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Afatinib versus cisplatin plus pemetrexed in Japanese patients with advanced non-small cell lung cancer harboring activating *EGFR* mutations: Subgroup analysis of LUX-Lung 3

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Key words

Afatinib, chemotherapy, epidermal growth factor receptor, Japanese, non-small cell lung cancer

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In LUX-Lung 3, afatinib significantly improved progression-free survival (PFS) versus cisplatin/pemetrexed in *EGFR* mutation-positive lung adenocarcinoma patients and overall survival (OS) in Del19 patients. Preplanned analyses in Japanese patients from LUX-Lung 3 were performed. Patients were randomized 2:1 to afatinib or cisplatin/pemetrexed, stratified by mutation type (Del19/L858R/Other). Primary endpoint was PFS (independent review). Secondary endpoints included OS, objective response, and safety. Median PFS (data cut-off: February 2012) for afatinib versus cisplatin/pemetrexed was 13.8 *vs* 6.9 months (hazard ratio [HR], 0.38; 95% confidence interval [CI], 0.20–0.70; $P = 0.0014$) in all Japanese patients ($N = 83$), with more pronounced improvements in those with common mutations (Del19/L858R; HR, 0.28; 95% CI, 0.15–0.52; $P < 0.0001$) and Del19 mutations (HR, 0.16; 95% CI, 0.06–0.39; $P < 0.0001$). PFS was also improved in L858R patients (HR, 0.50; 95% CI, 0.20–1.25; $P = 0.1309$). Median OS (data cut-off: November 2013) with afatinib versus cisplatin/pemetrexed was 46.9 *vs* 35.8 months (HR, 0.75; 95% CI, 0.40–1.43; $P = 0.3791$) in all Japanese patients, with greater benefit in patients with common mutations (HR, 0.57; 95% CI, 0.29–1.12; $P = 0.0966$) and Del19 mutations (HR, 0.34; 95% CI, 0.13–0.87; $P = 0.0181$); OS was not significantly different in L858R patients (HR, 1.13; 95% CI, 0.40–3.21; $P = 0.8212$). Following study treatment discontinuation, most patients (93.5%) received subsequent anticancer therapy. The most common treatment-related adverse events were diarrhea, rash/acne, nail effects and stomatitis with afatinib and nausea, decreased appetite, neutropenia, and leukopenia with cisplatin/pemetrexed. Afatinib significantly improved PFS versus cisplatin/pemetrexed in Japanese *EGFR* mutation-positive lung adenocarcinoma patients and OS in Del19 but not L858R patients (www.clinicaltrials.gov; NCT00949650).

Epidermal growth factor receptor (*EGFR*) mutations are important drivers of non-small cell lung cancer (NSCLC) tumors. The frequency of *EGFR* mutations in NSCLC is higher in Asian populations (up to 50–60%) than in Caucasian patients (approximately 10%).[1–4] Treatment with the first-generation EGFR tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib demonstrated longer progression-free survival (PFS), versus platinum-based chemotherapy for first-line treatment of *EGFR* mutation-positive NSCLC in several randomized trials;[5–9] however, an overall survival (OS) benefit was not observed.[8,10–18]

Afatinib is an oral, irreversible ErbB family blocker of EGFR (ErbB1), human epidermal growth factor receptor 2 (HER2/ErbB2), ErbB3, and ErbB4 signaling.[19,20] In contrast to first-generation EGFR TKIs, erlotinib and gefitinib, which are reversible inhibitors of EGFR, afatinib covalently binds to the EGFR, HER2 and ErbB4 receptors, and irreversibly blocks signaling from all ErbB family dimers. Afatinib is approved in Europe for the treatment of EGFR TKI-naïve NSCLC patients with *EGFR*-activating mutations,[21] and in the United States for first-line treatment of NSCLC patients harboring common (Del19 or L858R) mutations,[22] based on the results of two large phase III studies: LUX-Lung 3 and LUX-Lung 6. Each of these studies, which were designed to meet regulatory requirements of different regions, compared afatinib with standard platinum-doublet chemotherapy in patients with metastatic lung adenocarcinoma with activating *EGFR* mutations. LUX-Lung 3 was a global trial which compared afatinib with cisplatin/pemetrexed[23] while LUX-Lung 6 recruited patients from China, South Korea, and Thailand and compared afatinib with cisplatin/gemcitabine.[24]

In LUX-Lung 3, 345 patients were randomized to afatinib or cisplatin/pemetrexed.[23] Median PFS was significantly pro-

longed with afatinib (11.1 months) versus cisplatin/pemetrexed (6.9 months; hazard ratio [HR], 0.58; 95% confidence interval [CI], 0.43–0.78; $P < 0.001$).[23] Among 308 patients with common mutations (Del19/L858R), median PFS was 13.6 months with afatinib versus 6.9 months with cisplatin/pemetrexed (HR, 0.47; 95% CI, 0.34–0.65; $P < 0.001$).[23] Subgroup analyses of PFS showed a consistent treatment effect for Asian and non-Asian patients. Afatinib was also associated with better control of cough and dyspnea than chemotherapy.[25] The most common treatment-related adverse events (AEs) were diarrhea, rash/acne, and stomatitis with afatinib and nausea, fatigue, and decreased appetite with chemotherapy.[23] In updated OS results from LUX-Lung 3, there was a trend towards an improvement in OS with afatinib in patients with common mutations (31.6 months with afatinib versus 28.2 months with chemotherapy; HR, 0.78; 95% CI, 0.58–1.06; $P = 0.1090$) and a significant improvement in OS with afatinib was observed in patients with Del19 mutations (33.3 *vs* 21.1 months; HR, 0.54; 95% CI, 0.36–0.79; $P = 0.0015$).[26] OS results in LUX-Lung 6 were consistent with those in LUX-Lung 3.[26]

We performed a preplanned subgroup analysis of Japanese patients in the LUX-Lung 3 trial to confirm if the efficacy and safety of afatinib in Japanese patients were consistent with the overall patient population.

Materials and Methods

Study design and patients. Details of the study design and methodology of the LUX-Lung 3 trial have been published previously.[23] In brief, LUX-Lung 3 was a phase III, randomized trial in which treatment-naïve patients with stage IIIB/IV lung adenocarcinoma and confirmed *EGFR* mutations were randomized 2:1 to receive afatinib 40 mg daily, or up to six cycles of intravenous cisplatin/pemetrexed at standard doses. Treatment continued until disease progression or unacceptable tolerability. Randomization was stratified by *EGFR* mutation (Del19 versus L858R versus Other) and race (Asian versus non-Asian). All patients provided informed consent. The study was conducted in accordance with the Declaration of Helsinki and guidelines on Good Clinical Practice and was approved by the institutional review boards of the participating centers.

Endpoints and assessments. The primary endpoint was PFS (independent review). PFS was analyzed after at least 217 progression events. Key secondary endpoints were objective response rate (complete response [CR] or partial response [PR]), disease control rate (CR, PR, or stable disease), and OS. Patient-reported outcomes and safety were also assessed.

Tumor assessments were performed by computed tomography or magnetic resonance imaging every 6 weeks for the first 48 weeks and every 12 weeks thereafter until progressive disease or starting new anticancer therapy. Tumor response was defined using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.[27] AEs were assessed using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.[28] Treatment compliance with afatinib was assessed from the start to the end of study treatment, after each treatment course, for all patients. Compliance was assessed by counting returned, unused tablets (for recovery from a drug-related AE, interruption of the treatment was allowed and the patient was still regarded as compliant).

Statistical analysis. For the overall LUX-Lung 3 population, sample size was specified assuming an HR of 0.64, equating to an increase in median PFS from an expected 7 months for chemotherapy to 11 months for afatinib. To provide 90% power at a two-sided 5% significance level, a minimum of 217 progression events (by independent review) or deaths was required. Primary and key secondary endpoints were analyzed following a hierarchical testing strategy to minimize the overall risk of type I error. OS analyses were planned for two time points: the first was concurrent with the primary PFS analysis; a Haybittle-Peto stopping boundary was used ($P < 0.0001$) to preserve the overall 5% type I error. The second (main) analysis was planned after 209 deaths, when it was estimated that the data would be mature.

All efficacy analyses, including preplanned analyses of the Japanese patients, were performed in an intent-to-treat manner and included all randomized patients. Cox proportional hazards models and stratified log-rank tests were used to compare PFS and OS between treatments, and Kaplan–Meier estimates were calculated. Objective response and disease control rates were compared between treatments via logistic regression models. Preplanned subgroups and analyses were defined, but no adjustment for multiplicity was performed. Median follow-up times were calculated using the reverse Kaplan–Meier method.

Safety analyses included all patients who received at least one dose of trial medication and were performed both at primary PFS analysis and the main OS analysis; the safety results presented here are from the latter time point.

Results

Patient demographics. The study was performed at 133 centers, including 16 centers in Japan. In total, 185 Japanese patients were screened for *EGFR* mutations. Of these, 83 patients were randomized (54 to afatinib and 29 to cisplatin/pemetrexed) and 82 received treatment (one patient randomized to cisplatin/pemetrexed did not receive treatment; Fig. S1).

Japanese patient demographics were similar across treatment arms (Table 1). Most patients had tumors with common *EGFR* mutations (47.0% had Del19 mutation and 45.8% had L858R mutation).

Treatment. At the time of the main OS analysis, median treatment duration for Japanese patients receiving afatinib was 419.5 days (range, 28–1323) and six patients are continuing on treatment. Mean overall compliance with afatinib was 96%. Forty-one patients (75.9%) had dose reductions due to AEs; 18 (33.3%) had one dose reduction and 23 (42.6%) had two dose reductions. Median time to first dose reduction was 57.0 days (range, 16–443). Further details on reasons for dose reduction are provided in the Safety section.

Median treatment duration for Japanese patients receiving chemotherapy was 74.0 days. Two patients (7.1%) had one treatment cycle, three (10.7%) had two cycles, three (10.7%) had three cycles, 11 (39.3%) had four cycles, one (3.6%) had five cycles, and eight (28.6%) had six cycles. Of patients receiving >1 course of chemotherapy, 10 patients (38.5%) had no treatment delays, two (7.7%) had a worst delay of 4–6 days, and 14 (53.8%) had a worst delay of >6 days.

Efficacy. *Progression-free survival.* At the time of data cut-off for the primary PFS analysis (February 2012), median follow-up time was 16.4 months for Japanese patients; 32 (59.3%) patients in the afatinib group and 20 (69.0%) in the cisplatin/pemetrexed group had progressed or died. Independently-assessed PFS was significantly longer with afatinib than cisplatin/pemetrexed (13.8 *vs* 6.9 months; HR, 0.38; 95% CI, 0.20–0.70; $P = 0.0014$; Table 2; Fig. 1a). The improvement in

Table 1. Patient demographics and clinical characteristics

Characteristic	Afatinib (n = 54)	Cisplatin + pemetrexed (n = 29)
Sex, *n* (%)		
Male	17 (31.5)	9 (31.0)
Female	37 (68.5)	20 (69.0)
Age, years		
Median	65.5	66.0
Range	37–76	38–78
Smoking status, *n* (%)		
Never	32 (59.3)	19 (65.5)
Former	21 (38.9)	9 (31.0)
Current	1 (1.9)	1 (3.4)
ECOG PS, *n* (%)		
0	27 (50.0)	17 (58.6)
1	27 (50.0)	12 (41.4)
Brain metastases at diagnosis, *n* (%)		
No	44 (81.5)	22 (75.9)
Yes	10 (18.5)	7 (24.1)
Adenocarcinoma stage, *n* (%)		
IIIB	6 (11.1)	5 (17.2)
IV	48 (88.9)	24 (82.8)
EGFR mutation, *n* (%)		
Del19	23 (42.6)	16 (55.2)
L858R	27 (50.0)	11 (37.9)
Other	4 (7.4)	2 (6.9)

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor.

PFS observed with afatinib versus cisplatin/pemetrexed was more pronounced in Japanese patients with common mutations (13.8 *vs* 6.9 months; HR, 0.28; 95% CI, 0.15–0.52; $P < 0.0001$) and those with Del19 mutations (16.4 *vs* 3.1 months; HR, 0.16; 95% CI, 0.06–0.39; $P < 0.0001$; Table 2; Fig. 1b,c). Though not statistically significant in this small subgroup, PFS was also improved with afatinib in Japanese patients with L858R mutations (13.7 *vs* 8.3 months; HR, 0.50; 95% CI, 0.20–1.25; $P = 0.1309$; Table 2; Fig. 1d).

Progression-free survival results in Japanese patients were consistent across subgroups examined (including gender, age, baseline Eastern Cooperative Oncology Group performance status, and smoking history; Fig. S2a).

A *post-hoc* analysis evaluating PFS in Japanese patients with common *EGFR* mutations, with or without brain metastases at baseline, was conducted. For patients with common mutations and without brain metastases ($n = 61$), median PFS was significantly improved with afatinib (16.4 months) versus cisplatin/pemetrexed (8.2 months; HR, 0.26; 95% CI, 0.13–0.55; $P = 0.0001$). A significant improvement in PFS with afatinib (19.2 months) versus cisplatin/pemetrexed (6.9 months) was observed in patients without brain metastases and with Del19 mutations ($n = 32$; HR, 0.14; 95% CI, 0.05–0.40; $P < 0.0001$). Although not statistically significant, PFS was also improved with afatinib (13.8 months) versus cisplatin/pemetrexed (8.3 months) in patients without brain metastases and with L858R mutations ($n = 29$; HR, 0.56; 95% CI, 0.18–1.80; $P = 0.3243$). In Japanese patients with brain metastases, median PFS with afatinib versus cisplatin/pemetrexed was 9.0 *vs* 3.9 months in those with common mutations ($n = 15$; HR, 0.45; 95% CI, 0.12–1.71; $P = 0.2233$), 9.5 *vs* 3.1 months in those with Del19 mutations ($n = 7$; HR, 0.38; 95% CI, 0.04–4.00; $P = 0.4072$), and 8.3 *vs* 7.4 months in patients with L858R mutations ($n = 8$; HR, 0.51; 95% CI, 0.09–3.11; $P = 0.4477$).

Objective response and disease control rate. In the overall Japanese population, a significantly higher proportion of patients achieved an objective response with afatinib versus cisplatin/pemetrexed (61.1% *vs* 20.7%, respectively; odds ratio, 6.52; 95% CI, 2.22–19.14; $P = 0.0007$; Table 2). Similar results were observed in Japanese patients with common *EGFR* mutations and those with Del19 or L858R mutations (Table 2).

Disease control rates were high for both treatment arms (96.3% for afatinib and 89.7% for cisplatin/pemetrexed). Results were consistent when evaluated according to *EGFR* mutation status (Table 2).

Overall survival. At the time of data cut-off for the main OS analysis (November 2013), median follow-up time was 41.0 months for Japanese patients. Twenty-four (44.4%) afatinib-treated patients and 16 (55.2%) cisplatin/pemetrexed-treated patients had died. There was a trend towards an improvement in median OS with afatinib versus cisplatin/pemetrexed, although this was not statistically significant (46.9 *vs* 35.8 months, respectively; HR, 0.75; 95% CI, 0.40–1.43; $P = 0.3791$; Table 2, Fig. 2a). Compared with the overall Japanese population, a more pronounced OS benefit for afatinib versus cisplatin/pemetrexed was observed in patients with common mutations (46.9 *vs* 35.0 months, respectively; HR, 0.57; 95% CI, 0.29–1.12; $P = 0.0966$; Table 2, Fig. 2b). In Japanese patients with Del19 mutation, median OS was significantly improved with afatinib (46.9 *vs* 31.5 months; HR 0.34; 95% CI, 0.13–0.87; $P = 0.0181$; Table 2, Fig. 2c), while in patients with L858R mutation, OS was similar between treatment arms (41.7 months with afatinib and 40.3 months with cisplatin/pemetrexed; HR, 1.13; 95% CI, 0.40–3.21; $P = 0.8212$; Table 2, Fig. 2d).

Overall survival results in Japanese patients were consistent across subgroups (Fig. S2b). In addition to the greater benefit observed in patients with Del19 mutations, female patients appeared to derive greater OS benefit from afatinib; however, this effect may be confounded with the mutation type effect, as a greater proportion of afatinib-treated female patients had a Del19 mutation compared with males.

Following discontinuation of the study drug, all Japanese patients receiving chemotherapy received a subsequent anticancer therapy. Of patients in the overall Japanese population who discontinued afatinib, 43/48 patients (89.6%) received a new anticancer therapy, with 77.1% receiving chemotherapy (Table S1).

Safety. An overall summary of AEs is shown in Table S2. The most common treatment-related AEs were diarrhea, rash/acne, nail effects, and stomatitis with afatinib and nausea, decreased appetite, neutropenia, and leukopenia with cisplatin/pemetrexed. Drug-related AEs of >grade 3 occurred in 37 patients (68.5%) in the afatinib group and 19 (67.9%) in the cisplatin/pemetrexed group (Table 3).

Adverse events leading to dose reduction occurred in 41 (75.9%) afatinib-treated Japanese patients and five (17.9%) chemotherapy-treated patients (Table S2). The most common AEs leading to afatinib dose reduction were nail effects ($n = 17$; 31.5%), rash/acne ($n = 15$; 27.8%), and diarrhea ($n = 12$; 22.2%). Ten patients (18.5%) receiving afatinib and seven patients (25.0%) receiving chemotherapy had an AE leading to discontinuation of study treatment. No treatment-related discontinuations with afatinib were due to an AE of diarrhea or rash/acne (Table S3).

Table 2. Efficacy of afatinib versus cisplatin + pemetrexed in the overall Japanese population and in subgroups based on *EGFR* mutation category (common mutations, L858R mutations and Del19 mutations)

	Overall Japanese population		Japanese patients with common mutations		Japanese patients with Del19 mutation		Japanese patients with L858R mutation		Overall LUX-Lung 3 population[23,26]	
	Afatinib	CT	Afatinib	CT	Afatinib	CT	Afatinib	CT	Afatinib	CT
Patients, *n* (%)	54	29	50	27	23	16	27	11	230	115
Data cut-off: February 2012										
Median PFS, months (95% CI)	13.8 (11.0–19.1)	6.9 (3.1–8.8)	13.8 (12.7–19.1)	6.9 (2.8–8.3)	16.4 (11.0–NE)	3.1 (2.6–8.2)	13.7 (8.1–19.1)	8.3 (2.4–13.7)	11.1 (9.6–13.6)	6.9 (5.4–8.3)
HR (95% CI); *P*-value	0.38 (0.20–0.70); 0.0014		0.28 (0.15–0.52); <0.0001		0.16 (0.06–0.39); <0.0001		0.50 (0.20–1.25); 0.1309		0.58 (0.43–0.78); 0.0004	
Objective response, *n* (%)	33 (61.1)	6 (20.7)	32 (64.0)	6 (22.2)	16 (69.6)	4 (25.0)	16 (59.3)	2 (18.2)	129 (56.1)	26 (22.6)
OR (95% CI); *P*-value	6.52 (2.22–19.14); 0.0007		6.22 (2.12–18.24); 0.0009		6.86 (1.63–28.90); 0.0087		6.55 (1.18–36.32); 0.0317		4.66 (2.77–7.83); <0.0001	
Disease control, *n* (%)	52 (96.3)	26 (89.7)	50 (100.0)	24 (88.9)	23 (100.0)	14 (87.5)	27 (100.0)	10 (90.9)	207 (90.0)	93 (80.9)
OR (95% CI); *P*-value	3.10 (0.46–20.93); 0.2462		NE		NE		NE		2.14 (1.13–4.04); 0.0189	
Data cut-off: November 2013										
Median OS, months (95% CI)	46.9 (35.1–NE)	35.8 (28.6–NE)	46.9 (35.3–NE)	35.0 (28.2–NE)	46.9 (35.1–46.9)	31.5 (14.0–NE)	41.7 (24.2–NE)	40.3 (28.2–NE)	28.2 (24.6–33.6)	28.2 (20.7–33.2)
HR (95% CI); *P*-value	0.75 (0.40–1.43); 0.3791		0.57 (0.29–1.12); 0.0966		0.34 (0.13–0.87); 0.0181		1.13 (0.40–3.21); 0.8212		0.88 (0.66–1.17); 0.3850	

CI, confidence interval; CT, chemotherapy; HR, hazard ratio; NE, not estimable; OR, odds ratio; OS, overall survival; PFS, progression-free survival.

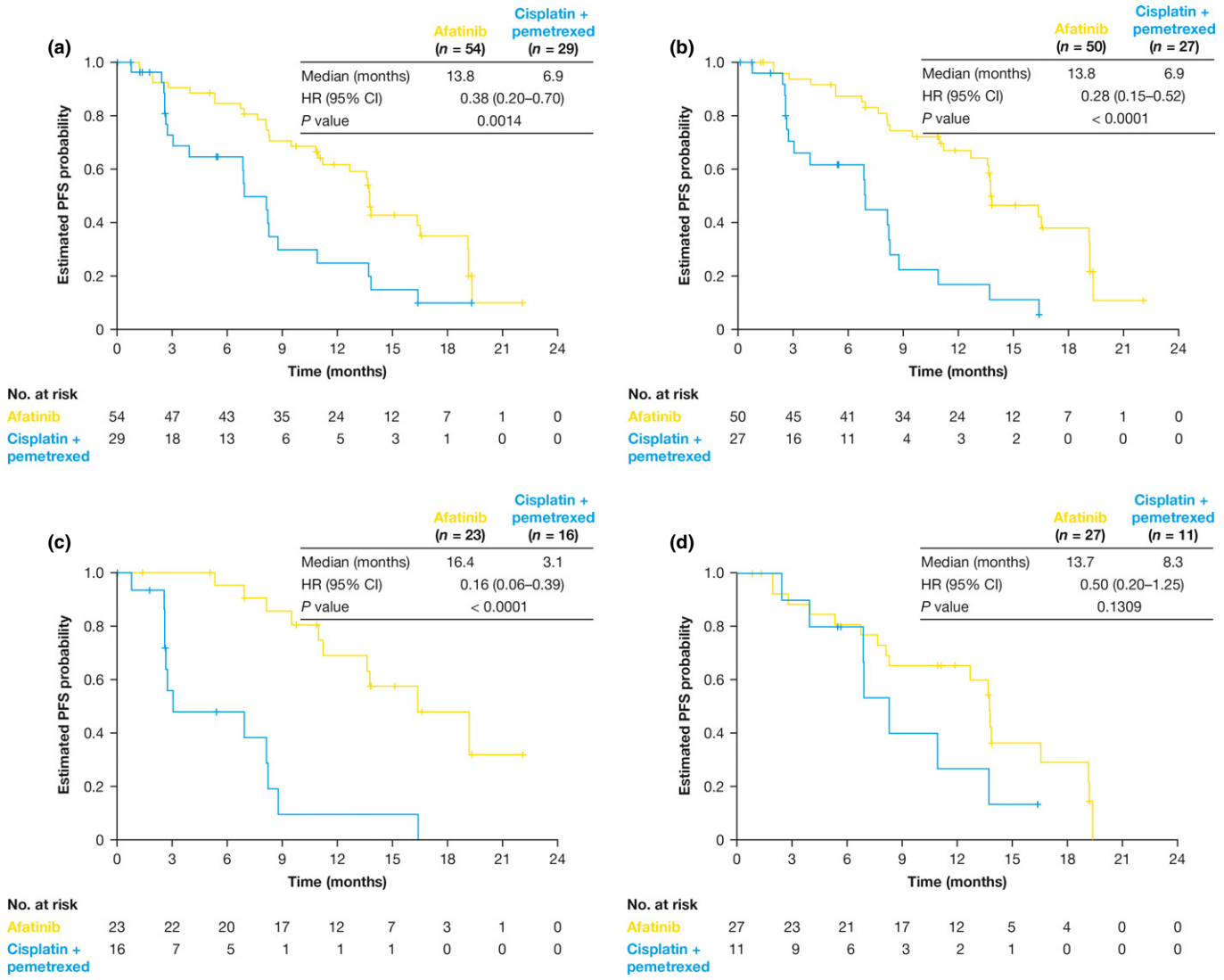

Fig. 1. PFS for afatinib versus cisplatin/pemetrexed according to independent review. (a) All randomized Japanese patients. (b) Japanese patients with common (Del19/L858R) mutations. (c) Japanese patients with Del19 mutation only. (d) Japanese patients with L858R mutation only. CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

The incidence of diarrhea and rash was significantly higher in Japanese patients receiving afatinib versus those receiving cisplatin/pemetrexed (Table S3). Time to first onset of diarrhea or rash/acne was 1–14 days after starting afatinib for most patients (Table S3). AEs of diarrhea and rash/acne were managed through standard therapy and dose reductions. Dose reductions enabled patients to remain on afatinib for as long as they experienced clinical benefit (Fig. 3).

Two Japanese patients receiving afatinib experienced drug-related interstitial lung disease (ILD) or an ILD-like event, and afatinib was discontinued. A patient with grade 3 interstitial pneumonia recovered after a course of antibiotics and corticosteroids, while another case (grade 1 ILD) resolved without supportive treatment.

There were no on-treatment deaths in either group. Ten (18.5%) afatinib-treated patients and four (14.3%) cisplatin /pemetrexed-treated patients experienced serious AEs (six [11.1%] and three [10.7%], respectively, were considered treatment-related).

Discussion

Afatinib significantly improved PFS and objective response versus cisplatin/pemetrexed in Japanese patients with *EGFR* mutation-positive NSCLC. The benefits of afatinib on PFS and objective response were observed for patients harboring either type of common *EGFR* mutation (Del19 or L8589R). Based on these data, afatinib was approved for the treatment of *EGFR* mutation-positive inoperable or recurrent NSCLC in Japan. There was a trend towards an improvement in OS with afatinib versus cisplatin/pemetrexed in the overall Japanese population and those with common mutations. OS was significantly improved in Japanese patients with Del19 mutation, while in patients with L858R mutation OS was similar between treatment arms.

LUX-Lung 3 is one of the largest prospective randomized trials conducted in patients with advanced *EGFR* mutation-positive NSCLC and the Japanese subgroup was one of the largest country groups included. Analysis is limited by the fact

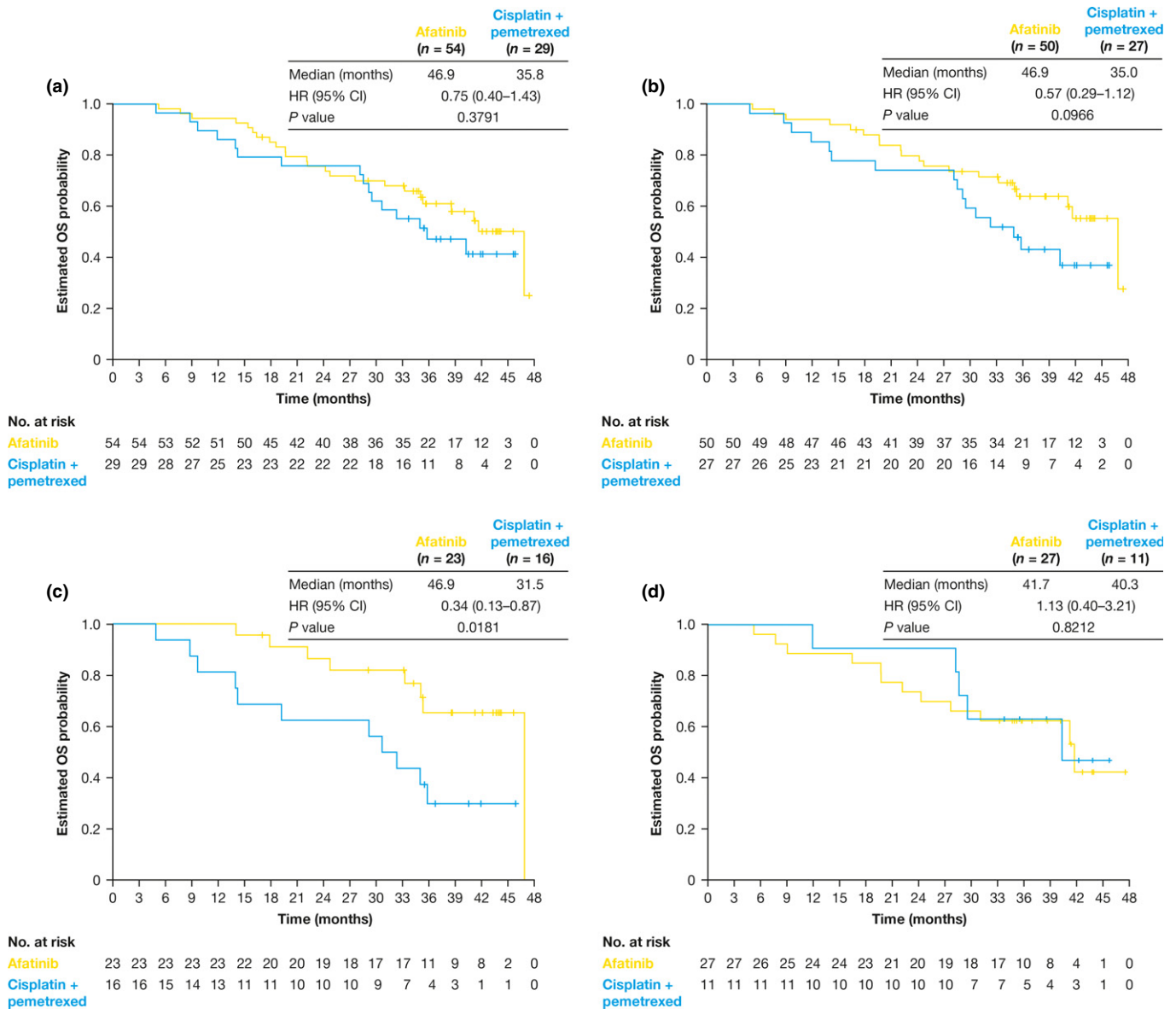

Fig. 2. OS for afatinib versus cisplatin/pemetrexed. (a) All randomized Japanese patients. (b) Japanese patients with common (Del19/L858R) mutations. (c) Japanese patients with Del19 mutation only. (d) Japanese patients with L858R mutation only. CI, confidence interval; HR, hazard ratio; OS, overall survival.

that this is a subgroup analysis with smaller patient numbers and, therefore, less power to identify potential differences between treatment groups.

Nevertheless, the clinical benefits of afatinib over chemotherapy observed in Japanese patients were consistent with the results observed in the global population of the LUX-Lung 3 trial.[23,26] However, numerically longer median OS in both treatment arms was observed in Japanese patients versus the LUX-Lung 3 population as a whole (Table 2).[23,26] There could be a number of reasons for this improved efficacy, one being that Japan has an effective and easily accessible health system versus countries which do not have universal reimbursement policies.[29] This is reflected in the subsequent therapies that Japanese patients received; for example, all chemotherapy-treated patients with common mutations received an EGFR TKI following disease progression and approximately 90% of afatinib-treated patients received subsequent therapy after discontinuing study treatment, which were covered by health insurances (Table S1). Despite the high rate of subsequent EGFR TKI therapy received by patients in the cisplatin/pemetrexed arm following discontinuation of study treatment, afatinib was still associated with numerically-improved OS versus chemotherapy in the overall Japanese population (46.9 *vs* 35.8 months, respectively) and significantly improved OS in those with Del19 mutations (46.9 *vs* 31.5 months, respectively).

Improvements in PFS versus chemotherapy in Japanese patients have been observed with erlotinib and gefitinib, although median PFS was numerically longer with afatinib (13.8 months) in the current study. In a phase III trial (NEJ002) conducted in Japan, patients with *EGFR* mutation-positive metastatic NSCLC were randomized to gefitinib or carboplatin /paclitaxel. In a planned interim analysis of the first 200 patients median PFS was 10.8 months with first-line gefitinib versus 5.4 months with carboplatin/paclitaxel.[6] Similarly, in a phase III trial (WJTOG3405) with 177 chemotherapy-naïve Japanese

Table 3. Most common treatment-related AEs with afatinib and cisplatin + pemetrexed with incidence of ≥20% (maximum grade of AE shown)

	Afatinib (n = 54)					Cisplatin + pemetrexed (n = 28)				
AE	All grades	Grade 1	Grade 2	Grade 3	Grade 4	All grades	Grade 1	Grade 2	Grade 3	Grade 4
Total	54 (100.0)	0 (0)	17 (31.5)	36 (66.7)	1 (1.9)	28 (100.0)	0 (0)	9 (32.1)	15 (53.6)	4 (14.3)
Symptomatic AEs										
Diarrhea	54 (100.0)	21 (38.9)	21 (38.9)	12 (22.2)	0 (0)	4 (14.3)	3 (10.7)	1 (3.6)	0 (0)	0 (0)
Rash/acne*	54 (100.0)	12 (22.2)	31 (57.4)	11 (20.4)	0 (0)	3 (10.7)	2 (7.1)	1 (3.6)	0 (0)	0 (0)
Nail effect*	50 (92.6)	7 (13.0)	29 (53.7)	14 (25.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Stomatitis*	49 (90.7)	30 (55.6)	15 (27.8)	4 (7.4)	0 (0)	7 (25.0)	7 (25.0)	0 (0)	0 (0)	0 (0)
Dry skin	25 (46.3)	13 (24.1)	12 (22.2)	0 (0)	0 (0)	1 (3.6)	1 (3.6)	0 (0)	0 (0)	0 (0)
Ocular effect*	23 (42.6)	13 (24.1)	9 (16.7)	1 (1.9)	0 (0)	2 (7.1)	1 (3.6)	1 (3.6)	0 (0)	0 (0)
Decreased appetite	22 (40.7)	12 (22.2)	6 (11.1)	4 (7.4)	0 (0)	22 (78.6)	13 (46.4)	8 (28.6)	1 (3.6)	0 (0)
Lip effect*	20 (37.0)	10 (18.5)	10 (18.5)	0 (0)	0 (0)	2 (7.1)	2 (7.1)	0 (0)	0 (0)	0 (0)
Fatigue*	14 (25.9)	10 (18.5)	2 (3.7)	2 (3.7)	0 (0)	14 (50.0)	10 (35.7)	3 (10.7)	1 (3.6)	0 (0)
Nausea	13 (24.1)	8 (14.8)	4 (7.4)	1 (1.9)	0 (0)	25 (89.3)	13 (46.4)	11 (39.3)	1 (3.6)	0 (0)
Weight decreased	13 (24.1)	4 (7.4)	9 (16.7)	0 (0)	0 (0)	3 (10.7)	2 (7.1)	1 (3.6)	0 (0)	0 (0)
Epistaxis	12 (22.2)	11 (20.4)	1 (1.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pruritus	11 (20.4)	6 (11.1)	5 (9.3)	0 (0)	0 (0)	1 (3.6)	1 (3.6)	0 (0)	0 (0)	0 (0)
Vomiting	11 (20.4)	8 (14.8)	3 (5.6)	0 (0)	0 (0)	12 (42.9)	8 (28.6)	3 (10.7)	1 (3.6)	0 (0)
Alopecia	7 (13.0)	7 (13.0)	0 (0)	0 (0)	0 (0)	6 (21.4)	6 (21.4)	0 (0)	0 (0)	0 (0)
Constipation	3 (5.6)	2 (3.7)	1 (1.9)	0 (0)	0 (0)	12 (42.9)	10 (35.7)	2 (7.1)	0 (0)	0 (0)
Headache	3 (5.6)	3 (5.6)	0 (0)	0 (0)	0 (0)	7 (25.0)	7 (25.0)	0 (0)	0 (0)	0 (0)
Hiccups	1 (1.9)	1 (1.9)	0 (0)	0 (0)	0 (0)	7 (25.0)	5 (17.9)	2 (7.1)	0 (0)	0 (0)
Edema	1 (1.9)	1 (1.9)	0 (0)	0 (0)	0 (0)	7 (25.0)	7 (25.0)	0 (0)	0 (0)	0 (0)
Laboratory or hematologic AEs										
Leukopenia	3 (5.6)	0 (0)	2 (3.7)	1 (1.9)	0 (0)	16 (57.1)	2 (7.1)	7 (25.0)	7 (25.0)	0 (0)
Hemoglobin decreased	2 (3.7)	1 (1.9)	1 (1.9)	0 (0)	0 (0)	9 (32.1)	1 (3.6)	5 (17.9)	2 (7.1)	1 (3.6)
Anemia	1 (1.9)	0 (0)	1 (1.9)	0 (0)	0 (0)	10 (35.7)	5 (17.9)	3 (10.7)	2 (7.1)	0 (0)
Blood creatinine increased	1 (1.9)	1 (1.9)	0 (0)	0 (0)	0 (0)	6 (21.4)	3 (10.7)	3 (10.7)	0 (0)	0 (0)
Neutropenia	1 (1.9)	0 (0)	0 (0)	1 (1.9)	0 (0)	20 (71.4)	1 (3.6)	5 (17.9)	11 (39.3)	3 (10.7)
Thrombocytopenia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (21.4)	3 (10.7)	2 (7.1)	1 (3.6)	0 (0)

*Grouped term. AEs, adverse events.

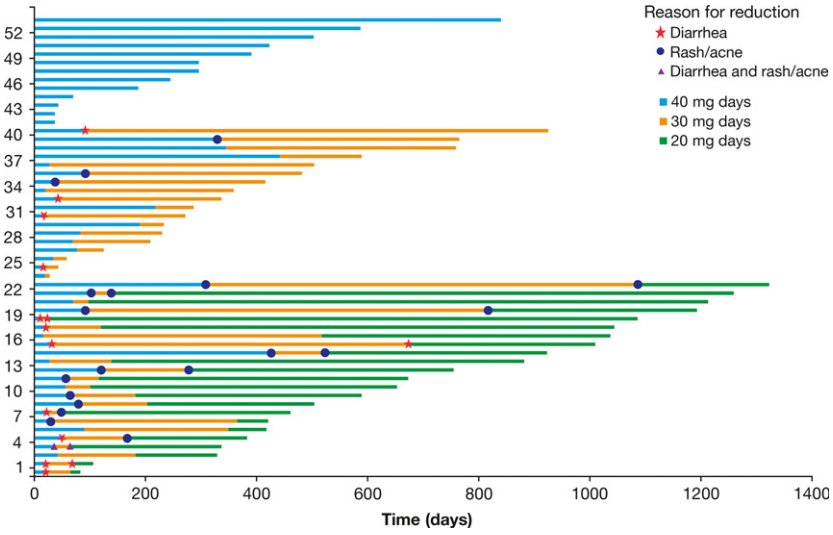

Fig. 3. Treatment duration and afatinib dosage for Japanese patients in the overall population. Stars represent dose reductions due to diarrhea; circles represent dose reductions due to rash/acne; and triangles represent dose reductions due to rash/acne and diarrhea.

patients with advanced NSCLC or postoperative recurrence with common (Del19/L858R) mutations, gefitinib was associated with median PFS of 9.2 months.[7] Erlotinib, as first-line treatment of 102 Japanese patients with tumors with common *EGFR* mutations was associated with median PFS of 11.8 months in a single-arm, phase II trial (JO22903).[30] Despite the PFS benefits reported for reversible EGFR TKIs over chemotherapy, improvements in OS have not been observed. Median survival for all 228 patients in the NEJ002 trial was 27.7 months for gefitinib versus 26.6 months for carboplatin/paclitaxel.[12] In the

WJTOG3405 trial, median survival was 34.8 months with gefitinib versus 37.3 months for cisplatin/docetaxel.[16]

A tendency towards improved efficacy outcomes with reversible EGFR TKIs in patients whose tumors harbor Del19 mutations, versus those with L858R mutations, has been previously observed. Retrospective analysis of five clinical trials with patients receiving first-line erlotinib or gefitinib for NSCLC illustrated that Del19 mutations were associated with improved outcomes versus L858R mutations.[31] Although this registry was conducted using mainly Western populations, our results in a Japanese subgroup support this differential benefit between patients with Del19 mutation and L858R mutation. Similarly, in the JO22903 trial of erlotinib in Japanese patients, PFS was longer in patients with Del19 mutations than those with L858R mutations.[30] The difference in outcomes between Del19 and L858R requires further research; however, preclinical studies suggest that Del19 and L858R mutations have different biological properties, with patterns of *EGFR* amplification and EGFR autophosphorylation differing between cell lines containing these mutations.[32,33]

Previous studies have not suggested substantial differences in efficacy with chemotherapy between mutation types (median PFS ranged from 4.3–5.6 months with chemotherapy in Del19 patients and 5.8–6.8 months in those with L858R mutations).[8,17,18] While comparison of the median values suggests that patients with Del19 mutations in our study had a poorer response to chemotherapy than those with L858R mutations, this may be partly due to the nature of a subgroup analysis. As noted earlier, this is a limitation of our study and results in relatively small patient numbers within the Del19 and L858R groups, wherein individual patient data can have a large impact on the median values. This is exemplified by the wide CIs observed for the median PFS and OS values in the Del19 and L858R subgroups (Table 2). Rather, the HRs and supporting Kaplan–Meier curves provide a more reliable summary of the PFS/OS data across the entire observation period. It should also be noted that differences in OS across the mutation groups for chemotherapy may be affected by multiple post-progression therapies. Overall, results in Japanese patients in this analysis, are generally consistent with those observed in the overall global population of LUX-Lung 3, and the similarly-designed LUX-Lung 6 trial,[23,24,26] supporting the conclusion that afatinib significantly improves PFS versus chemotherapy in Japanese patients with *EGFR* mutation-positive lung cancer, and OS in Del19 patients.

The most common treatment-related AEs (all-grade) with afatinib in the Japanese population were diarrhea (100.0%), rash/acne (100.0%), nail effects (92.6%), and stomatitis (90.7%). This is generally consistent with the safety profile observed in the overall LUX-Lung 3 trial, although the frequency of AEs was lower in the overall population (diarrhea, 95.2%; rash/acne, 89.1%; stomatitis/mucositis 72.1% and nail effects, 61.1%).[23] Although grade 3 diarrhea and rash/acne occurred in Japanese patients receiving afatinib, these AEs did not lead to discontinuation. Time to first onset of diarrhea or rash/acne was within 14 days after starting afatinib for most patients; as such, early preventative treatments are essential. Of note, there was a local protocol amendment for diarrhea management in Japan, with grade 2 diarrhea allowed to persist for 7 days (rather than 2 days) before dose reduction. Compared with the overall LUX-Lung 3 population, Japanese patients were more likely to have an AE leading to dose reduction (57.2% *vs* 75.9%, respectively). As such, there was greater use of afatinib 20 mg in Japanese patients than in the overall population. Dose reductions with afatinib enabled patients to remain on treatment while they were experiencing clinical benefit. Among three patients who reported drug-related ILD-like events in LUX-Lung 3,[23] two were Japanese. ILD has previously been observed with the reversible EGFR TKIs in Japanese patients. With all patients, careful observation is required to avoid the serious clinical course of ILD.

In conclusion, first-line treatment with afatinib was associated with significant PFS and tumor response improvements versus cisplatin/pemetrexed in Japanese patients with advanced *EGFR* mutation-positive NSCLC. Although all patients in the cisplatin/pemetrexed arm received subsequent anticancer therapy following discontinuation of study treatment, a trend towards improved OS with afatinib was observed in the overall Japanese population, with significant improvements in median OS (>15 months) seen in those with tumors harboring Del19 mutation (46.9 *vs* 31.5 months) and similar OS observed in patients with the L858R mutation (41.7 *vs* 40.3 months). Safety of afatinib in Japanese patients was consistent with the overall population; AEs were manageable with standard therapy and dose reductions. Based on these findings, afatinib should be the preferred first-line treatment for Japanese patients with advanced NSCLC harboring the *EGFR* Del19 mutation and an option for patients with the L858R mutation.

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Abbreviations

AE	adverse event
CI	confidence interval
CR	complete response
CT	chemotherapy
CTC	common terminology criteria
disc	discontinuation

ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	epidermal growth factor receptor
HER2/ErbB2	human epidermal growth factor receptor 2
ILD	interstitial lung disease
NSCLC	non-small cell lung cancer
OR	odds ratio
OS	overall survival
PFS	progression-free survival
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
TKI	tyrosine kinase inhibitors
yrs	years

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Supporting Information

Additional supporting information may be found in the online version of this article:

Fig. S1. Patient disposition at the time of OS analysis (data cut-off: November 2013). OS, overall survival.

Fig. S2. Forest plot of subgroups of Japanese patients showing (a) PFS by independent review and (b) OS. ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; yrs, years.

Table S1. Summary of subsequent anticancer therapy after discontinuing study treatment (data cut-off: November 2013) *Patients received erlotinib or gefitinib in a combination regimen. EGFR, epidermal growth factor receptor; disc, discontinuation; TKI, tyrosine kinase inhibitor.

Table S2. Overall summary of AEs among Japanese patients receiving afatinib or cisplatin + pemetrexed (data cut-off November 2013) AEs, adverse events; CTC, common terminology criteria.

Table S3. Frequency of diarrhea and rash/acne (data cut-off: November 2013) *Number of patients with initial onset within the interval (cumulative Kaplan–Meier estimate % of AE onset by interval end). AE, adverse event; CI, confidence interval; CTC, common terminology criteria; HR, hazard ratio.