



# Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring *EGFR* mutations (LUX-Lung 6): an open-label, randomised phase 3 trial

Yi-Long Wu, Caicun Zhou, Cheng-Ping Hu, Jifeng Feng, Shun Lu, Yunchao Huang, Wei Li, Mei Hou, Jian Hua Shi, Kye Young Lee, Chong-Rui Xu, Dan Massey, Miyoung Kim, Yang Shi, Sarayut L Geater

## Summary

**Background** Afatinib—an oral irreversible ErbB family blocker—improves progression-free survival compared with pemetrexed and cisplatin for first-line treatment of patients with *EGFR* mutation-positive advanced non-small-cell lung cancer (NSCLC). We compared afatinib with gemcitabine and cisplatin—a chemotherapy regimen widely used in Asia—for first-line treatment of Asian patients with *EGFR* mutation-positive advanced NSCLC.

**Methods** This open-label, randomised phase 3 trial was done at 36 centres in China, Thailand, and South Korea. After central testing for *EGFR* mutations, treatment-naïve patients (stage IIIB or IV cancer [American Joint Committee on Cancer version 6], performance status 0–1) were randomly assigned (2:1) to receive either oral afatinib (40 mg per day) or intravenous gemcitabine 1000 mg/m<sup>2</sup> on day 1 and day 8 plus cisplatin 75 mg/m<sup>2</sup> on day 1 of a 3-week schedule for up to six cycles. Randomisation was done centrally with a random number-generating system and an interactive internet and voice-response system. Randomisation was stratified by *EGFR* mutation (Leu858Arg, exon 19 deletions, or other; block size three). Clinicians and patients were not masked to treatment assignment, but the independent central imaging review group were. Treatment continued until disease progression, intolerable toxic effects, or withdrawal of consent. The primary endpoint was progression-free survival assessed by independent central review (intention-to-treat population). This study is registered with ClinicalTrials.gov, NCT01121393.

**Findings** 910 patients were screened and 364 were randomly assigned (242 to afatinib, 122 to gemcitabine and cisplatin). Median progression-free survival was significantly longer in the afatinib group (11·0 months, 95% CI 9·7–13·7) than in the gemcitabine and cisplatin group (5·6 months, 5·1–6·7; hazard ratio 0·28, 95% CI 0·20–0·39; *p*<0·0001). The most common treatment-related grade 3 or 4 adverse events in the afatinib group were rash or acne (35 [14·6%] of 239 patients), diarrhoea (13 [5·4%]), and stomatitis or mucositis (13 [5·4%]), compared with neutropenia (30 [26·5%] of 113 patients), vomiting (22 [19·5%]), and leucopenia (17 [15·0%]) in the gemcitabine and cisplatin group. Treatment-related serious adverse events occurred in 15 (6·3%) patients in the afatinib group and nine (8·0%) patients in the gemcitabine and cisplatin group.

**Interpretation** First-line afatinib significantly improves progression-free survival with a tolerable and manageable safety profile in Asian patients with *EGFR* mutation-positive advanced lung NSCLC. Afatinib should be considered as a first-line treatment option for this patient population.

**Funding** Boehringer Ingelheim.

## Introduction

In the past, four chemotherapeutic regimens—cisplatin and gemcitabine, cisplatin and docetaxel, carboplatin and paclitaxel, and cisplatin and paclitaxel—have been used for treatment of advanced non-small-cell lung cancer (NSCLC), affording a median overall survival of around 8–10 months.<sup>1–3</sup> More recently, the identification of lung tumours harbouring mutations in *EGFR* has led to a focus on targeted treatments—*EGFR* tyrosine kinase inhibitors<sup>4</sup>—resulting in median overall survival of more than 2 years for patients with *EGFR* mutation-positive NSCLC.<sup>5</sup> However, despite these advances, there remains considerable room for improvement.

Afatinib is a novel, irreversible ErbB family blocker that selectively and potently blocks signalling from ErbB family receptors (*EGFR*, *HER2* [ErbB2], and *ErbB4*)<sup>6</sup> and transphosphorylation of *ErbB3*.<sup>7</sup> Unlike reversible *EGFR* tyrosine kinase inhibitors (erlotinib and gefitinib), afatinib covalently binds to proteins of the ErbB receptor network, and irreversibly and completely abrogates signalling, which causes a sustained and broad-spectrum anti-mitogenic activity. In preclinical studies, afatinib was highly potent, with 50% inhibitory concentrations of 0·5 nmol/L for *EGFR*, 14 nmol/L for *HER2*, and 1 nmol/L for *ErbB4*,<sup>6–8</sup> compared with 0·1 μmol/L for gefitinib against *EGFR*,<sup>5</sup> and 2 nmol/L for erlotinib against *EGFR*.<sup>9</sup> Afatinib has also shown greater anticancer activity than

*Lancet Oncol* 2014

Published Online

January 15, 2014

[http://dx.doi.org/10.1016/S1470-2045\(13\)70604-1](http://dx.doi.org/10.1016/S1470-2045(13)70604-1)

See Online/Comment

[http://dx.doi.org/10.1016/S1470-2045\(14\)70002-6](http://dx.doi.org/10.1016/S1470-2045(14)70002-6)

Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China

(Prof Y-L Wu MD, C-R Xu MD); Shanghai Pulmonary Hospital, Yangpu District, Shanghai, China (Prof C Zhou MD);

Department of Pulmonary Medicine, Xiangya Hospital, Central South University, Changsha, China

(Prof C-P Hu MD); Department of Internal Medicine, Jiangsu Provincial Tumor Hospital, Nanjing, Jiangsu, China

(Prof J Feng MD); Shanghai Lung Tumor Clinical Medical Center, Shanghai Chest

Hospital, Shanghai Jiao Tong University, Shanghai, China

(Prof S Lu MD); Yunnan Tumor Hospital (The Third Affiliated Hospital of Kunming Medical University), Kunming, Yunnan Province, China

(Prof Y Huang MD); Cancer Center, First Hospital of Jilin University, Changchun, China

(Prof W Li PhD); West China Hospital, Sichuan University, Chengdu, Sichuan, China

(Prof M Hou MD); Lin Yi Tumor Hospital, Linyi, Shandong Province, China

(Prof J Hua Shi MD); Konkuk University Medical Center, Seoul, South Korea

(Prof K Young Lee MD);

Boehringer Ingelheim, Bracknell, UK (D Massey MSc);

Boehringer Ingelheim Korea, Seoul, South Korea

(M Kim MD);

Boehringer Ingelheim International Trading, Shanghai, China

(Y Shi MD); and Division of Respiratory and Respiratory Critical Care Medicine, Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand (S L Geater MD)

Correspondence to: Prof Yi-Long Wu, Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China [syylwu@live.cn](mailto:syylwu@live.cn)

have reversible EGFR tyrosine kinase inhibitors, both in EGFR tyrosine kinase inhibitor-sensitive and inhibitor-resistant cell lines and xenograft models of NSCLC.<sup>6</sup>

Several randomised studies<sup>10–15</sup> support the use of EGFR tyrosine kinase inhibitors as the standard first-line treatment for patients with activating *EGFR* mutations, showing high tumour response rates and long progression-free survival compared with chemotherapy. Most of these trials were done in Asian populations because *EGFR* mutations are more common in Asian patients (47%) with lung adenocarcinoma than in non-Asian patients (13–15%).<sup>16</sup> LUX-Lung 3 was the first global trial to compare an irreversible ErbB family blocker (afatinib) with chemotherapy and the first to use the recently established best-in-class chemotherapy treatment—pemetrexed and cisplatin—as a comparator.<sup>17</sup> The investigators reported that patients taking afatinib had significantly longer progression-free survival than patients taking the chemotherapy regimen. As a

companion trial to LUX-Lung 3, we did LUX-Lung 6 to compare afatinib with gemcitabine and cisplatin in Asian patients. Gemcitabine and cisplatin is a widely used and approved first-line chemotherapeutic regimen in Asian countries (eg, China) where pemetrexed and cisplatin has not been approved for first-line treatment of NSCLC.

## Methods

### Study design and patients

We did this randomised, open-label, phase 3 trial at 36 centres in China, Thailand, and South Korea. Eligible patients had pathologically confirmed and previously untreated stage IIIB (with pleural effusion) or IV lung adenocarcinoma according to American Joint Committee on Cancer criteria,<sup>18</sup> an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST),<sup>19</sup> and adequate organ function. Tumour tissue had to be *EGFR* mutation-positive at the screening stage, as assessed at a central laboratory with a validated test kit (Therascreen *EGFR* 29; Qiagen, Manchester, UK). The test enabled us to identify 29 mutations, including common (Leu858Arg, exon 19 deletions) and other mutations (see appendix for full eligibility criteria and *EGFR* mutations tested).

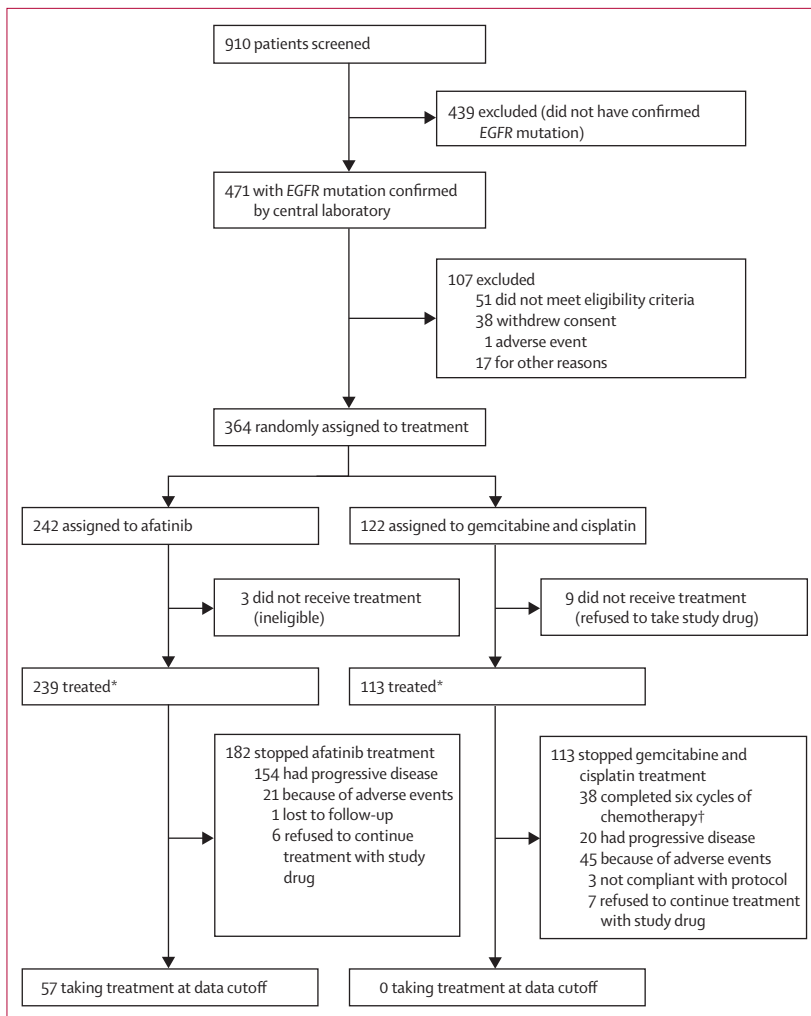
All patients provided written, informed consent for participation in the study and provision of tumour samples. An independent data and safety monitoring committee monitored safety throughout the trial. The study was done in accordance with the Declaration of Helsinki, International Conference on Harmonisation good clinical practice, local laws, and applicable regulatory requirements. The study was approved by the institutional review board or independent ethics committee of each centre.

### Randomisation and masking

Eligible patients were randomly allocated to receive afatinib or gemcitabine and cisplatin (2:1), stratified by *EGFR* mutation (Leu858Arg, exon 19 deletions, or other). A block size of three was used and randomisation was done centrally with a validated random number-generating system at Boehringer Ingelheim, verified by a trial-independent statistician, and implemented centrally via an interactive internet and voice-response system. Access to the randomisation code was supervised by the clinical trial support group; those directly involved in the conduct and analysis of the trial had no access to the randomisation schedule.

Clinicians and patients were not masked to treatment assignment. The study investigators who did assessments of patient-reported outcomes and safety, along with supportive assessments of tumour response (used for sensitivity analyses), were not masked to treatment assignment. The independent central imaging review group who assessed tumour response (used for primary

See Online for appendix



**Figure 1: Trial profile**

\*Received at least one dose of study drug (afatinib or gemcitabine and cisplatin). †Including patients who had disease progression after six cycles of treatment.

and key secondary efficacy analyses) were masked to treatment assignment. During the study, employees of the sponsor were masked to treatment assignment until the database was locked and ready for statistical analyses.

### Procedures

Pre-treatment testing of fresh or archived tumour samples for *EGFR* mutations was done by standardised allele-specific quantitative real-time PCR at central laboratories. Patients with inadequate tumour tissue were not entered into the screening phase. Patients received either oral continuous afatinib (40 mg per day) or intravenous gemcitabine (1000 mg/m<sup>2</sup>, on day 1 and day 8) plus cisplatin (75 mg/m<sup>2</sup>, on day 1), in a 3-week schedule until disease progression, intolerable toxic effects, or withdrawal of consent. Gemcitabine and cisplatin was given for a maximum of six cycles.

Adverse events were assessed throughout the study and documented with the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Severity of all adverse events was graded with these criteria. Regular physical (including assessment of symptoms) and laboratory assessments, as well as 12-lead electrocardiograms and echocardiogram or multigated acquisition scans, were also used to monitor safety.

Patients treated with afatinib 40 mg per day could have their dose increased to 50 mg per day from the second cycle to account for interpatient variability in afatinib exposure and to tailor dosing to individual tolerability. Dose escalation to 50 mg per day was allowed in the absence of predefined levels of toxic effects—ie, rash, diarrhoea, mucositis, or any other treatment-related adverse event greater than grade 1 in the first 21 days of treatment. As per protocol, if the patient had any grade 3 or higher treatment-related adverse event, prolonged grade 2 diarrhoea (≥48 h), grade 2 nausea or vomiting for 7 days or more consecutively despite appropriate supportive care, or grade 2 or more worsening renal function, afatinib was withheld for up to 14 days until the severity fell to grade 1 or less or to baseline levels. Afatinib could then be resumed at a lower dose (10 mg reductions to a minimum dose of 20 mg).

In the gemcitabine and cisplatin group, patients received six treatment courses unless they had disease progression or unacceptable adverse events, or if the patient or investigator requested permanent discontinuation of study drug. For patients who had adverse events related to gemcitabine and cisplatin, treatment was delayed or the dose was reduced (by 50% for non-haematological toxic effects or 75% for haematological toxic effects as judged by the treating physicians) on the basis of the patient's tolerability and abnormal laboratory measurements, in accordance with the guidance in the current summary of product characteristics and institutional guidelines.

Tumours were assessed by CT scan or MRI every 6 weeks for the first 48 weeks, then subsequently every

12 weeks until objective disease progression or start of further cancer treatment. Brain imaging and bone scans were done if clinically indicated. All scans were reviewed by an independent central imaging review group that consisted of radiologists and oncologists.

Patient-reported outcomes were assessed at randomisation and every 3 weeks until disease progression or start of new cancer treatment with the self-administered cancer-specific European Organisation for Research and Treatment of Cancer (EORTC) quality of life core questionnaire QLQ-C30,<sup>20</sup> and the lung cancer-specific module QLQ-LC13.<sup>21</sup>

### Outcomes

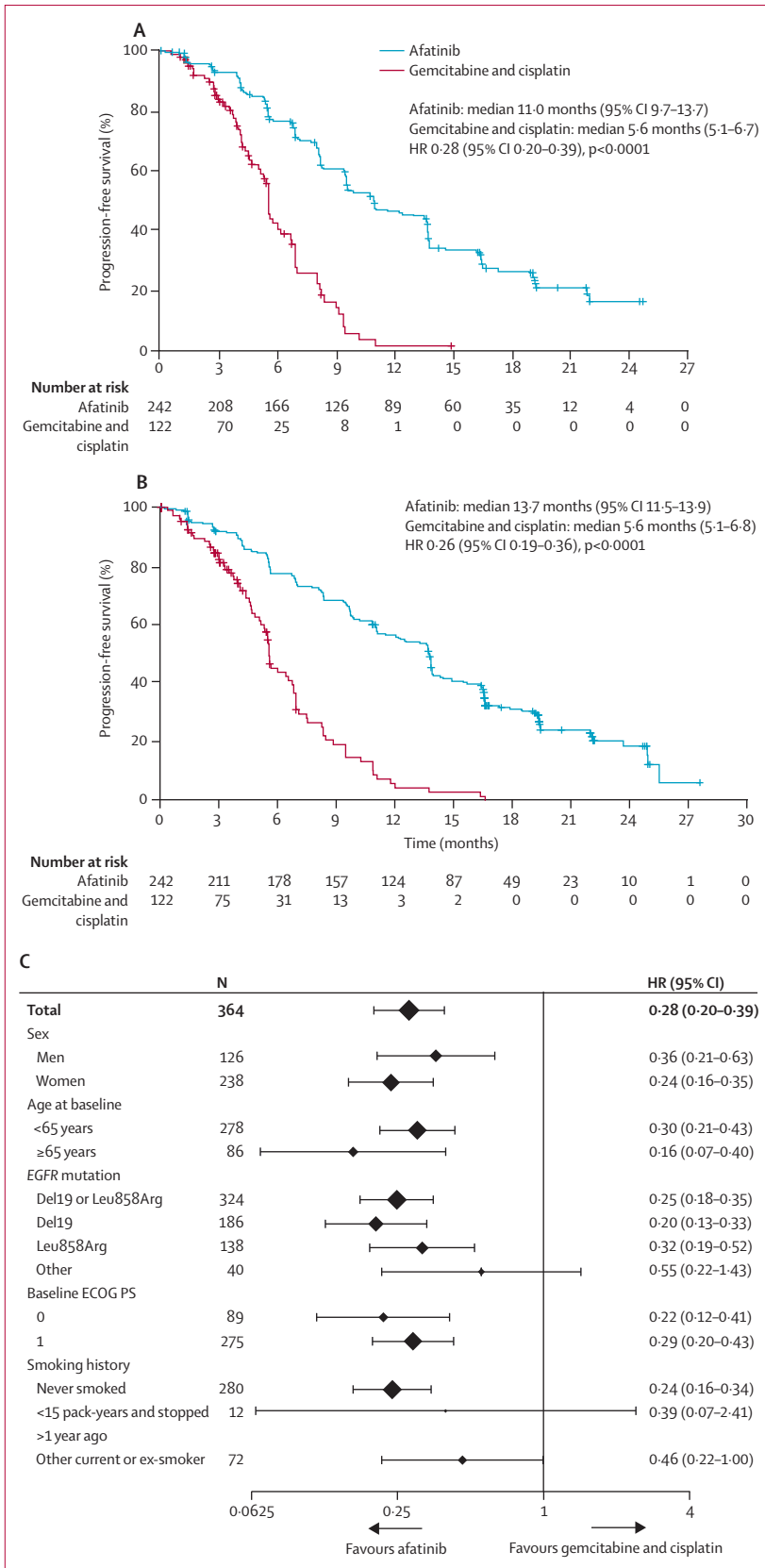
The primary endpoint was progression-free survival by independent review (time from randomisation to disease progression or death from any cause, whichever occurred first). Key secondary endpoints were the proportion of patients who achieved an overall response<sup>14</sup> (ie, the percentage of patients with complete response [CR] or partial response [PR]), the proportion of patients who achieved disease control (ie, the percentage of patients with the best overall response of CR, PR, or stable disease [SD]) both by independent review, and overall survival. Other secondary endpoints included duration of

For the adverse event criteria see [http://ctep.cancer.gov/protocoldevelopment/electronic\\_applications/docs/ctcae3.pdf](http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae3.pdf)

	Afatinib group (n=242)	Gemcitabine and cisplatin group (n=122)
Age (years)	58 (49–65)	58 (49–62)
Sex		
Men	87 (36.0%)	39 (32.0%)
Women	155 (64.0%)	83 (68.0%)
Ethnic origin		
South-east Asian	14 (5.8%)	10 (8.2%)
South Korean	11 (4.5%)	2 (1.6%)
Chinese	217 (89.7%)	110 (90.2%)
Smoking history		
Never smoked	181 (74.8%)	99 (81.1%)
Other current or ex-smoker	53 (21.9%)	19 (15.6%)
<15 pack-years and stopped >1 year ago	8 (3.3%)	4 (3.3%)
ECOG performance status		
0	48 (19.8%)	41 (33.6%)
1	194 (80.2%)	81 (66.4%)
Adenocarcinoma stage*		
IIIB with pleural or pericardial effusion	16 (6.6%)	6 (4.9%)
IV	226 (93.4%)	116 (95.1%)
EGFR mutation		
Common	..	..
Exon 19 deletions	124 (51.2%)	62 (50.8%)
Leu858Arg	92 (38.0%)	46 (37.7%)
Uncommon	26 (10.7%)	14 (11.5%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group.  
\*According to American Joint Committee on Cancer Edition 6 criteria.<sup>18</sup>

**Table 1: Patient demographics and baseline characteristics**



response and disease control, patient-reported outcomes, safety, and pharmacokinetics of afatinib.

**Statistical analysis**

We calculated that at least 330 patients would need to be enrolled with a minimum of 217 progression-free survival events to detect a 57% or greater improvement in progression-free survival with afatinib versus gemcitabine and cisplatin, with 90% power and a two-sided significance level of 5% with a log-rank test. This calculation assumed a hazard ratio (HR)<sup>5</sup> of 0.64 and an expected progression-free survival of 11 months with afatinib and 7 months with gemcitabine and cisplatin.<sup>12–15</sup> No interim analysis was planned.

Efficacy endpoints and patient characteristics were assessed for the intention-to-treat population, including all randomly assigned patients. Safety was assessed for all randomised patients who received at least one dose of study medication. Primary and key secondary endpoints were analysed following a hierarchical testing strategy to minimise the overall risk of type I error. Progression-free survival was compared between groups with a stratified (by mutation type) log-rank test. Cox proportional hazard models and Kaplan-Meier estimates were also used to compare progression-free survival between treatment groups. Logistic regression models were used to compare objective response rates and disease control rates between treatment groups. The primary analysis of overall survival is planned for when the data are sufficiently mature, after roughly 237 deaths.

We did pre-specified sensitivity analyses with investigator assessment (rather than independent assessment) of efficacy outcomes to test the robustness of the results. We also did pre-specified subgroup analyses by sex, age (<65 years vs ≥65 years), EGFR mutation type (exon 19 deletions vs Leu858Arg vs others), ECOG performance status (0 vs 1), and smoking history.

Pre-specified analysis of patient-reported outcomes focused on the NSCLC-related symptoms of cough (question 1 of QLQ-LC13), dyspnoea (questions 3–5 of QLQ-LC13 and question 8 of QLQ-C30), and pain (questions 9 and 19 of QLQ-C30 and questions 10–12 of QLQ-LC13). Three pre-specified analyses were done, comparing treatment groups in terms of: the distribution of patients whose symptoms had improved (≥10-point increase from baseline score), remained stable, or worsened (≥10-point decrease from baseline score); the time to deterioration of symptoms; and the mean difference in symptom scores over time (longitudinal analysis). Scales and items were scored according to the

**Figure 2: Progression-free survival for afatinib versus gemcitabine and cisplatin**

(A) According to independent review of all randomly assigned patients (primary endpoint). (B) According to investigator assessment for all randomly assigned patients. (C) Subgroup analysis of progression-free survival by independent review of all randomly assigned patients. HR=hazard ratio. ECOG PS=Eastern Cooperative Oncology Group performance status.

EORTC algorithm.<sup>22</sup> For each scale or item, a linear transformation was applied to standardise the raw score to a range of 0–100,<sup>22</sup> and a 10-point change was considered to be clinically meaningful.<sup>23</sup> The longitudinal analysis was done with a mixed-effects growth curve model, with the average profile over time for each endpoint described by a piecewise linear model (as reported previously<sup>24</sup>). Statistical analyses were done with SAS (version 9.2).

This study is registered with ClinicalTrials.gov, number NCT01121393.

### Role of the funding source

The sponsor provided the study drug, and was responsible for trial design, the collection, analysis, and interpretation of data, and coordination of article preparation. The corresponding author had full access to all the data and final responsibility to submit for publication.

### Results

910 patients were screened between April 27, 2010, and Nov 16, 2011. 364 eligible patients with *EGFR* mutations were assigned to afatinib (n=242) or gemcitabine and cisplatin (n=122; figure 1). Of these patients, 352 received at least one dose of study drug (figure 1). Data cutoff date for the primary analysis was Oct 29, 2012. The primary analysis was done after 221 progression events had occurred as assessed by independent review. At that time, 57 (15.7%) of 364 patients (all in the afatinib group) were still taking study treatment. Median duration of follow-up for progression-free survival was 16.6 months (IQR 4.7–19.4).

Baseline demographics and patient characteristics were generally balanced between treatment groups (table 1), with the exception of performance score: a higher proportion of patients had a score of 0 in the gemcitabine and cisplatin group than in the afatinib group (table 1). *EGFR* mutations were mainly exon 19 deletions and Leu858Arg mutations (table 1); uncommon mutation types were not balanced between treatment groups (appendix).

Median duration of treatment with afatinib was 398 days (IQR 173–537). At the end of treatment, 122 of 182 (67.0%) patients were still receiving the starting dose of afatinib 40 mg. After the first cycle of treatment, 38 of 239 (15.9%) patients in the afatinib group had their dose escalated to 50 mg per day. 67 of 239 (28.0%) patients in the afatinib group had their dose reduced to 30 mg, and ten (4.2%) had further reductions to 20 mg. Median duration of gemcitabine and cisplatin treatment was 89 days (IQR 60–119), with 40 of 113 (35.4%) patients completing six cycles. Overall, 62 of 101 (61.4%) patients receiving more than one cycle of gemcitabine and cisplatin required dose delay. The median number of treatment cycles with gemcitabine and cisplatin was four.

Median independently assessed progression-free survival was 11.0 months (95% CI 9.7–13.7) in the

	Independent review		Investigator review	
	Afatinib group (n=242)	Gemcitabine and cisplatin group (n=122)	Afatinib group (n=242)	Gemcitabine and cisplatin group (n=122)
Disease control	224 (92.6%)	93 (76.2%)	225 (93.0%)	92 (75.4%)
Objective response	162 (66.9%)	28 (23.0%)	180 (74.4%)	38 (31.1%)
Complete response	3 (1.2%)	0 (0%)	0 (0%)	0 (0%)
Partial response	159 (65.7%)	28 (23.0%)	180 (74.4%)	38 (31.1%)
Stable disease	52 (21.5%)	65 (53.3%)	45 (18.6%)	54 (44.3%)
Progressive disease	9 (3.7%)	6 (4.9%)	10 (4.1%)	10 (8.2%)
Not evaluable*	9 (3.7%)	23 (18.9%)	7 (2.9%)	20 (16.4%)

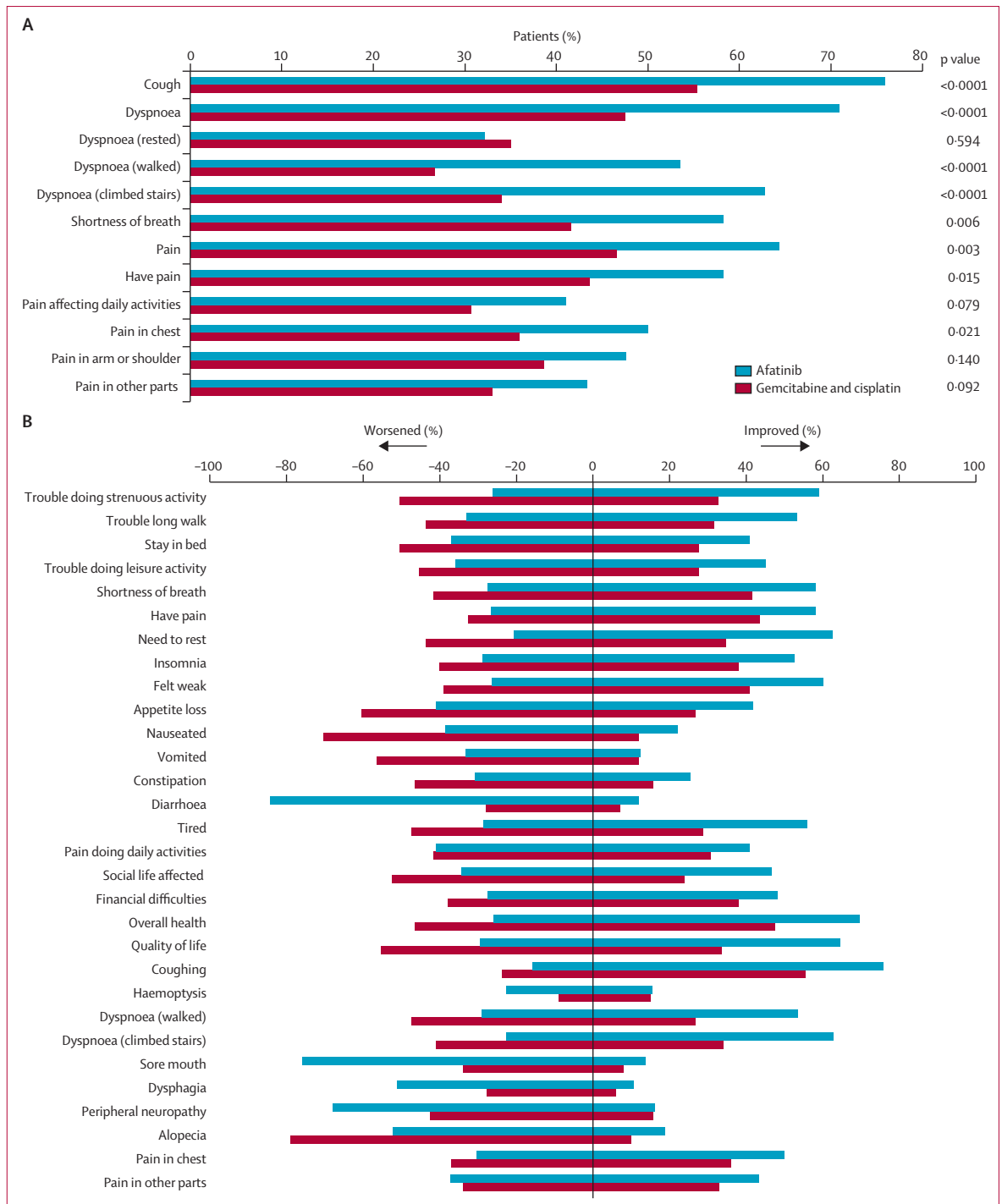
Data are n (%). \*Withdrawn with insufficient data for RECIST assessment after baseline. For the independent review, reasons for withdrawal were: withdrawal of consent (one in the afatinib group vs 11 in the gemcitabine and cisplatin group), adverse event (four vs seven), non-compliance with protocol (three vs one), and classed as progressive disease but insufficient imaging for central review (one vs four). For the investigator review, reasons for withdrawal were: withdrawal of consent (one vs 11), adverse event (three vs eight), and non-compliance with protocol (three vs one).

Table 2: Best overall tumour response

afatinib group versus 5.6 months (5.1–6.7) in the gemcitabine and cisplatin group (HR 0.28, 95% CI 0.20–0.39;  $p < 0.0001$ ; figure 2A). Investigator assessment gave much the same result: median progression-free survival was 13.7 months (95% CI 11.5–13.9) versus 5.6 months (5.1–6.8; HR 0.26, 95% CI 0.19–0.36;  $p < 0.0001$ ; figure 2B).

Progression-free survival was numerically longer in the afatinib group than in the gemcitabine and cisplatin group for all subgroups; except for the two smallest subgroups, the differences were statistically significant (figure 2C). Additionally, progression-free survival was much the same for the overall population compared with patients with the two common mutations (exon 19 deletions and Leu858Arg; by independent assessment 11.0 months, [95% CI 9.7–13.7] vs 5.6 months [4.5–6.2], HR 0.25, 95% CI 0.18–0.35;  $p < 0.0001$ ; by investigator assessment 13.8 months [95% CI 12.5–14.4] vs 5.6 months [4.7–6.7] months, HR 0.21, 95% CI 0.15–0.30;  $p < 0.0001$ ). The appendix shows progression-free survival over time.

A significantly greater proportion of patients in the afatinib group had an objective response than in the gemcitabine and cisplatin group (162 of 242 [66.9%] vs 28 of 122 [23.0%]) according to independent review (odds ratio [OR] 7.28, 95% CI 4.36–12.18;  $p < 0.0001$ ). Investigator assessment gave much the same results (OR 6.53, 95% CI 4.02–10.60;  $p < 0.0001$ ; table 2). By week 6, 119 of 242 (49.2%) patients in the afatinib group versus 16 of 122 (13.1%) in the gemcitabine and cisplatin group had had an objective response. Median duration of response according to independent review was 9.7 months (95% CI 8.3–12.5) for afatinib and 4.3 months (2.8–5.8) for gemcitabine and cisplatin. Disease control according to independent review was also significantly more common in the afatinib group than in the gemcitabine and cisplatin group (OR 3.84, 95% CI 2.04–7.24;  $p < 0.0001$ ; table 2), with a median duration of disease control of 11.1 months



**Figure 3: Patient-reported outcomes**

(A) Percentage of patients who had improvements in cough, dyspnoea, and pain. (B) Patient-reported outcomes with more than a 10% difference in the percentage of patients for whom symptoms improved or worsened. Outcomes assessed according to the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (QLQ-C30) and its lung cancer-specific module QLQ-LC13.<sup>20,21</sup>

(95% CI 9.7–13.8) versus 5.7 months (5.5–6.9). Furthermore, objective response and disease control both occurred in much the same proportions of patients in the overall population as in patients with common mutations

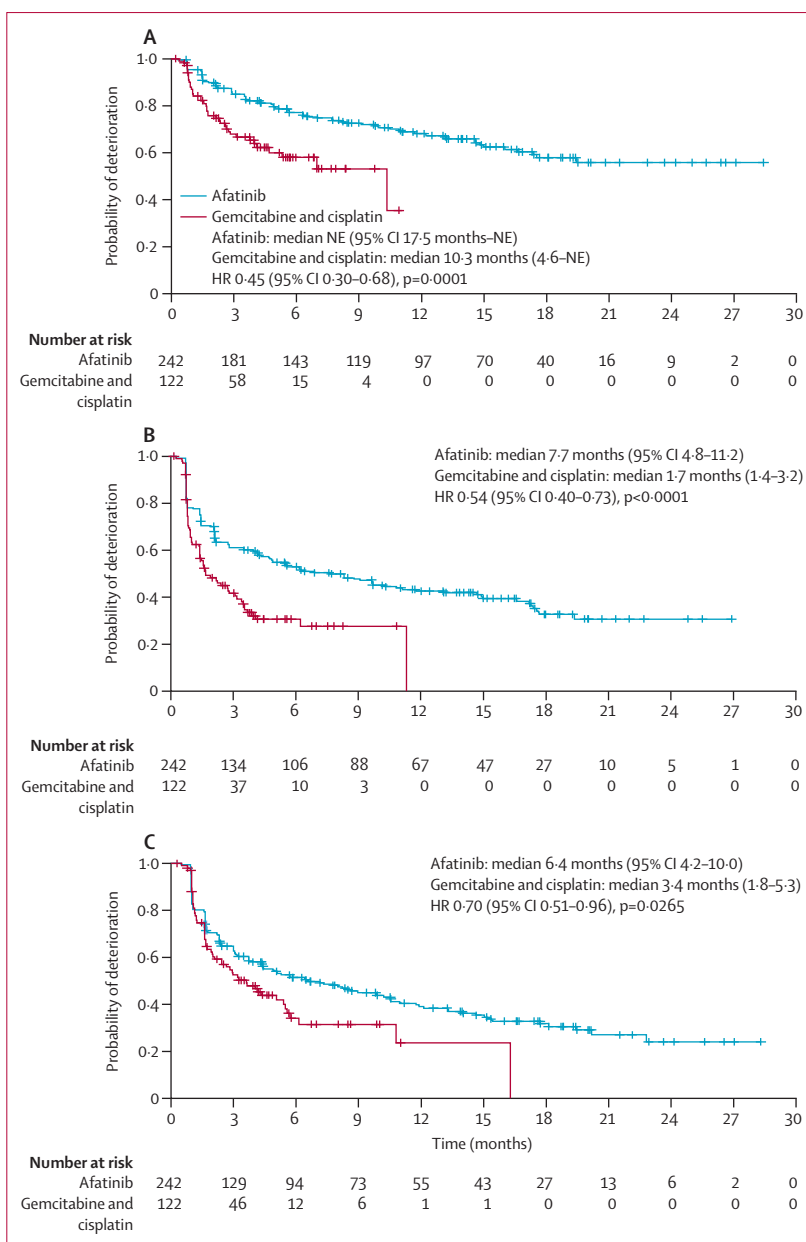
(appendix). Of three patients with Thr790Met mutations (two in the afatinib group, one in the gemcitabine and cisplatin group; appendix), one patient in each group had a partial response.

Overall survival data were immature at the time of the primary analysis of progression-free survival: 155 of 364 (42.6%) patients had died. Median overall survival was 22.1 months (95% CI 20.0–not estimable) for afatinib versus 22.2 months (18.0–not estimable) for gemcitabine and cisplatin (HR 0.95, 95% CI 0.68–1.33;  $p=0.76$ ; appendix). The final OS analysis will be presented once sufficient follow-up has been achieved.

At the time of analysis, almost 60% of patients who discontinued study drug went on to receive at least one subsequent cancer treatment (108 of 185 [58.4%] patients in the afatinib group vs 74 of 122 [60.7%] in the gemcitabine and cisplatin group). Of these patients, 101 (54.6%) in the afatinib group were subsequently treated with gemcitabine and cisplatin in any line of treatment, whereas in the gemcitabine and cisplatin group, 59 of 122 (48.4%) patients were subsequently treated with EGFR tyrosine kinase inhibitors. Full data for post-progression treatment are not yet available.

Approximately 85% of patients who were alive and progression-free during the study had completed and returned patient-reported questionnaires (appendix). A greater proportion of patients in the afatinib group than in the gemcitabine and cisplatin group had improvements in cough, dyspnoea, and pain (figure 3A). Time to deterioration was significantly longer in the afatinib group than in the gemcitabine and cisplatin group for cough, dyspnoea, and pain (figure 4). Additionally, afatinib significantly improved mean scores over time compared with gemcitabine and cisplatin for cough (mean treatment difference  $-6.34$ , 95% CI  $-9.10$  to  $-3.58$ ;  $p<0.0001$ ), dyspnoea ( $-9.89$ ,  $-12.13$  to  $-7.66$ ;  $p<0.0001$ ), and pain ( $-5.89$ ,  $-8.50$  to  $-3.27$ ;  $p<0.0001$ ). For overall health status and quality of life, a higher proportion of patients in the afatinib group than in the gemcitabine and cisplatin group had improvement (143 of 228 [62.7%] vs 33 of 101 [32.7%];  $p<0.0001$ ), had significantly longer time to deterioration (HR 0.56, 95% CI 0.41–0.77;  $p=0.0002$ ), and had greater improvement in mean scores over time (mean treatment difference  $-8.78$ , 95% CI  $-11.19$  to  $-6.36$ ;  $p<0.0001$ ). Figure 3B shows self-reported outcomes for which a more than 10% difference existed in the percentage of patients whose symptoms improved or worsened.

Table 3 summarises the most common treatment-related adverse events. The appendix shows the most common adverse events irrespective of relation to study drug. Based on maximum Common Toxicity Criteria grade for each patient, treatment-related adverse events of grade 1–2 were reported by 150 of 239 (62.8%) patients receiving afatinib and 44 of 113 (38.9%) patients receiving gemcitabine and cisplatin. Treatment-related adverse events of grade 3 or greater occurred in 86 of 239 (36.0%) patients receiving afatinib and 68 of 113 (60.2%) receiving gemcitabine and cisplatin. Diarrhoea, rash or acne, and stomatitis or mucositis were the most common adverse events in the afatinib group, whereas vomiting,



**Figure 4: Time to deterioration**

For cough (A), dyspnoea (B), and pain (C). NE=not estimable.

nausea, neutropenia, and leucopenia were the most common in the gemcitabine and cisplatin group (table 3). No ECG abnormalities were reported. 14 of 239 (5.9%) patients treated with afatinib versus 45 of 113 (39.8%) treated with gemcitabine and cisplatin had treatment-related adverse events leading to permanent treatment discontinuation. Treatment-related serious adverse events were reported by 15 of 239 (6.3%) patients in the afatinib group and nine of 113 (8.0%) in the gemcitabine and cisplatin group. The most common treatment-related serious adverse events were rash or acne

	Afinib group (n=239)					Gemcitabine and cisplatin group (n=113)				
	All grades	Grade 1-2	Grade 3	Grade 4	Grade 5	All grades	Grade 1-2	Grade 3	Grade 4	Grade 5
Total	236 (98.7%)	150 (62.8%)	82 (34.3%)	3 (1.3%)	1 (0.4%)	112 (99.1%)	44 (38.9%)	45 (39.8%)	22 (19.5%)	1 (0.9%)
Symptomatic adverse events										
Diarrhoea	211 (88.3%)	198 (82.8%)	13 (5.4%)	0 (0%)	0 (0%)	12 (10.6%)	12 (10.6%)	0 (0)	0 (0%)	0 (0%)
Rash or acne*	193 (80.8%)	158 (66.1%)	34 (14.2%)	1 (0.4%)	0 (0%)	10 (8.8%)	10 (8.8%)	0 (0%)	0 (0%)	0 (0%)
Stomatitis or mucositis*	124 (51.9%)	111 (46.4%)	13 (5.4%)	0 (0.0%)	0 (0%)	6 (5.3%)	6 (5.3%)	0 (0%)	0 (0%)	0 (0%)
Paronychia	78 (32.6%)	78 (32.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Epistaxis	30 (12.6%)	29 (12.1%)	1 (0.4%)	0 (0%)	0 (0%)	1 (0.9%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)
Pruritus	26 (10.9%)	25 (10.5%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Decreased appetite	24 (10.0%)	21 (8.8%)	3 (1.3%)	0 (0%)	0 (0%)	46 (40.7%)	44 (38.9%)	2 (1.8%)	0 (0%)	0 (0%)
Fatigue*	24 (10.0%)	23 (9.6%)	1 (0.4%)	0 (0%)	0 (0%)	41 (36.3%)	40 (35.4%)	1 (0.9%)	0 (0%)	0 (0%)
Vomiting	23 (9.6%)	21 (8.8%)	2 (0.8%)	0 (0%)	0 (0%)	91 (80.5%)	69 (61.1%)	18 (15.9%)	4 (3.5%)	0 (0%)
Nausea	18 (7.5%)	18 (7.5%)	0 (0%)	0 (0%)	0 (0%)	85 (75.2%)	76 (67.3%)	8 (7.1%)	1 (0.9%)	0 (0%)
Constipation	4 (1.7%)	4 (1.7%)	0 (0%)	0 (0%)	0 (0%)	14 (12.4%)	14 (12.4%)	0 (0%)	0 (0%)	0 (0%)
Bone marrow failure	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (4.4%)	3 (2.7%)	2 (1.8%)	0 (0%)	0 (0%)
Laboratory or haematological adverse events†										
ALT concentration increase	48 (20.1%)	44 (18.4%)	4 (1.7%)	0 (0%)	0 (0%)	18 (15.9%)	15 (13.3%)	2 (1.8%)	1 (0.9%)	0 (0%)
AST concentration increase	36 (15.1%)	35 (14.6%)	1 (0.4%)	0 (0%)	0 (0%)	12 (10.6%)	10 (8.8%)	2 (1.8%)	0 (0%)	0 (0%)
Anaemia	13 (5.4%)	12 (5.0%)	1 (0.4%)	0 (0%)	0 (0%)	31 (27.4%)	21 (18.6%)	8 (7.1%)	2 (1.8%)	0 (0%)
Hypokalaemia	13 (5.4%)	10 (4.2%)	3 (1.3%)	0 (0%)	0 (0%)	15 (13.3%)	6 (5.3%)	9 (8.0%)	0 (0%)	0 (0%)
Leucopenia	8 (3.3%)	7 (2.9%)	1 (0.4%)	0 (0%)	0 (0%)	58 (51.3%)	41 (36.3%)	15 (13.3%)	2 (1.8%)	0 (0%)
Neutropenia	5 (2.1%)	4 (1.7%)	1 (0.4%)	0 (0%)	0 (0%)	61 (54.0%)	31 (27.4%)	20 (17.7%)	10 (8.8%)	0 (0%)
Hyponatraemia	4 (1.7%)	1 (0.4%)	3 (1.3%)	0 (0%)	0 (0%)	10 (8.8%)	6 (5.3%)	4 (3.5%)	0 (0%)	0 (0%)
Haemoglobin concentration decreased	4 (1.7%)	3 (1.3%)	1 (0.4%)	0 (0%)	0 (0%)	20 (17.7%)	16 (14.2%)	3 (2.7%)	1 (0.9%)	0 (0%)
Neutrophil count decreased	2 (0.8%)	2 (0.8%)	0 (0%)	0 (0%)	0 (0%)	29 (25.7%)	18 (15.9%)	8 (7.1%)	3 (2.7%)	0 (0%)
White blood cell count decreased	2 (0.8%)	2 (0.8%)	0 (0%)	0 (0%)	0 (0%)	27 (23.9%)	20 (17.7%)	7 (6.2%)	0 (0%)	0 (0%)
Thrombocytopenia	2 (0.8%)	1 (0.4%)	1 (0.4%)	0 (0%)	0 (0%)	21 (18.6%)	10 (8.8%)	8 (7.1%)	3 (2.7%)	0 (0%)
Platelet count decreased	2 (0.8%)	2 (0.8%)	0 (0%)	0 (0%)	0 (0%)	12 (10.6%)	7 (6.2%)	3 (2.7%)	2 (1.8%)	0 (0%)

Data are n (%). Events are included if reported for more than 10% of patients at grade 1-2 or more than 1% of patients for grades 3-5 in any treatment group. In addition, two deaths occurred that were considered related to treatment: one sudden death deemed related to afatinib and one cardiac failure deemed related to gemcitabine and cisplatin. ALT=alanine aminotransferase. AST=aspartate aminotransferase. \*Group term. †Numbers are based on the adverse events reported by the investigator, not derived from the laboratory data.

**Table 3: Most common treatment-related adverse events**

(three, 1.3%) and diarrhoea (two, 0.8%) in the afatinib group and thrombocytopenia (two, 1.8%) in the gemcitabine and cisplatin group. No patients taking afatinib permanently discontinued treatment because of diarrhoea only, five (2.1%) afatinib-treated patients discontinued treatment because of rash or acne. In the gemcitabine and cisplatin group, the most common treatment-related adverse events resulting in treatment discontinuation were vomiting (16, 14.2%), nausea (11, 9.7%), neutropenia (ten, 8.8%), and leucopenia (eight, 7.1%). One patient died in each group. Both were considered to be potentially treatment-related by the investigator (sudden death in the afatinib group and cardiac failure in the gemcitabine and cisplatin group). One patient in the afatinib group had grade 4 treatment-related interstitial pneumonitis. This male Korean patient permanently discontinued afatinib treatment and eventually recovered from pneumonitis after antibiotic and steroid treatment. Pharmacokinetic data will be published separately.

**Discussion**

To our knowledge, this study is the largest prospective, randomised trial to compare EGFR-directed treatment with chemotherapy for first-line treatment of advanced EGFR mutation-positive lung adenocarcinoma (panel). The results show that afatinib significantly delayed progression of advanced EGFR mutation-positive NSCLC compared with gemcitabine and cisplatin in Asian patients. Clear benefits occurred according to both independent and investigator review, and were consistent across predefined subgroups. The effect on progression-free survival was substantiated by the improvement for the secondary endpoints—objective response, disease control, and patient-reported outcomes—showing better control of lung cancer-related symptoms. These benefits were present despite higher ECOG performance scores in the afatinib group than in the gemcitabine and cisplatin group at baseline. At the time of analysis, overall survival did not differ significantly between treatment groups, which is unsurprising for a trial of a first-line



treatment with substantial subsequent crossover between treatments (ie, patients in the gemcitabine and cisplatin later receiving EGFR tyrosine kinase inhibitors and those in the afatinib group later receiving chemotherapy). Indeed, neither of the previous studies<sup>14,25</sup> in this setting showed differences in survival, despite meeting the primary endpoint of progression-free survival.

Our findings for afatinib in an Asian population are comparable to results of the global trial—LUX-Lung 3—in which afatinib was compared with pemetrexed and cisplatin.<sup>17</sup> Progression-free survival, objective responses, disease control, and progression-free survival over time were similar in the overall population and in patients with common mutations (appendix), further supporting the robustness of our findings.<sup>17,24</sup> The HR for progression-free survival differed in our study compared with LUX-Lung 3 (HR 0.58, 95% CI 0.43–0.78), perhaps a result of differences in the efficacy of the chemotherapy comparators used in each study. LUX-Lung 6 included patients with uncommon mutations (not del19 or Leu858Arg), and although the population with these rare mutations was small and genetically diverse, our study contributes to the body of data already collected in other trials of afatinib, which will be presented in the future.

Most patients in LUX-Lung 6 had treatment-related adverse events. Treatment with afatinib was associated with the expected EGFR-mediated adverse events, including gastrointestinal<sup>26</sup> and dermatological disorders,<sup>27</sup> which were managed by supportive care and protocol-defined dose reductions. Few patients discontinued afatinib because of adverse events and no patients discontinued afatinib because of diarrhoea. This result suggests that the systematically established management of adverse events used in this trial worked well to keep patients on treatment, enabling the maximum benefit from afatinib. The most commonly reported adverse events—diarrhoea, rash or acne, and stomatitis or mucositis—are the same as those reported with erlotinib (diarrhoea 25–81%, rash 73–85%)<sup>14,15,28</sup> and gefitinib (diarrhoea 31–54%, rash 45–85%).<sup>10–13,29</sup> Liver dysfunction has been reported in 8–70% of patients treated with gefitinib<sup>11,12,29</sup> and 6–37% of patients treated with erlotinib,<sup>14,15</sup> although it was not an important adverse event with afatinib. Cross-trial comparisons of adverse events with different drugs have some limitations because of differences in the patient populations and how adverse events were reported. Although adverse events were common, substantial improvements in overall health status and quality of life compared with gemcitabine and cisplatin support the efficacy benefits and suggest that—with proactive management—the safety profile of afatinib was acceptable in this population. Although adverse events were rare in LUX-Lung 6 compared with LUX-Lung 3, we think that this difference was because physicians in LUX-Lung 6 had more experience in treatment of adverse events that commonly occur after EGFR inhibition—all patients

### Panel: Research in context

#### Systematic review

We searched PubMed for the terms “locally advanced” or “metastatic NSCLC” and “EGFR” for studies published in English between Jan 1, 2002, and July 30, 2013. We identified randomised, controlled trials comparing an EGFR tyrosine kinase inhibitor with chemotherapy for the treatment of newly diagnosed EGFR mutation-positive non-small-cell lung cancer. We identified four trials of gefitinib,<sup>10–13</sup> two of erlotinib,<sup>14,15</sup> and one trial of afatinib.<sup>17</sup> Studies of the reversible EGFR tyrosine kinase inhibitors used platinum-based chemotherapy combined with gemcitabine or a taxane as the chemotherapy comparator, and all showed that progression-free survival was greater with the EGFR tyrosine kinase inhibitor than with chemotherapy.<sup>10–15</sup> Two studies—IPASS<sup>13</sup> and EURTAC<sup>14</sup>—should be considered along with LUX-Lung 6, because these studies led to the registration of erlotinib and gefitinib for treatment of patients with EGFR mutation-positive non-small-cell lung cancer; however, direct comparisons of outcomes are not possible because of differences between the methods used, including differences in patient eligibility and the use of independent versus investigator assessments.

#### Interpretation

EGFR tyrosine kinase inhibitors are the currently recommended first-line treatment for patients with EGFR mutation-positive lung adenocarcinoma.<sup>23</sup> LUX-Lung 6 is—to the best of our knowledge—the largest study of first-line treatment for EGFR mutation-positive non-small-cell lung cancer and is the second trial (after LUX-Lung 3<sup>17</sup>) to show the efficacy, safety, and quality-of-life benefits of afatinib. The improvement in progression-free survival—combined with improvements in quality of life—suggests that clinicians should consider afatinib as a standard first-line treatment option for patients with EGFR mutation-positive non-small-cell lung cancer.

(n=364) were recruited from only 36 sites in LUX-Lung 6, compared with LUX-Lung 3, in which a similar number of patients (n=345) was recruited from 133 sites.

Key strengths of this study include the use of central standardised EGFR mutation test and central imaging review, and the detailed assessment of patient-reported outcomes. These procedures are fundamental to guaranteeing the reproducibility of the results and high quality of data and—when combined with the large sample size—contribute to the robustness of this trial. Although the open-label design is a potential source of bias, the study included several features to minimise this risk, including independent central review of patients' scans by radiologists and oncologists who were masked to treatment assignment and sensitivity analyses, which did not suggest any such bias. A further potential source of bias was the different performance score in each group at baseline; however, with more patients having a score of 1 in the afatinib group than in the gemcitabine and cisplatin group, any resulting bias should favour the comparator.

One limitation of LUX-Lung 6 is the use of gemcitabine and cisplatin as a control treatment. The treatment for advanced lung adenocarcinoma in patients with EGFR mutations has developed quickly since this study was started, with erlotinib and gefitinib becoming the first choice for EGFR mutation-positive patients. Indeed, recruitment for LUX-Lung 6 began in 2010, despite being designed earlier and—at that time—little data for gefitinib

and none for erlotinib in this patient population had been published. However, platinum-based treatment is still an option, and the choice of comparator was approved by the regulatory authorities. The chemotherapy regimen and dose of gemcitabine and cisplatin was commonly used in Asia at the time that the study was designed. Recruitment for a head-to-head trial of afatinib compared with gefitinib for first-line treatment of *EGFR* common mutation-positive lung adenocarcinoma has been completed (NCT01466660; LUX-Lung 7), with the results expected to provide the first evidence of the comparative efficacy and safety of these drugs for this setting.

The results of LUX-Lung 6 show a more profound and durable effect of afatinib than standard first-line chemotherapy with gemcitabine and cisplatin for Asian patients with NSCLC tumours harbouring *EGFR* mutations. Afatinib should therefore be considered as a first-line treatment option for this patient population.

#### Contributors

Y-LW searched the published work, designed the figures, designed the study, collected, analysed, and interpreted data, recruited patients, and wrote the article. CZ and YS collected, analysed, and interpreted data, and wrote the article. C-PH, MH, and JHS collected data. JF searched the published work, designed the figures, collected, analysed, and interpreted data, and wrote the article. SL and KYL collected and interpreted data. YH collected data and recruited patients. WL recruited patients. C-RX collected data and wrote the article. DM and MK designed the study, analysed and interpreted data, and wrote the article. SLG searched the published work, collected, analysed, and interpreted data, recruited patients, and wrote the article.

#### Conflicts of interest

Y-LW has received honoraria from Roche, AstraZeneca, Eli Lilly, Sanofi, and Pfizer. DM, MK, and YS are employees of Boehringer Ingelheim. The other authors declare that they have no conflicts of interest.

#### Acknowledgments

This trial was funded by Boehringer Ingelheim. We thank the patients, their families, and all of the investigators who participated in the study. Editorial support—paid for by Boehringer Ingelheim—was provided by Suzanne Patel and Claire Smart of Ogilvy Healthworld Medical Education.

#### References

- Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002; **346**: 92–98.
- Azzoli CG, Temin S, Aliff T, et al. 2011 Focused update of 2009 American Society of Clinical Oncology clinical practice guideline update on chemotherapy for stage IV non-small-cell lung cancer. *J Clin Oncol* 2011; **29**: 3825–31.
- Peters S, Adjei AA, Gridelli C, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012; **23** (suppl 7): VII56–64.
- Buettner R, Wolf J, Thomas RK. Lessons learned from lung cancer genomics: the emerging concept of individualized diagnostics and treatment. *J Clin Oncol* 2013; **31**: 1858–65.
- Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004; **350**: 2129–39.
- Li D, Ambrogio L, Shimamura T, et al. BIBW2992, an irreversible *EGFR*/*HER2* inhibitor highly effective in preclinical lung cancer models. *Oncogene* 2008; **27**: 4702–11.
- Solca F, Dahl G, Zoepfel A, et al. Target binding properties and cellular activity of afatinib (BIBW 2992), an irreversible ErbB family blocker. *J Pharmacol Exp Ther* 2012; **343**: 342–50.
- Wind S, Schmid M, Erhardt J, Goeldner RG, Stopfer P. Pharmacokinetics of afatinib, a selective irreversible ErbB family blocker, in patients with advanced solid tumours. *Clin Pharmacokinet* 2013; **52**: 1101–09.
- Moyer JD, Barbacci EG, Iwata KK, et al. Induction of apoptosis and cell cycle arrest by CP-358,774, an inhibitor of epidermal growth factor receptor tyrosine kinase. *Cancer Res* 1997; **57**: 4838–48.
- Han JY, Park K, Kim SW, et al. First-SIGNAL: first-line single-agent irressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. *J Clin Oncol* 2012; **30**: 1122–28.
- Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated *EGFR*. *N Engl J Med* 2010; **362**: 2380–88.
- Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010; **11**: 121–28.
- Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; **361**: 947–57.
- Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced *EGFR* mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012; **13**: 239–46.
- Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced *EGFR* mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011; **12**: 735–42.
- Sekine I, Yamamoto N, Nishio K, Saijo N. Emerging ethnic differences in lung cancer therapy. *Br J Cancer* 2008; **99**: 1757–62.
- Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexid in patients with metastatic lung adenocarcinoma with *EGFR* mutations. *J Clin Oncol* 2013; **31**: 3327–34.
- Greene FL, Page DL, Fleming ID, et al, eds. *AJCC Cancer Staging Manual*, 6th edn. *Ann Oncol* 2003; **14**: 345–46.
- Eisenhauer EA, Therasse P, Bogarts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228–247.
- Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85**: 365–76.
- Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. *Eur J Cancer* 1994; **30A**: 635–42.
- Fayers P, Aaronson N, Bjordal K, Groenvold M, Curran C, Bottomley A. EORTC QLQ-C30 Scoring Manual, third edn. 2001. <http://www.eortc.be/qol/files/SCManualQLQ-C30.pdf> (accessed July 1, 2013).
- Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998; **16**: 139–44.
- Yang JC, Hirsh V, Schuler M, et al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexid in patients with advanced lung adenocarcinoma with *EGFR* mutations. *J Clin Oncol* 2013; **31**: 3342–50.
- Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J Clin Oncol* 2011; **29**: 2866–74.
- Yang JC, Reguart N, Barinoff J, et al. Diarrhea associated with afatinib: an oral ErbB family blocker. *Expert Rev Anticancer Ther* 2013; **13**: 729–36.
- Lacouture ME, Schadendorf D, Chu CY, et al. Dermatologic adverse events associated with afatinib: an oral ErbB family blocker. *Expert Rev Anticancer Ther* 2013; **13**: 721–28.
- Horiike A, Nishio M, Goto K, et al. A phase II study of erlotinib as first-line treatment in Japanese advanced NSCLC patients harboring *EGFR* mutations. *Ann Oncol* 2012; **23**: IX413.
- Douillard J, Ostoros G, Cobo M, et al. Efficacy, safety and tolerability results from a phase IV, open-label, single arm study of 1st-line gefitinib in Caucasian patients (PTS) with epidermal growth factor receptor (*EGFR*) mutation-positive non-small cell lung cancer (NSCLC). *Lung Cancer* 2013; **80**: S31.