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ORIGINAL REPORT

# 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

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See accompanying editorial on page 3303 and articles on pages 3327 and 3342

A B S T R A C T

**Purpose**

New molecular targeted agents are needed for patients with non–small-cell lung cancer (NSCLC) who progress while receiving erlotinib, gefitinib, or both. Afatinib, an oral irreversible ErbB family blocker, has preclinical activity in epidermal growth factor receptor (EGFR [ErbB1]) mutant models with EGFR-activating mutations, including T790M.

**Patients and Methods**

This was a Japanese single-arm phase II trial conducted in patients with stage IIIB to IV pulmonary adenocarcinoma who progressed after ≥ 12 weeks of prior erlotinib and/or gefitinib. Patients received afatinib 50 mg per day. The primary end point was objective response rate (complete response or partial response) by independent review. Secondary end points included progression-free survival (PFS), overall survival (OS), and safety.

**Results**

Of 62 treated patients, 45 (72.6%) were *EGFR* mutation positive in their primary tumor according to local and/or central laboratory analyses. Fifty-one patients (82.3%) fulfilled the criteria of acquired resistance to erlotinib and/or gefitinib. Of 61 evaluable patients, five (8.2%; 95% CI, 2.7% to 18.1%) had a confirmed objective response rate (partial response). Median PFS was 4.4 months (95% CI, 2.8 to 4.6 months), and median OS was 19.0 months (95% CI, 14.9 months to not achieved). Two patients had acquired T790M mutations: L858R + T790M, and deletion in exon 19 + T790M; they had stable disease for 9 months and 1 month, respectively. The most common afatinib-related adverse events (AEs) were diarrhea (100%) and rash/acne (91.9%). Treatment-related AEs leading to afatinib discontinuation were experienced by 18 patients (29%), of whom four also had progressive disease.

**Conclusion**

Afatinib demonstrated modest but noteworthy efficacy in patients with NSCLC who had received third- or fourth-line treatment and who progressed while receiving erlotinib and/or gefitinib, including those with acquired resistance to erlotinib, gefitinib, or both.

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## INTRODUCTION

Epidermal growth factor receptor (*EGFR* [ErbB1]) somatic mutations occur in 30% of patients with non–small-cell lung cancer (NSCLC) who are of East Asian ethnicity (eg, from Japan or Taiwan) compared with 8% of patients of other ethnicities (eg, from the United States or Australia).[1] The predictive significance of these mutations in NSCLC and the association with a considerable improvement in response and progression-free survival (PFS) with currently available tyrosine kinase inhibitor (TKI) therapy have been shown in several phase III trials.[2-7] Despite promising results, patients with NSCLC who harbor *EGFR* mutations will eventually experience disease progression as a result of the inevitable development of resistance mechanisms, in particular, the T790M mutation in exon 20, which is found in more than 50% of patients who received an EGFR TKI.[8,9] Currently, there are no treatments with proven efficacy for these patients; thus, there is an increased demand to develop novel molecular targeted agents.

Afatinib is an irreversible ErbB family blocker, the preclinical activity of which includes *EGFR*-mutant cell lines that have common mutations, including T790M.[10,11] Results from phase I/II trials have complemented these two preclinical studies, demonstrating the efficacy of afatinib in patients with NSCLC who harbor EGFR-activating mutations.[12] These trials also included a phase I study in Japan that suggested modest clinical activity of afatinib in such patients following progression on erlotinib, gefitinib, or both and identified the maximum-tolerated dose of afatinib as 50 mg.[13]

This phase II trial was conducted in Japan to evaluate the efficacy of 50-mg afatinib monotherapy in third- and fourth-line patients with NSCLC who had progressed while receiving erlotinib and/or gefitinib treatment.

## PATIENTS AND METHODS

### Study Design

This was a multicenter, single-arm, open-label phase II trial of afatinib monotherapy in patients with NSCLC who had progressed on currently available EGFR TKIs. The primary end point was objective response rate (ORR) by independent review according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.0.[14] Secondary end points were time to ORR, duration of ORR, frequency and duration of clinical benefit (complete response [CR], partial response [PR], and stable disease [SD]), PFS, overall survival (OS), and disease control rate (DCR).

The study was conducted in line with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines and with the approval of each institutional review board. All patients provided written informed consent before study participation.

### Study Population

Patients were required to have had at least 12 weeks of prior EGFR TKIs, which served as an enrichment strategy for patients with EGFR-activating mutations and subsequent acquired resistance mutations. Although *EGFR* mutation status at screening, including T790M status, was not required, mutation analysis was performed if adequate tumor tissue was available from existing specimens or by rebiopsy.

Patients were at least age 20 years, had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and a life expectancy of at least 3 months. Patients had to have either pathologically or cytologically confirmed stage IIIB to IV adenocarcinoma, with at least one tumor lesion measurable by computed tomography or magnetic resonance imaging. Patients who were incurable with radiotherapy and had received at least one, but not more than two, lines of chemotherapy (including at least one platinum-based regimen) were eligible. Following initial clinical benefit from chemotherapy, eligible patients should have had radiographically confirmed progression according to RECIST 1.0 following at least 12 weeks of erlotinib and/or gefitinib treatment. However, they should not have received either of these drugs within 2 weeks of starting afatinib nor should they have received any other investigational drug within 4 weeks before enrollment. Thoracic radiotherapy was not permitted nor was any radiotherapy permitted within 4 weeks before enrollment.

Patients were excluded if they had gastrointestinal disorders with diarrhea as a major symptom, significant cardiovascular disease, serious drug hypersensitivity, coelomic fluid retention, uncontrolled concomitant diseases, inadequate baseline organ function, additional significant malignancies diagnosed within the past 5 years, and brain tumors and/or brain metastases (symptomatic or requiring treatment).

### Treatment

Patients received a single daily oral dose of afatinib at a starting dose of 50 mg 1 hour before food until progressive disease (PD), withdrawal of consent, or withdrawal due to adverse events (AEs). If patients experienced any grade $\geq$ 3 drug-related AE, as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 or grade 2 diarrhea, nausea, or vomiting for $\geq$ 7 consecutive days despite appropriate supportive care, afatinib was stopped for up to 14 days. Following this and recovery to a grade $\leq$ 1 AE or baseline (whichever was higher), afatinib could be restarted with the dose reduced by 10 mg; this dose reduction could be repeated a second time. However, after a third occurrence, afatinib was discontinued. Treatment of tumor-related symptoms and AEs by medications such as antidiarrheals, antibiotics, analgesics, and antiemetics was allowed.

### Efficacy Assessments

Baseline tumor assessments used computed tomography or magnetic resonance imaging scans of one to 10 target lesions at the initial screening. Patients who received at least one dose of afatinib and who had baseline disease measurable by RECIST were included in the efficacy analysis. ORR was measured by monitoring the same target lesions at 4, 8, and 12 weeks following the initial treatment and then every 8 weeks thereafter until study end. Patients were assigned by best response to one of the following RECIST categories: CR, PR, SD, or PD. Patients experiencing a CR or PR lasting for more than 4 weeks were defined as those with an ORR, whereas clinical benefit also included patients experiencing SD, which must have been observed after at least 6 weeks on the study. All imaging data were independently reviewed by a separate central evaluation committee, which consisted of two independent radiologists and a specialist for chest diseases, none of whom were involved in the study.

### Safety and Tolerability Assessments

AEs defined by NCI-CTCAE version 3.0 were assessed during and after afatinib treatment.

### Mutation Analyses

Molecular marker studies were performed on the majority of baseline primary tumors (by using tissue or serum samples or pleural effusion specimens). Only two tumor samples (pleural effusion specimen and tumor tissue) underwent rebiopsy at the time of disease progression with prior EGFR TKIs. At the central laboratory, tumor and serum samples were analyzed by the Scorpion amplification refractory mutation system method. By using tumor samples, K-ras codon 12/13 and exons 18 to 21 in the tyrosine kinase domain of the EGFR were analyzed by the direct sequencing method if there was a sufficient volume of DNA.

### Acquired Resistance Criteria

Acquired resistance to erlotinib and/or gefitinib was defined by using the Jackman criteria: (1) being *EGFR* mutation positive, (2) having CR/PR to erlotinib and/or gefitinib or SD for at least 6 months with erlotinib and/or gefitinib, (3) receiving no erlotinib and/or gefitinib for less than 4 weeks, and (4) receiving no intervening chemotherapy.[15]

### Statistical Analyses

A planned analysis (September 15, 2010) was performed 36 weeks after the initiation of afatinib treatment in the last entered patient, and a second planned analysis was done (February 14, 2011) to include mature efficacy data based on the independent review. A sample size of 60 patients was required to provide 94% power to detect statistically significant evidence of afatinib activity based on the assumption that the true response rate was $\geq$ 10%. The null hypothesis was a $\leq$ 1% ORR using an exact binomial test with a one-sided significance level of 0.025. Patients documented as having taken at least one dose of afatinib who had at least one response assessment were included in the primary analysis. Median PFS and OS calculations used Kaplan-Meier methods, and 95% CIs were calculated by using Greenwood's SE estimates.

## RESULTS

### Patient Population

Between June 16, 2009, and February 14, 2011, at 20 sites across Japan, 62 patients were entered onto the trial and received at least one dose of afatinib. At the second planned analysis, 58 patients (93.5%) had discontinued treatment because of PD (64.5%), AEs (25.8%), and

  

**Table 1.** Patient Demographics and Baseline Characteristics

| Characteristic | Afatinib No. | Afatinib % |
|---|---|---|
| No. of patients | 62 | 100 |
| Sex | | |
| Male | 14 | 22.6 |
| Female | 48 | 77.4 |
| Age, years | | |
| Median | 65.0 | |
| Range | 33-84 | |
| Baseline ECOG PS | | |
| 0 | 29 | 46.8 |
| 1 | 33 | 53.2 |
| Smoking history | | |
| Never-smokers | 43 | 69.4 |
| < 15 pack-years and stopped > 1 year before diagnosis | 7 | 11.3 |
| Current or other ex-smoker | 12 | 19.4 |
| Clinical stage at screening | | |
| IIIB | 5 | 8.1 |
| IV | 57 | 91.9 |
| *EGFR* mutation test* | 56 | 90.3 |
| Positive | 45 | 72.6 |
| Exon 19 deletion | 22 | 35.5 |
| Exon 19 deletion + L858R | 1 | 1.6 |
| Exon 19 deletion + T790M | 1 | 1.6 |
| Exon 19 deletion + other | 1 | 1.6 |
| L858R | 15 | 24.2 |
| L858R + T790M | 1 | 1.6 |
| L858R + other | 3 | 4.8 |
| L861Q | 1 | 1.6 |
| Negative | 11 | 17.7 |
| *EGFR* mutation unknown | 6 | 9.7 |
| No. of previous chemotherapy regimens | | |
| 1 | 52 | 83.9 |
| 2 | 10 | 16.1 |
| Other previous anticancer therapies | | |
| Surgery | 15 | 24.2 |
| Radiotherapy | 21 | 33.9 |
| Other | 1 | 1.6 |
| Best response to previous EGFR TKI | | |
| CR | 2 | 3.2 |
| PR | 38 | 61.3 |
| SD | 22 | 35.5 |
| Previous EGFR TKIs | | |
| Erlotinib only | 7 | 11.3 |
| Gefitinib only | 49 | 79.0 |
| Both erlotinib and gefitinib | 6 | 9.7 |
| Duration of previous EGFR TKI, weeks | | |
| 12 to < 24 | 3 | 4.8 |
| 24 to < 36 | 10 | 16.1 |
| 36 to < 48 | 13 | 21.0 |
| ≥ 48 | 36 | 58.1 |
| Interval from discontinuation of EGFR TKI to start of afatinib, weeks | | |
| < 4 | 52 | 83.9 |
| 4 to < 8 | 7 | 11.3 |
| 8 to < 12 | 2 | 3.2 |
| ≥ 12 | 1 | 1.6 |
| Patients fulfilling Jackman et al[15] criteria of acquired resistance to prior EGFR TKI | 51 | 82.3 |

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; PR, partial response; PS, performance status; SD, stable disease; TKI, tyrosine kinase inhibitor.
*Tumor tissue, pleural effusion specimens, or serum samples tested locally and/or by central laboratory.

refusal to continue treatment (3.2%). Four patients (6.5%) were continuing treatment and, as of February 8, 2012, one patient was still receiving afatinib. Mean total treatment time was 4.59 months (maximum treatment time, 16.3 months) for all 62 patients.

Patient demographics and baseline characteristics are provided in Table 1. The majority of patients were female (77.4%), 46.8% had an ECOG PS of 0, and 69.4% were never-smokers. Mutation testing was performed on 56 patients (90.3%), and 45 (72.6%) were determined to be *EGFR* mutation positive in their primary tumor according to local and/or central laboratory analyses (Appendix Table A1, online only). Acquired T790M was reported as a mutation sequence code in two patients (3.2%). No *KRAS* mutations were found among 12 patients with tissue sample test results.

The majority of patients (79.0%) had previously received gefitinib, 11.3% had received erlotinib, and 9.7% had received both. Patients had been on previous EGFR TKIs for a median of 57.5 weeks, and 95.2% had been on previous EGFR TKIs for at least 24 weeks. Approximately two thirds of patients (64.5%) had a response (PR/CR) to prior EGFR TKI therapy. The median interval from EGFR TKI discontinuation to afatinib treatment initiation was 3 weeks (range, 2 to 13 weeks). Fifty-one patients (82.3%) met the Jackman definition of having acquired resistance to erlotinib and/or gefitinib.

### *Antitumor Activity*

Sixty-one patients were evaluable for tumor response (Table 2); one was excluded because of lack of evaluable tumor imaging data. Of 61 evaluable patients, five (8.2%; 95% CI, 2.7% to 18.1%) achieved a confirmed response, all of which were PRs, and 35 (57.4%) had SD for at least 6 weeks, with a DCR of 65.6% by independent review. Most responses were seen within 8 weeks of afatinib initiation. The mean duration of response was 24.4 weeks. Afatinib reduced the size of target lesions in 79% of all patients during the treatment period (Fig 1), with nine patients (16%) having at least a 30% reduction in tumor size. However, tumor size reduction did not last for more than 4 weeks in four of nine patients.

Median PFS was 4.4 months (95% CI, 2.8 to 4.6 months) by independent review (Fig 2A). The PFS data were mature, with 72.1% of patients having a PFS event at the time of the second planned analysis. Median OS was 19.0 months (95% CI, 14.9 months to not

**Table 2.** Overview of Response Rate by Independent Review

| Response | Response Rate No. | Response Rate % | 95% CI |
|---|---|---|---|
| Total No. of patients | 61 | 100* | |
| DCR (CR, PR, or SD) | 40 | 65.6 | 52.3 to 77.3 |
| ORR (CR or PR) | 5 | 8.2 | 2.7 to 18.1 |
| CR | 0 | 0.0 | — |
| PR | 5 | 8.2 | — |
| SD | 35 | 57.4 | — |
| PD | 17 | 27.9 | — |
| Not evaluable | 4 | 6.6 | — |

Abbreviations: CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
*One patient with exon 19 deletion was excluded from the efficacy evaluation because of lack of evaluable tumor imaging data after the start of afatinib treatment.

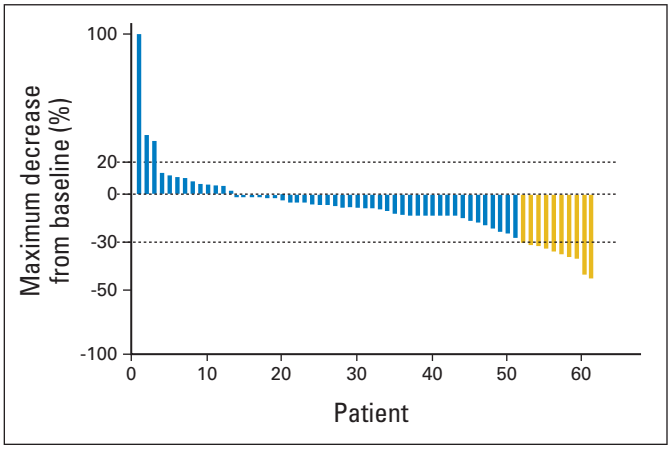


**Fig 1.** Waterfall plot of percent change from baseline in measurable tumor at the time of best response (by independent review). Data for patients with a decrease from baseline of 30% or more are shown in gold; data for patients with an increase from baseline of more than 100% to a decrease from baseline of less than 30% are shown in blue.

achieved; Fig 2B), with the probability of survival at 12 months estimated to be 73.0%; in addition, 34.4% of patients had an OS event. As of February 9, 2012, median OS was 18.4 months, and 63.9% of patients had an OS event.

Subgroup analysis of the efficacy data based on sex (women *v* men), ECOG PS (0 *v* 1), type of prior EGFR TKI (erlotinib *v* gefitinib), and the number of previous chemotherapy regimens (one *v* two) showed little variation in ORRs and DCRs (Appendix Table A2, online only). Efficacy data by mutation type were also similar among deletions in exon 19 (del19), L858R, and others (Table 3).

Patients meeting the Jackman criteria for acquired resistance had a median PFS of 4.4 months, PR of 5.9%, and DCR of 68.6%. Of the two patients with T790M mutations who underwent rebiopsy at the time of disease progression with prior EGFR TKI therapy, one patient harboring an L858R + T790M mutation had durable SD for 9 months, and the other patient with a del19 + T790M mutation had SD for 1 month. In *EGFR* mutation–negative patients, the ORR was 27% (three of 11), which was higher than in *EGFR* mutation–positive (4.5%; two of 44) or mutation-unknown (0%; zero of six) patients.

### *Safety and Tolerability*

All 62 patients experienced an AE, with diarrhea and skin events being the most frequently reported (Table 4). Diarrhea occurred in all 62 patients, rash/acne in 57 patients (91.9%), and stomatitis in 53 patients (85.5%). Grade 3 diarrhea occurred in 37.1% of patients, and rash/acne occurred in 27.4% of patients. Loperamide use was capped at 8 mg per day for treatment of diarrhea (90.3% of patients received loperamide), and less than 10% of patients received systemic antibiotics for rash.

All patients received a starting dose of afatinib 50 mg per day, with 69.4% of patients requiring dose reduction to 40 mg per day, and 35.5% requiring further dose reduction to 30 mg per day. The most common AE leading to dose reduction was diarrhea, affecting 41.9% of patients. Treatment-related AEs leading to discontinuation of afatinib were experienced by 18 patients (29.0%) and were due to rash/acne (n = 7); decreased appetite (n = 3); diarrhea, interstitial lung disease, and stomatitis in two patients each; and dehydration, fatigue, nail effects, and pyrexia in one patient each. Four of these patients (three with rash, one with paronychia) had PD confirmed by tumor assessments at the same time as afatinib discontinuation due to AEs. Drug-related serious AEs occurred in 11.3% of patients, with diarrhea (6.5%) being the most common. Two interstitial lung disease-like AEs (grade 3 and grade 1) were considered to be related to study drug; in each case, the patient fully recovered after stopping afatinib. One on-treatment death as a result of hypoxia occurred after disease progression, which was not considered by the investigator to be drug related.

## DISCUSSION

There is an increasing need to develop new molecular targeted agents that address the issue of resistance to erlotinib and/or gefitinib in patients with NSCLC who initially respond to treatment and then subsequently progress.[16] Previous phase II studies with criteria similar

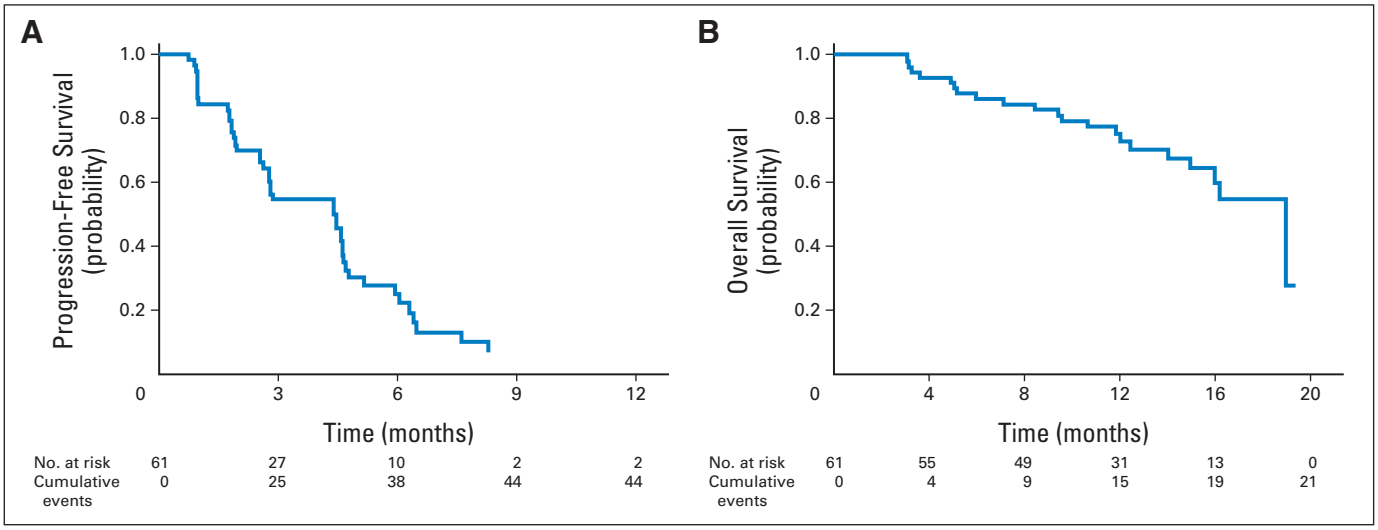


**Fig 2.** Kaplan-Meier plot of (A) progression-free survival by independent review and (B) median overall survival.

  

**Table 3.** Overview of DCR, ORR, and PFS by Mutation Type

| | *EGFR* Mutation Type | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Exon 19 Deletion | | | | L858R | | | | Other | | | |
| Response | No. | % | 95% CI | Percentile | No. | % | 95% CI | Percentile | No. | % | 95% CI | Percentile |
| Total No. of patients | 21 | 100* | | | 15 | 100 | | | 8 | 100.0 | | |
| DCR (CR, PR, or SD) | 14 | 66.7 | 43.0 to 85.4 | | 10 | 66.7 | 38.4 to 88.2 | | 5 | 62.5 | 24.5 to 91.5 | |
| ORR (CR or PR) | 1 | 4.8 | 0.1 to 23.8 | | 1 | 6.7 | 0.2 to 31.9 | | 0 | 0.0 | 0 | |
| Median PFS, months | 1.9 | | | 25th | 1.9 | | | 25th | 1.3 | | | 25th |
| | 4.6 | | | | 3.6 | | | | 3.7 | | | |
| | 5.2 | | | 75th | 5.3 | | | 75th | 8.3 | | | 75th |

Abbreviations: CR, complete response; DCR, disease control rate; EGFR, epidermal growth factor receptor; ORR, objective response rate; PFS, progression-free survival; PR, partial response; SD, stable disease.

*One patient who had an exon 19 deletion was excluded from the efficacy evaluation because of lack of evaluable tumor imaging data after the start of afatinib treatment.

to that of the current LUX-Lung 4 trial with prior failure of erlotinib and/or gefitinib and an enrichment strategy for patients with *EGFR* mutations by using XL-647, dasatinib, neratinib, and the combination of cetuximab plus erlotinib showed low ORR ranging from 0% to 3%.[17-20] The results of our trial demonstrated modest but noteworthy activity of afatinib in this difficult-to-treat population, with a median PFS of 4.4 months and an ORR of 8.2% (independent review).

As might be expected for a group of patients with NSCLC who derived significant benefit from prior erlotinib and/or gefitinib therapy, the study population was highly enriched (85%) for patients with *EGFR* mutations. This was further reflected in the patient demographics, with a large percentage of women and never-smokers. The trial was also highly enriched (82%) for patients meeting the Jackman criteria of acquired resistance, and the efficacy findings were similar in that subpopulation compared with the overall study population, with similar PFS results for the Jackman group of patients shown in LUX-Lung 1.[21] In the LUX-Lung 1 double-blind, placebo-controlled phase IIB/III study of afatinib plus best supportive care in patients with NSCLC who had progressed after prior chemotherapy and erlotinib and/or gefitinib treatment, a median PFS of 4.5 months was reported in those patients fulfilling the Jackman criteria for acquired resistance, which is consistent with the median PFS of 4.4 months reported in this trial.[21]

**Table 4.** All AEs for All Grades and NCI-CTCAE Grade 3 in ≥ 10% of Patients

| | All Grades | | Grade 3 | |
|---|---|---|---|---|
| Preferred Term | No. | % | No. | % |
| No. of patients | 62 | 100.0 | 62 | 100.0 |
| Total with AEs | 62 | 100.0 | 49 | 79.0 |
| Diarrhea | 62 | 100.0 | 23 | 37.1 |
| Rash/acne | 57 | 91.9 | 17 | 27.4 |
| Stomatitis | 53 | 85.5 | 6 | 9.7 |
| Nail effect | 43 | 69.4 | 7 | 11.3 |
| Decreased appetite | 38 | 61.3 | 3 | 4.8 |
| Fatigue | 25 | 40.3 | 5 | 8.1 |
| Nausea | 23 | 37.1 | 1 | 1.6 |
| Vomiting | 17 | 27.4 | 1 | 1.6 |
| Weight decreased | 17 | 27.4 | 0 | 0.0 |
| Epistaxis | 16 | 25.8 | 0 | 0.0 |
| Lip effect | 16 | 25.8 | 0 | 0.0 |
| Ocular event | 15 | 24.2 | 1 | 1.6 |
| Dry skin | 14 | 22.6 | 0 | 0.0 |
| Dysgeusia | 11 | 17.7 | 0 | 0.0 |
| Dehydration | 9 | 14.5 | 5 | 8.1 |
| Nasal inflammation | 8 | 12.9 | 0 | 0.0 |
| Nasopharyngitis | 7 | 11.3 | 0 | 0.0 |

NOTE. For all adverse events (AEs) listed, no grade 4 or grade 5 events occurred.

Abbreviations: AE, adverse event; NCI-CTCAE, National Cancer Institute–Common Terminology Criteria for Adverse Events.

The estimated median OS of 19 months observed in this trial is of interest. However, nearly half the patients entering this trial were symptom-free with an ECOG PS of 0, and 72.6% had an EGFR-mutant tumor, suggesting the selection of a relatively good prognostic cohort despite their extensive pretreatment.

The Jackman criteria of acquired resistance to EGFR TKIs were fulfilled by 82% of the patients in this trial. The efficacy of afatinib in this subgroup of patients suggests that the clinical effect of afatinib is not merely due to re-exposure to another EGFR TKI, a phenomenon that was previously reported.[22] Although the literature reports that approximately 50% of the patients who develop acquired resistance to EGFR TKIs show secondary T790M mutation,[23] a relatively low incidence of T790M mutations was observed in this study. This may be due to the fact that tissue sampling was obtained before erlotinib and/or gefitinib exposure, and very few patients underwent rebiopsy.

The AEs observed in this phase II trial were consistent with the known safety profile reported for inhibitors of EGFR.[6] All patients experienced an AE considered to be drug related, with diarrhea, rash/acne, and stomatitis being the most common AEs. AEs were mostly managed by dose reduction and/or medical treatment. The rates of grade 3 diarrhea and rash/acne reported in this trial were similar to those of the LUX-Lung 2 phase II trial, in which a large proportion of patients (87%) were Asian.[24] In LUX-Lung 2 (afatinib 50 mg per day in first- and second-line patients whose tumors harbored *EGFR* mutations), diarrhea and rash/acne occurred in 94% of patients, with grade 3 diarrhea reported in 22% of patients and grade 3 rash/acne in 28% of patients.[24] The frequency and severity of AEs and treatment discontinuation due to AEs appears to be higher with afatinib compared with the historical data reported with erlotinib and gefitinib.[2-7,25] However, the early and proactive management of AEs, including dose

reduction and the use of additional symptomatic therapies, could have been effective in our study, allowing patients who benefited from afatinib to continue on treatment as observed in the LUX-Lung 1 trial (afatinib 50 mg was the starting dose).[21] Proactive supportive management also has the potential to maintain quality of life by reducing the impact of AEs.

On the basis of the modest but noteworthy activity of afatinib observed in this trial in patients with NSCLC who have acquired resistance to erlotinib and/or gefitinib, additional studies to improve on the activity of afatinib in this setting are ongoing. In preclinical T790M tumor models, combined EGFR targeting with afatinib and cetuximab induced near CRs that were not seen with either agent alone or with a cetuximab plus erlotinib combination.[26] On the basis of these early observations, a phase IB trial is currently testing the combination of afatinib and cetuximab in a patient population similar to that of LUX-Lung 4. Preliminary results have shown that more than 90% of patients thus far have derived clinical benefit, including approximately 40% ORR in both T790M-positive and T790M-negative settings.[27,28]

To extend the investigation of afatinib in advanced NSCLC, the ongoing LUX-Lung 3 and LUX-Lung 6 randomized phase III studies are comparing the efficacy of first-line afatinib monotherapy with cisplatin and either pemetrexed or gemcitabine in white and Asian patients with NSCLC who are harboring *EGFR* mutations. Initial results from LUX-Lung 3 demonstrated a significant improvement in PFS of 11.1 months with afatinib compared with 6.9 months for chemotherapy.[29]

In conclusion, this phase II study conducted in Japan in a study population with NSCLC enriched for *EGFR* mutations showed modest but noteworthy efficacy of oral afatinib, an irreversible ErbB family blocker, in third- and fourth-line patients with NSCLC with acquired resistance to erlotinib and/or gefitinib. Further evaluation of the potential of afatinib in patients with advanced NSCLC will be addressed by the LUX-Lung phase III clinical trial program and the ongoing study of the afatinib plus cetuximab combination in the resistance setting.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

*Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.*

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## *Appendix*

**Table A1.** Results of *EGFR* Mutation Testing Performed in Either a Local or Central Laboratory

| Mutation | *EGFR* Mutation Test | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Central Laboratory Using Tissue and Pleural Effusion Specimens | | Central Laboratory Using Serum Samples | | Local Laboratory* | | Central or Local Laboratory† | |
| | No. | % | No. | % | No. | % | No. | % |
| No. of patients treated | 62 | | 62 | | 62 | | 62 | |
| No. of patients with *EGFR* mutation test results | 27 | 43.5 | 45 | 72.6 | 37 | 59.7 | 56 | 90.3 |
| Positive | 23 | 85.2 | 3 | 6.7 | 37 | 100.0 | 45 | 72.6 |
| Exon 19 deletion | 10 | 37.0 | 2 | 4.4 | 18‡ | 48.6 | 22‡ | 35.5 |
| Exon 19 deletion + L858R | 0 | 0.0 | 0 | 0.0 | 1 | 2.7 | 1 | 1.6 |
| Exon 19 deletion + T790M | 1 | 3.7 | 0 | 0.0 | 0 | 0.0 | 1 | 1.6 |
| Exon 19 deletion + other | 1 | 3.7 | 0 | 0.0 | 0 | 0.0 | 1 | 1.6 |
| L858R | 8 | 29.6 | 1 | 2.2 | 16 | 43.2 | 15 | 24.2 |
| L858R + T790M | 0 | 0.0 | 0 | 0.0 | 1 | 2.7 | 1 | 1.6 |
| L858R + other | 3 | 11.1 | 0 | 0.0 | 0 | 0.0 | 3 | 4.8 |
| L861Q | 0 | 0.0 | 0 | 0.0 | 1 | 2.7 | 1 | 1.6 |
| Negative | 4 | 14.8 | 42 | 93.3 | 0 | 0.0 | 11 | 17.7 |

Abbreviation: EGFR, epidermal growth factor receptor.
*Information on sample/specimen type unavailable.
†Results using tissue, pleural effusion specimens, or serum samples. If multiple data were available for a patient, positive data and/or more detailed data were selected.
‡Included one patient who was excluded from the efficacy analysis because the patient had no evaluable tumor imaging data after the start of afatinib treatment.

**Table A2.** Summary of DCR and ORR by Sex, ECOG PS, Previous Chemotherapy Regimens, and Type of Prior EGFR TKI

| Variable | DCR | | | ORR | | |
|---|---|---|---|---|---|---|
| | No. | % | 95% CI | No. | % | 95% CI |
| Sex | | | | | | |
| Male (n = 14) | 10 | 71.4 | 41.9 to 91.6 | 1 | 7.1 | 0.2 to 33.9 |
| Female (n = 47) | 30 | 63.8 | 48.5 to 77.3 | 4 | 8.5 | 2.4 to 20.4 |
| Baseline ECOG PS | | | | | | |
| 0 (n = 29) | 20 | 69.0 | 49.2 to 84.7 | 2 | 6.9 | 0.8 to 22.8 |
| 1 (n = 32) | 20 | 62.5 | 43.7 to 78.9 | 3 | 9.4 | 2.0 to 25.0 |
| No. of previous chemotherapy regimens | | | | | | |
| 1 (n = 51) | 31 | 60.8 | 46.1 to 74.2 | 4 | 7.8 | 2.2 to 18.9 |
| 2 (n = 10) | 9 | 90.0 | 55.5 to 99.7 | 1 | 10.0 | 0.3 to 44.5 |
| Prior use of EGFR TKI | | | | | | |
| Erlotinib (n = 7) | 4 | 57.1 | 18.4 to 90.1 | 1 | 14.3 | 0.4 to 57.9 |
| Gefitinib (n = 48) | 32 | 66.7 | 51.6 to 79.6 | 4 | 8.3 | 2.3 to 20.0 |
| Erlotinib and gefitinib (n = 6) | 4 | 66.7 | 22.3 to 95.7 | 0 | | 0 |

Abbreviations: DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ORR, objective response rate; PS, performance status; TKI, tyrosine kinase inhibitor.