefits, these findings substantiate the value of using afatinib over chemotherapy in these patient groups.

Key Points for Decision Makers

The benefits of afatinib compared with chemotherapy, with regard to symptom control of cough and dyspnea, are observed regardless of common epidermal growth factor receptor (EGFR) (Del19 or L858R) mutation type.

Improvements reported in lung cancer-related symptoms in patients with advanced non-small-cell lung cancer harboring the Del19 and L858R mutations add further support to use of afatinib as a first-choice treatment in these patient populations.

1 Introduction

The first-generation reversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors erlotinib and gefitinib, and the irreversible ErbB family blocker, afatinib, were all approved as first-line therapy in patients with non-small-cell lung cancer (NSCLC) harboring EGFR mutations based on results from phase III trials showing improved progression-free survival (PFS) versus standard platinum-based chemotherapy [1–3]. Findings from these and other studies showed that PFS benefit was less pronounced in patients with EGFR exon 21 L858R point mutations than in patients with exon 19 deletion (Del19) mutations [2, 4–8]. Data also suggest that Del19 and L858R mutations might have distinct biological properties that might affect response to treatment [9, 10].

Differences in overall survival (OS) have not been reported between erlotinib or gefitinib and chemotherapy, irrespective of mutation type [8, 11–16]. However, recently published data have shown differences in OS outcomes between patients with tumors harboring EGFR Del19 mutations and L858R mutations when treated with afatinib compared with chemotherapy [17]. OS was substantially and significantly longer for patients with tumors harboring Del19 mutations treated with afatinib than for those treated with chemotherapy in two independent trials; however, OS was similar in both treatment arms for the L858R mutation subgroup [17]. There is some uncertainty as to how this data should be used to guide treatment selection in patients with NSCLC and if type of common mutation, Del19 or L858R mutation, should influence treatment choice.

Patient-reported outcomes (PROs) including quality of life (QoL) are important and clinically relevant endpoints that can be used to substantiate the clinical benefits of prolonged PFS and guide treatment choice. Although data suggests that erlotinib and gefitinib improve QoL compared with chemotherapy in the total population of patients with EGFR-mutation-positive NSCLC [18–20], data by mutation type has not been reported for either agent. Here, we report the analysis of the PROs, by EGFR mutation type, from two large phase III studies in patients with EGFR-mutation-positive advanced NSCLC that compared afatinib with standard of care chemotherapy (LUX-Lung 3 [3] and LUX-Lung 6 [5]). These analyses were exploratory in nature and designed to investigate whether both types of common EGFR mutation experience similar improvements in PROs and discuss the implications of these findings for daily clinical practice.

2 Methods

2.1 Study Population and Design

The study design, inclusion and exclusion criteria, and methods of LUX-Lung 3 and LUX-Lung 6, have been reported in full elsewhere [3, 5]. Both studies were conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. In brief, both trials randomized eligible patients with stage IIIB/IV lung adenocarcinoma and confirmed EGFR mutations (Therascreen EGFR 29; Qiagen, Manchester, UK) in a 2:1 fashion to receive once-daily oral afatinib 40 mg or up to six cycles of chemotherapy until disease progression, death, or withdrawal due to adverse events (AEs). Chemotherapy in LUX-Lung 3 was intravenous cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 every 21 days, whereas

chemotherapy in LUX-Lung 6 was intravenous gemcitabine 1000 mg/m^2 on Day 1 and Day 8 plus cisplatin 75 mg/m^2 on Day 1 every 21 days. LUX-Lung 3 was a global study and LUX-Lung 6 was conducted in China, South Korea, and Thailand. Treatment randomization was stratified by EGFR mutation type (Del19 vs L858R vs other uncommon mutations) in both studies and by ethnic origin (Asian vs non-Asian) in LUX-Lung 3.

In both studies, PFS, defined as time from randomization to progression, determined by independent review, was the primary endpoint. OS was a key secondary endpoint in both studies and PROs were an additional secondary endpoint.

2.2 Patient-Reported Outcomes (PROs)

2.2.1 Assessment

Both the LUX-Lung 3 and LUX-Lung 6 studies included assessment of lung cancer symptoms and global health status (GHS)/QoL [21, 22]. Symptoms and GHS/QoL were assessed using the validated self-administered 30-item European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire (QLQ-C30) [23, 24], which includes both multi-item and single-item measures covering symptoms as well as adverse events associated with treatment. The 13-question EORTC lung cancer-specific module QLQ-LC13 [25, 26] was also used as it was specifically designed for use in patients with lung cancer undergoing treatment and has been validated for use in this setting. PROs were assessed at randomization and every 3 weeks until disease progression. Further details of these assessments have been reported in detail previously [21, 22].

Prespecified PRO measures of interest included cough (assessed by QLQ-LC13 question 1), dyspnea (assessed by a prespecified composite of QLQ-LC13 questions 3–5), and pain (assessed by a prespecified composite of QLQ-C30 questions 9 and 19). These symptoms were selected as they are established to be key lung cancer symptoms. The five functional scale scores (physical, role, functional, cognitive, and social functioning) were also of interest. Concomitant medications prescribed for cough, dyspnea, and pain were documented to enable analysis of their potential impact on reported symptoms.

2.2.2 Statistical Analysis

Analyses were exploratory in nature and neither study was powered to detect differences in PROs. Data from these studies are reported together due to the similarity in the trial designs; data were not pooled as chemotherapy comparator arms were different. Three analyses were prespecified for each symptom of interest and included: (i) comparison between the treatment groups of the percentage of patients who improved (defined as a $\geq$ 10-point decrease from baseline at any time during the trial) compared with those without improvement (stable or worsened) using a logistic regression model stratified by race in LUX-Lung 3, without adjustment for baseline scores; (ii) time to deterioration in symptoms analysis (measured in months from randomization to the first instance of a 10-point worsening in symptom from baseline)—treatment groups were compared using a Cox proportional hazards regression model stratified by race in LUX-Lung 3; and (iii) mean difference in symptom scores over time (longitudinal analysis) with the assumption that data are missing at random. For the longitudinal analyses all data up to the median follow-up time (calculated across all patients) were included, this was a constant value used across all analyses. Criteria for clinically meaningful symptom improvement, as well as details of statistical analysis of these outcomes, have been reported previously [21, 22]. Functional scale scores were analyzed using longitudinal analysis only. Updated PRO analyses were completed at the time of primary OS analysis (January 2014). Analyses were conducted on the prespecified lung cancer symptoms of interest as well as AE-related symptoms of interest as they are commonly associated with treatment (nausea, vomiting, diarrhea, and sore mouth).

Each analysis was conducted for the population of patients with tumors harboring each of the common EGFR mutation types (Del19 or L858R), as well as in the total intention-to-treat population. All analyses were exploratory and *p*-values are provided for information only; there were no adjustments for multiple testing.

3 Results

3.1 Patient Population

Full details of the disposition and the baseline characteristics of patients in LUX-Lung 3 and LUX-Lung 6 have been reported previously [3, 5]. Briefly, the majority of patients were female (afatinib 64% vs chemotherapy 68%), never smokers (71% vs 76%), had stage IV disease (92% vs 90%), and had an Eastern Cooperative Oncology Group performance status of 1 (70% vs 65%). In LUX-Lung 3, 72% of patients were Asian; all patients were Asian in LUX-Lung 6. In LUX-Lung 3, 88% ($n = 203$: Del19, $n = 112$; L858R, $n = 91$) of afatinib-treated patients and 90% ($n = 104$: Del19, $n = 57$; L858R, $n = 47$) of chemotherapy-treated patients had common mutations, whereas in LUX-Lung 6, 89% ($n = 216$: Del19, $n = 124$; L858R, $n = 92$) of afatinib-treated patients and 89% ($n = 108$: Del 19, $n = 62$; L858R, $n = 46$) of

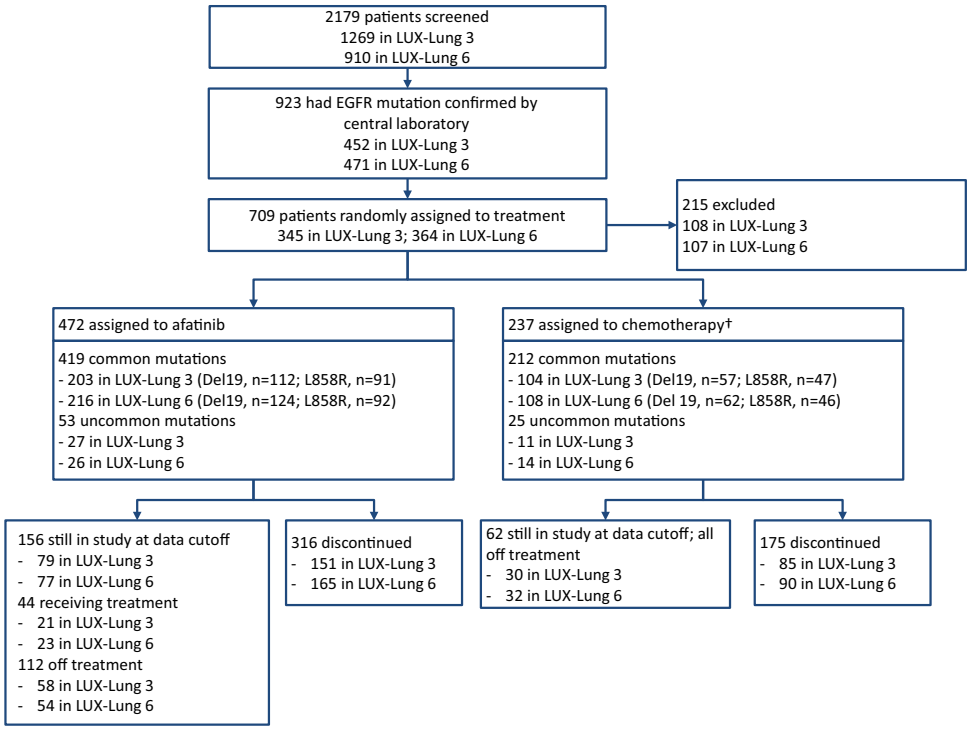

Fig. 1 Study profile. † Cisplatin-pemetrexed in LUX-Lung 3; cisplatin-gemcitabine in LUX-Lung 6. *EGFR*, epidermal growth factor receptor

chemotherapy-treated patients had common mutations (Fig. 1). Baseline characteristics in patients with Del19 or L858R mutations were similar to those of the overall population in both studies. At the time of analysis reported here, 21 patients in LUX-Lung 3 and 23 patients in LUX-Lung 6 were still receiving afatinib treatment; no patients were receiving chemotherapy.

Mean (standard deviation) baseline symptom scores for cough, dyspnea, pain, and GHS/QoL indicated a low overall symptom burden for patients in both studies and in both treatment arms, although symptom burden was greatest for cough (Table 1). Symptom burden was well balanced between treatment arms and mutation types. Compliance rates for EORTC QLQ-C30 questionnaire completion were high in both trials across treatment arms and mutation types and were above 90% at all study visits. Average completion rates over the course of LUX-Lung 3 were 97.1% in Del19 and 96.5% in L858R patients treated with afatinib and 96.9% in Del19 and 96.1% in L858R patients treated with chemotherapy. Average completion rates in LUX-Lung 6 were 97.7% in Del19 and 97.0% in L858R patients treated with afatinib and 93.9% in Del19 and 93.1% in L858R patients treated with chemotherapy.

3.2 PROs in Patients by Mutation Type

3.2.1 Patients with Lung Cancer Symptom Improvement

The percentages of patients that experienced clinically meaningful improvements in symptom scores by mutation type are shown in Fig. 2. In patients with tumors harboring Del19 mutations, a higher proportion of afatinib-treated patients experienced clinically meaningful improvements in dyspnea symptom scores compared with chemotherapy-treated patients in both studies (LUX-Lung 3: 69% vs 48%; LUX-Lung 6: 70% vs 43%). In the Del19 population, the proportion of patients with improvements in pain was higher for afatinib in LUX-Lung 3 (60% vs 43%) and the proportion of patients with improvements in cough washigher for afatinib in LUX-Lung 6 (75% vs 55%).

For patients with tumors harboring L858R mutations in LUX-Lung 3, a higher proportion of afatinib-treated patients experienced clinically meaningful improvements in dyspnea (64% vs 45%) symptom scores, and a higher proportion of afatinib-treated patients in LUX-Lung 6 experienced clinically meaningful improvements in cough (78% vs 58%) and pain (71% vs 34%) symptom scores compared with chemotherapy-treated patients.

3.2.2 Time to Deterioration of Lung Cancer Symptoms

Afatinib significantly delayed the time to deterioration of cough and dyspnea, compared with chemotherapy, in patients with tumors harboring Del19 mutations in both studies; (Fig. 3 and Supplemental Fig. 1 [see electronic supplementary material]).

In the group of patients with tumors harboring L858R mutations, afatinib significantly delayed the time to deterioration of dyspnea in both studies compared with

Table 1 Mean (SD) baseline symptom scores[a] for all prespecified patient-reported outcomes symptoms of interest (cough, dyspnea, and pain) and GHS/QoL by mutation type (Del19 and L858R)

Mean (SD)	Del19		L858R	
LUX-Lung 3	Afatinib $n = 110$	Chemotherapy $n = 56$	Afatinib $n = 90$	Chemotherapy $n = 45$
Cough	36.7 (27.2)	33.9 (23.6)	32.6 (24.6)	31.8 (27.8)
Dyspnea	22.1 (18.3)	24.8 (23.8)	21.9 (19.1)	23 (23.7)
Pain	22.6 (23.0)	23.5 (26.2)	28.8 (24.6)	23.1 (25.0)
GHS/QoL	66.4 (19.3)	60 (23.4)	66.0 (20.8)	60.4 (20.2)
Functional scales				
Physical	81.2 (19.0)	77.4 (22.2)	80.52 (19.13)	77.27 (20.70)
Role	76.5 (27.0)	72.6 (29.9)	78.28 (26.52)	73.11 (25.72)
Emotional	80.0 (16.8)	73.2 (23.0)	76.97 (18.08)	72.54 (22.70)
Cognitive	87.6 (15.6)	87.5 (17.5)	84.83 (17.52)	81.82 (19.95)
Social	79.8 (22.3)	74.1 (25.2)	78.84 (22.01)	76.14 (27.23)
LUX-Lung 6	$n = 124$	$n = 59$	$n = 90$	$n = 43$
Cough	36.6 (24.5)	27.5 (23.7)	37.9 (23.4)	32.5 (28.4)
Dyspnea	24 (19.4)	24.2 (19.0)	25.6 (19.1)	24.7 (22.8)
Pain	21.2 (20.0)	24.6 (20.9)	27.5 (23.1)	21.1 (25.3)
GHS/QoL	64.5 (20.7)	65.4 (15.9)	60.1 (21.2)	66.9 (22.6)
Functional scales				
Physical	80.2 (20.1)	80.5 (18.4)	77.62 (15.8)	80.5 (18.5)
Role	79.6 (25.4)	79.2 (23.2)	74.90 (23.1)	82.5 (23.0)
Emotional	84.8 (16.3)	80.7 (17.4)	81.13 (18.2)	79.7 (22.5)
Cognitive	89.3 (13.4)	86.8 (15.7)	83.14 (19.6)	86.6 (16.3)
Social	74.4 (23.5)	73.1 (21.8)	73.18 (24.0)	73.2 (25.0)

GHS global health status, *QoL* quality of life, *SD* standard deviation

[a]All scores range from 0 to 100. For the GHS/QoL scale, a value of 100 was equivalent to the best possible score and 0 to the worst possible score. For cough, dyspnea, and pain, 100 was equivalent to the highest burden of symptoms and 0 to the lowest burden. Total patient numbers represent the number of patients with at least one baseline and one on treatment assessment and, as such, differ slightly from the number of patients randomized to treatment

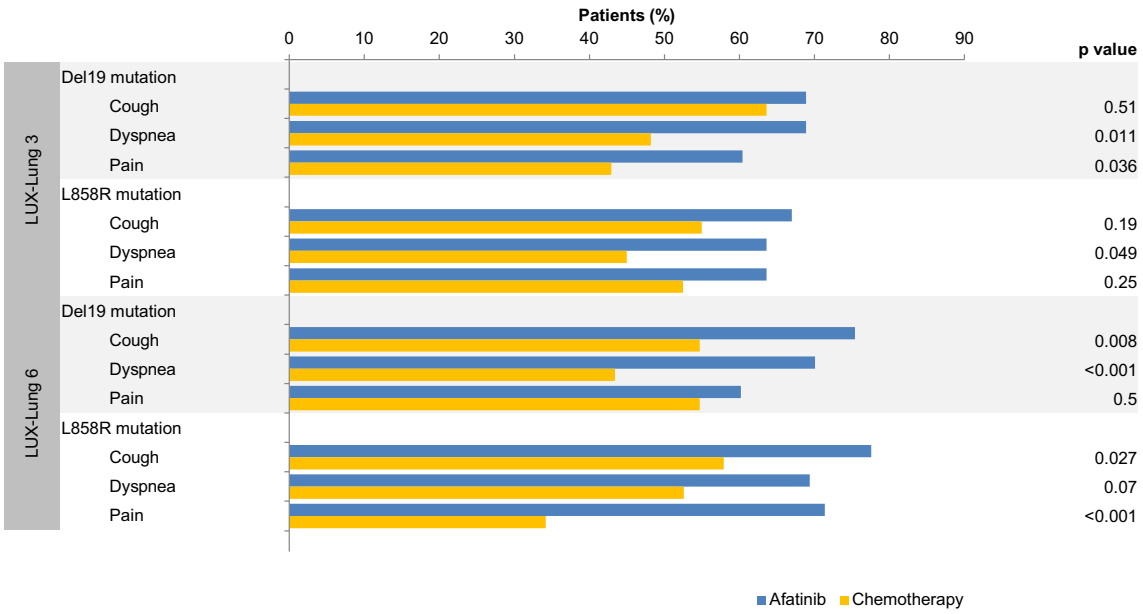

Fig. 2 Percentages of patients with improvement in all prespecified PROs symptoms of interest: cough, dyspnea, and pain by mutation type (Del19 and L858R). *p*-values from logistic regression analysis of 'improved/not improved'. *PRO*, patient-reported outcome

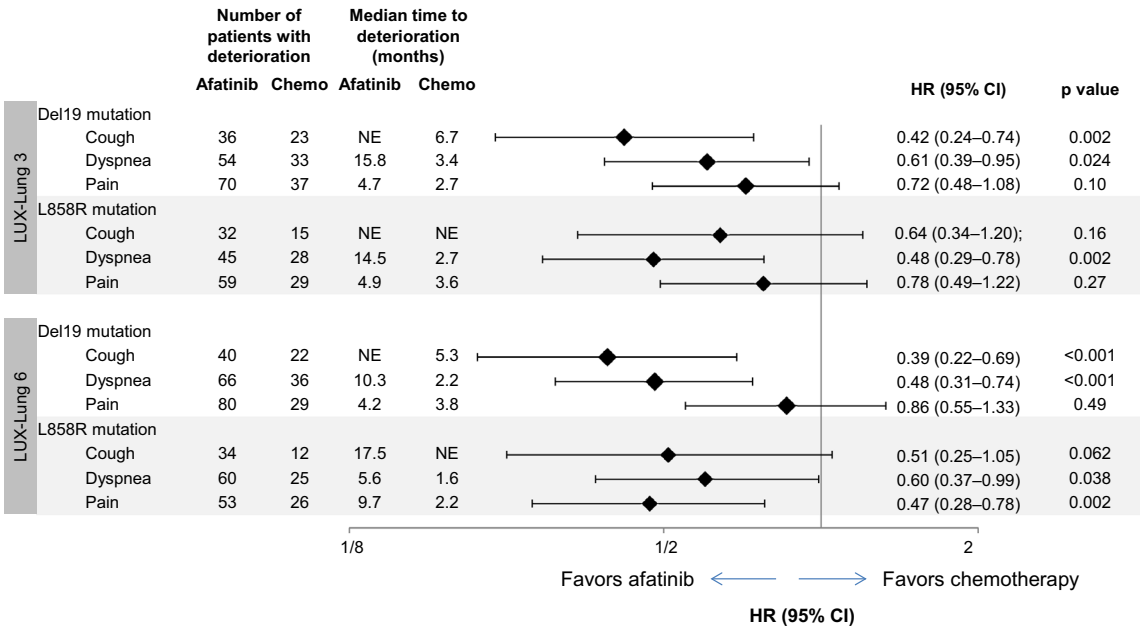

Fig. 3 Time to deterioration of all prespecified PROs symptoms of interest: cough, dyspnea, and pain by mutation type (Del19 and L858R). HRs from Cox proportional hazard model stratified by race in LUX-Lung 3. *p*-values calculated from log-rank test. The median time to deterioration was not evaluable in some groups because there were not sufficient events at the time of analysis for the median value to be reached. *CI*, confidence interval; *HR*, hazard ratio; *NE*, not evaluable; *PRO*, patient-reported outcome

chemotherapy, as well as time to deterioration of pain in LUX-Lung 6. A trend towards delayed time to deterioration of pain in LUX-Lung 3, and time to deterioration in cough, was also observed in patients with tumors harboring L858R mutations receiving afatinib compared with chemotherapy.

3.2.3 Longitudinal Analysis of Lung Cancer Symptoms

In patients with tumors harboring Del19 mutations, differences in mean symptom scores over time significantly favored afatinib over chemotherapy for cough and dyspnea in LUX-Lung 3, and cough, dyspnea, and pain in LUX-Lung 6 (Fig. 4). For patients with tumors harboring L858R mutations, differences in mean symptom scores over time significantly favored afatinib over chemotherapy for cough and dyspnea in LUX-Lung 3, and cough, dyspnea and pain in LUX-Lung 6.

3.2.4 Adverse-Event-Related Symptoms

Consistent findings were reported in the time to deterioration analysis in patients with either L858R or Del19 mutations (shorter time to deterioration of nausea and vomiting with chemotherapy and shorter time to deterioration of diarrhea and sore mouth with afatinib). Longitudinal analyses in patients with tumors harboring either L858R or Del19 mutations were also consistent (worse scores for nausea and vomiting with chemotherapy and worse scores for diarrhea and sore mouth with afatinib). Time to deterioration and longitudinal analyses of fatigue were significantly different, favoring afatinib, in patients with Del19 mutations in both studies and in patients with L858R mutations in LUX-Lung 6, although were not significantly different between treatment groups in patients with L858R mutations in LUX-Lung 3.

There were no significant differences in the prescription of concomitant medications for cough, dyspnea, and pain between treatment arms in LUX-Lung 3. In LUX-Lung 6, a lower level of concomitant medication use was observed overall, with greater use of cough (13.6% vs 4.9%) and pain (46.3% vs 28.7%) medication in the afatinib treatment arm compared with chemotherapy.

3.2.5 Global Health Status

In longitudinal analysis of LUX-Lung 3 data, patients with tumors harboring Del19 mutations on afatinib had significantly better mean scores over time for GHS/QoL (Fig. 5). In LUX-Lung 3, no significant difference between treatment arms was observed in the proportion of patients with improvement or time to deterioration analyses of GHS/QoL with tumors harboring Del19 mutations.

In patients with tumors harboring Del19 mutations in LUX-Lung 6, GHS/QoL improvements in afatinib-treated patients were also observed in all three prespecified methods of analysis; patients on afatinib had significantly better mean scores over time [mean treatment difference:

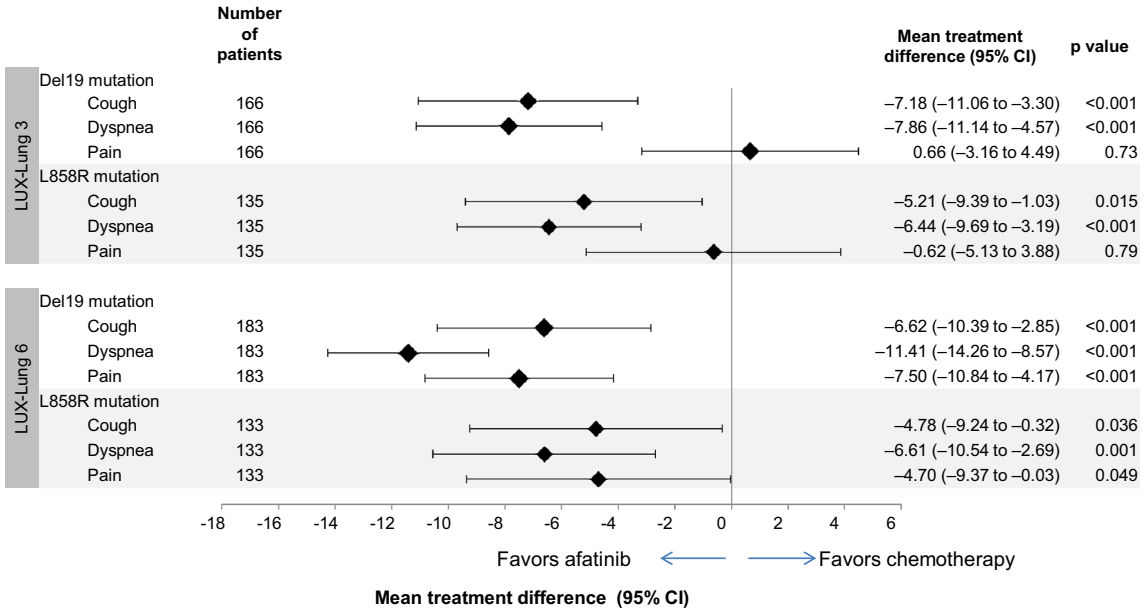

Fig. 4 Longitudinal analysis of all prespecified PROs symptoms of interest: cough, dyspnea, and pain by mutation type (Del19 and L858R). Scores range from 0 to 100 (100 is equivalent to the highest burden of symptoms and 0 to the lowest burden); mean treatment difference shown as afatinib minus chemotherapy and, as such, a negative score favors afatinib treatment. *CI*, confidence interval; *PRO*, patient-reported outcome

− 11.68 (95% CI: − 14.96 to − 8.41); $p < 0.001$; Fig. 5]; afatinib significantly delayed time to deterioration for GHS/QoL [HR: 0.53 (95% CI: 0.35–0.82); $p = 0.003$]; and a significantly greater number of patients had an improvement in GHS/QoL (63% vs 34%; $p < 0.001$). In patients with tumors harboring L858R mutations in LUX-Lung 6, mean scores over time significantly favored afatinib compared with chemotherapy [mean treatment difference: − 6.53 (95% CI: −10.69 to −2.36); $p = 0.002$; Fig. 5] and a significantly higher number of patients treated with afatinib had an improvement in GHS/QoL (61.2% vs 34.2%; $p = 0.007$).

3.2.6 Functional Scales

In the longitudinal analysis of data from LUX-Lung 3, patients with tumors harboring Del19 mutations who received afatinib had significantly better mean scores over time for physical, role, and cognitive functioning than patients treated with chemotherapy (Fig. 5). In LUX-Lung 3, patients on afatinib with tumors harboring L858R mutations had significantly better mean scores over time for role and cognitive functioning. In LUX-Lung 6, patients with tumors harboring common mutations had significantly better mean scores over time for all functional scales; results were observed regardless of whether patients had tumors harboring Del19 mutations or L858R mutations (Fig. 5).

3.3 PROs in the Intention-to-treat Population

For the intention-to-treat population, the percentage of patients experiencing clinically meaningful improvements in symptom scores is shown in Supplemental Fig. 2A, time to deterioration of symptom scores is shown in Supplemental Fig. 2B and differences in mean symptom scores over time are shown in Supplemental Fig. 2C. Longitudinal analysis of GHS/QoL and functional scale scores are shown in Supplemental Fig. 2D (see electronic supplementary material). All findings were comparable to the data reported by mutation type.

4 Discussion

The new analyses described here suggest that the benefits of afatinib compared with chemotherapy, with regard to symptom control of cough and dyspnea, are observed regardless of common EGFR (Del19 or L858R) mutation type. In patients with Del19 or L858R, differences favoring afatinib over chemotherapy for cough and dyspnea were observed in all three prespecified analyses, with differences substantially favoring afatinib over chemotherapy in a number of comparisons. All three prespecified analyses of pain generally showed a trend favoring afatinib over chemotherapy, although the differences between treatments reached significance in only a few of the analyses and were sometimes inconclusive.

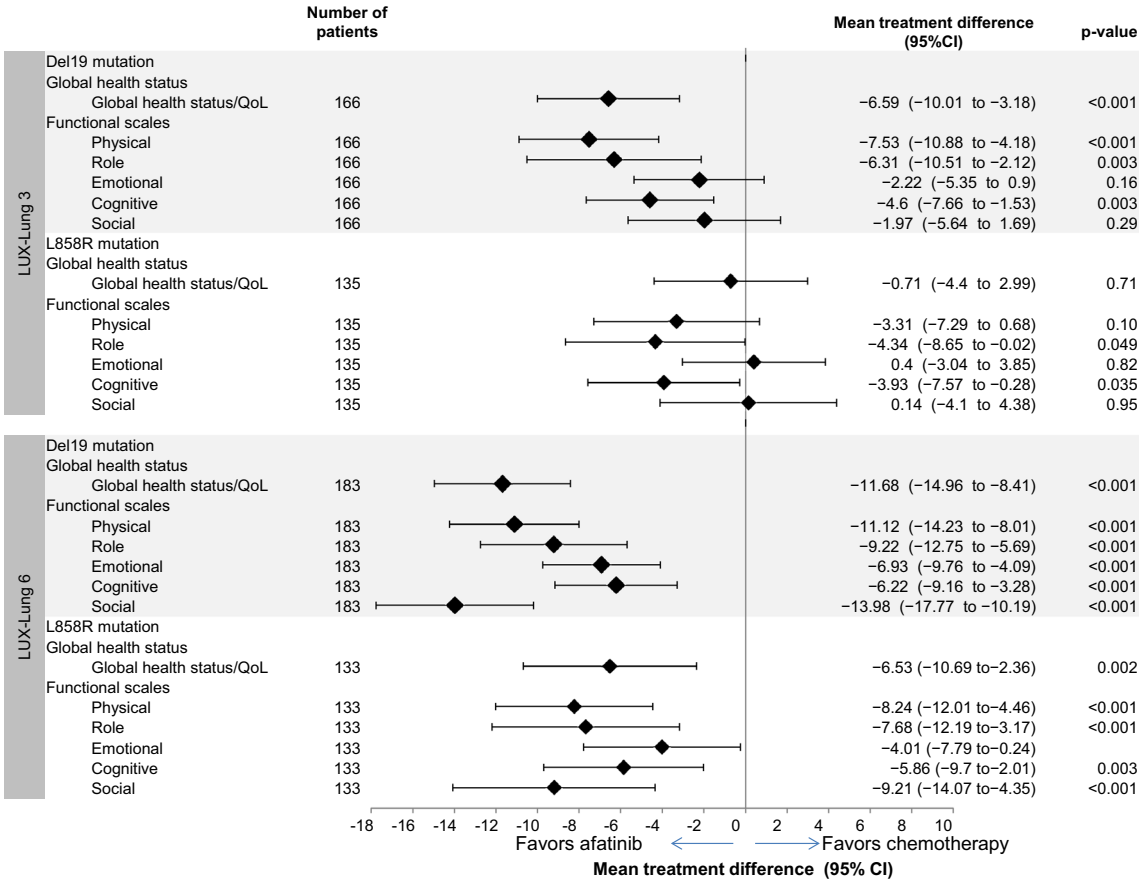

Fig. 5 Longitudinal analysis of GHS/QoL and functional scale domains by mutation type (Del19 and L858R). For the GHS/QoL scale, a value of 100 was equivalent to the best possible score and 0 to the worst possible score; mean treatment difference shown as chemotherapy minus afatinib and, as such, a negative score favors afatinib treatment. *CI*, confidence interval; *GHS*, global health status; *QoL*, quality of life

These new findings support previous analyses that have shown that first-line treatment with afatinib was associated with better control of cough and dyspnea compared with chemotherapy and better control of pain in patients with EGFR-mutation-positive NSCLC [3, 5].

What are the implications of these findings to clinical practice? Use of afatinib as first-line therapy significantly prolongs OS and PFS compared with chemotherapy in patients with advanced NSCLC harboring the Del19 mutation [3, 5]. As such, afatinib should be considered a first-choice, first-line agent in patients with tumors harboring Del19 mutations, with the additional improvements reported in lung cancer-related symptoms and overall GHS adding further support to this recommendation.

Treatment guidelines recommend both erlotinib and gefitinib over chemotherapy as first-line treatment in patients with EGFR-mutation-positive NSCLC [27, 28]. These recommendations are based on data showing that both treatments significantly improve PFS [1, 2, 4, 7, 11, 29, 30] and QoL symptoms [18–20] compared with chemotherapy, as benefits in OS have not been reported in either the overall study population [8, 11–15] or by mutation type; specifically, hazard ratios for patients with L858R mutations, where reported, are greater than (favoring chemotherapy) [14] or close to 1 [12, 13]. In agreement with these recommendations, demonstrated improvements in PFS, combined with improvements in symptom control, substantiate the value of also recommending afatinib over chemotherapy in patients with L858R mutations despite the lack of OS benefit [17]. Data from the LUX-Lung 7 global, randomized, phase IIb trial comparing first-line afatinib with gefitinib showed that afatinib significantly improved PFS versus gefitinib in patients with common EGFR mutations, with efficacy improvements being observed in both L858R and Del19 mutations [31], and a trend towards improved OS with afatinib versus gefitinib in both mutation types [32] adding further support to the use of afatinib in both mutation types.

The longitudinal analysis of these parameters provided statistically significant improvements for afatinib over chemotherapy in both studies for patients with tumors harboring Del19 mutations, as well as for patients with tumors harboring L858R mutations, in LUX-Lung 6. This suggests that the GHS/QoL of patients with NSCLC with common EGFR mutations (both for Del19 and L858R) receiving afatinib is potentially better than with chemotherapy. These new data also indicate that the symptoms of diarrhea and sore mouth, as well as other AEs more commonly observed with afatinib compared with chemotherapy, did not adversely affect patients' overall QoL. Afatinib treatment also showed consistent significant improvements in scores of all functional scales compared with chemotherapy in LUX-Lung 6, regardless of common mutation type, whereas significant differences in functional scale scores between treatment arms were not as uniformly seen in the LUX-Lung 3 trial. This likely reflects the differential impact of the chemotherapy arms used in each trial on patient outcome rather than the responsiveness of the mutation type to improvements in aspects of patient function with afatinib; the cisplatin/pemetrexed chemotherapy comparator used in LUX-Lung 3 is generally considered to have a better tolerability profile than cisplatin/gemcitabine used in LUX-Lung 6 and, as such, is likely to have less of an impact on functioning compared with the LUX-Lung 6 chemotherapy comparator.

The EORTC QLQ-C30 and QLQ-LC13 instruments used in our analyses have been well validated for the assessment of PROs and, although LUX-Lung 3 and LUX-Lung 6 both used comprehensive and prespecified methods for the assessment of PROs, the analyses reported here were conducted post hoc and should be considered to be exploratory. It should be noted that the studies on which these analyses were based were not powered to detect significant differences in PRO outcomes and the number of analyses conducted does increase the chance of false-positive results being observed (a type I error). The strengths and limitations of each analysis method should also be considered: analysis of the percentage of patients with symptom improvement is of clinical interest yet the threshold that constitutes a clinically relevant change is often debated and the presence of asymptomatic patients at baseline can impact on the results. The event time for symptom improvement or deterioration could occur at any stage during the assessment period; time to deterioration analysis is easy to interpret, yet has limitations associated with censoring due to progression, and longitudinal analysis offers comprehensive use of available data, yet is a complex method of analysis that requires certain assumptions regarding missing data. However, collectively, the three methods of analysis broaden the perspective of the results, thereby enhancing their interpretation. The overall inferential strategy was to provide a comprehensive analysis relying on the consistency (and potential inconsistency) of the results to reflect the strength of the evidence. As such, the general consistency of the results favoring afatinib treatment compared with chemotherapy across studies, mutation groups (Del19 or L858R), and analysis methods suggests that the differences observed represent a true treatment effect rather than a chance occurrence. An additional consideration in interpreting the findings reported here is that baseline pain scores were low; as such, only a limited number of patients had a chance to show improvements in this item. Despite this, a trend towards better control of pain was observed in both studies.

5 Conclusion

Compared with chemotherapy, first-line treatment with afatinib generally improves lung cancer-related symptoms in patients with EGFR-mutation-positive NSCLC, with comparable benefits being observed regardless of common mutation type. Afatinib also results in improvements in overall QoL and functional improvements compared with chemotherapy, providing further support for the use of afatinib in the first-line treatment of this patient group.

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Compliance with Ethical Standards

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Conflict of interest Dr. Wu reports grants and personal fees from Boehringer Ingelheim during the conduct of the study, personal fees from AstraZeneca, Lilly, Pierre Fabre, Pfizer, Sanofi, and Merck, and grants and personal fees from Roche, outside the submitted work. Dr. Hirsh reports personal fees from Boehringer Ingelheim during the

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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