Afatinib versus gefitinib as first-line treatment of patients with *EGFR* mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial

Keunchil Park, Eng-Huat Tan, Ken O'Byrne, Li Zhang, Michael Boyer, Tony Mok, Vera Hirsh, James Chih-Hsin Yang, Ki Hyeong Lee, Shun Lu, Yuankai Shi, Sang-We Kim, Janessa Laskin, Dong-Wan Kim, Catherine Dubos Arvis, Karl Kölbeck, Scott A Laurie, Chun-Ming Tsai, Mehdi Shahidi, Miyoung Kim, Dan Massey, Victoria Zazulina, Luis Paz-Ares

Summary

Background The irreversible ErbB family blocker afatinib and the reversible EGFR tyrosine kinase inhibitor gefitinib are approved for first-line treatment of *EGFR* mutation-positive non-small-cell lung cancer (NSCLC). We aimed to compare the efficacy and safety of afatinib and gefitinib in this setting.

Methods This multicentre, international, open-label, exploratory, randomised controlled phase 2B trial (LUX-Lung 7) was done at 64 centres in 13 countries. Treatment-naive patients with stage IIIB or IV NSCLC and a common *EGFR* mutation (exon 19 deletion or Leu858Arg) were randomly assigned (1:1) to receive afatinib (40 mg per day) or gefitinib (250 mg per day) until disease progression, or beyond if deemed beneficial by the investigator. Randomisation, stratified by *EGFR* mutation type and status of brain metastases, was done centrally using a validated number generating system implemented via an interactive voice or web-based response system with a block size of four. Clinicians and patients were not masked to treatment allocation; independent review of tumour response was done in a blinded manner. Coprimary endpoints were progression-free survival by independent central review, time-to-treatment failure, and overall survival. Efficacy analyses were done in the intention-to-treat population and safety analyses were done in patients who received at least one dose of study drug. This ongoing study is registered with ClinicalTrials.gov, number NCT01466660.

Findings Between Dec 13, 2011, and Aug 8, 2013, 319 patients were randomly assigned (160 to afatinib and 159 to gefitinib). Median follow-up was 27·3 months (IQR 15·3–33·9). Progression-free survival (median 11·0 months [95% CI 10·6–12·9] with afatinib *vs* 10·9 months [9·1–11·5] with gefitinib; hazard ratio [HR] 0·73 [95% CI 0·57–0·95], p=0·017) and time-to-treatment failure (median 13·7 months [95% CI 11·9–15·0] with afatinib *vs* 11·5 months [10·1–13·1] with gefitinib; HR 0·73 [95% CI 0·58–0·92], p=0·0073) were significantly longer with afatinib than with gefitinib. Overall survival data are not mature. The most common treatment-related grade 3 or 4 adverse events were diarrhoea (20 [13%] of 160 patients given afatinib *vs* two [1%] of 159 given gefitinib) and rash or acne (15 [9%] patients given afatinib *vs* five [3%] of those given gefitinib) and liver enzyme elevations (no patients given afatinib *vs* 14 [9%] of those given gefitinib). Serious treatment-related adverse events occurred in 17 (11%) patients in the afatinib group and seven (4%) in the gefitinib group. Ten (6%) patients in each group discontinued treatment due to drug-related adverse events. 15 (9%) fatal adverse events occurred in the afatinib group and ten (6%) in the gefitinib group. All but one of these deaths were considered unrelated to treatment; one patient in the gefitinib group died from drug-related hepatic and renal failure.

Interpretation Afatinib significantly improved outcomes in treatment-naive patients with *EGFR*-mutated NSCLC compared with gefitinib, with a manageable tolerability profile. These data are potentially important for clinical decision making in this patient population.

Funding Boehringer Ingelheim.

Introduction

Non-small-cell lung cancer (NSCLC) with *EGFR* mutations represents a molecularly distinct type of lung cancer with established first-line treatment options; these include the EGFR-targeting tyrosine kinase inhibitors gefitinib, erlotinib, and afatinib.[1–3] All three drugs have been approved on the basis of randomised trials showing superior progression-free survival,

objective responses, and more favourable safety profiles when compared with standard first-line platinum-based doublet chemotherapy in patients with *EGFR*-mutant NSCLC.[4–11] In the absence of prospective randomised head-to-head comparisons of these EGFR tyrosine kinase inhibitors, a series of meta-analyses were done to identify the most efficacious drug. These studies did not identify any significant differences in efficacy between gefitinib,

Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea (Prof K Park MD); **National Cancer Centre, Singapore** (E-H Tan MD); **Princess Alexandra Hospital and Queensland University of Technology, Brisbane, QLD, Australia** (Prof K O'Byrne MD); **State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-Sen University Cancer Center, Guangzhou, China** (Prof L Zhang MD); **Chris O'Brien Lifehouse, Camperdown, NSW, Australia** (Prof M Boyer MD); **Key Laboratory of South China, Department of Clinical Oncology, The Chinese University of Hong Kong Sha Tin, Hong Kong** (Prof T Mok MD); **McGill University, Montreal, QC, Canada** (Prof V Hirsh MD); **National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei, Taiwan** (Prof J C-H Yang MD); **Chungbuk National University Hospital, Cheongju, Chungbuk, South Korea** (K H Lee MD); **Shanghai Chest Hospital, Shanghai, China** (Prof S Lu MD); **Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College; Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China** (Y Shi MD); **Asan Medical Center, Seoul, South Korea** (S-W Kim MD); **BC CancerAgency, Vancouver, BC, Canada** (J Laskin MD); **Seoul**

1

National University Hospital, Seoul, South Korea (Prof D-W Kim MD)**; Centre François Baclesse, Oncology, Caen, France** (C Dubos Arvis MD)**; Karolinska University Hospital, Solna, Stockholm, Sweden** (K Kölbeck MD)**; The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada** (S A Laurie MD)**; Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan** (Prof C-M Tsai MD)**; Boehringer Ingelheim Ltd UK, Bracknell, Berkshire, UK** (M Shahidi MD, D Massey PhD, V Zazulina MD)**; Boehringer Ingelheim GmbH, Ingelheim, Germany** (M Kim MD)**; and Hospital Universitario Doce de Octubre and CNIO, Madrid Spain** (L Paz-Ares MD)

Correspondence to:
Prof Keunchil Park, Division of Hematology/Oncology, Innovative Cancer Medicine Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, South Korea
kpark@skku.edu

See **Online** for appendix

Research in context

Evidence before this study

We searched the literature published from Jan 1, 2009, to Jan 5, 2016, using PubMed and of trials presented as abstracts at major oncology meetings (annual meetings of the American Society of Clinical Oncology, the European Society for Medical Oncology, and the World Conference of Lung Cancer). Using the search terms "NSCLC" and "randomised", and "erlotinib" or "gefitinib", or "afatinib", we reviewed manuscripts and abstracts reporting phase 2 and 3 trials investigating EGFR-targeted drugs in patients with *EGFR* mutation-positive NSCLC in a first-line setting. Based on this review, we confirmed that to the best of our knowledge, apart from LUX-Lung 7, only one other first-line head-to-head trial has been completed to date (gefitinib vs erlotinib in Chinese patients; completed in 2014, NCT01024413). Therefore, at the onset of LUX-Lung 7, there were no prospective data to guide the selection of the most appropriate tyrosine kinase inhibitor in patients with *EGFR* mutation-positive NSCLC. A search of ClinicalTrials.gov showed that several randomised trials comparing EGFR tyrosine kinase inhibitors are ongoing, including: a phase 2 trial comparing erlotinib and gefitinib (NCT01955421); a phase 3 trial comparing dacomitinib (a second-generation tyrosine kinase inhibitor) versus gefitinib (NCT01774721); and two phase 3 trials comparing the third-generation tyrosine kinase inhibitors, osimertinib and ASP8273, versus gefitinib or erlotinib (NCT02296125 and NCT02588261, respectively).

Added value of this study

To our knowledge, this study is the first randomised multicentre trial comparing two EGFR-targeting drugs in a setting in which both are approved, providing efficacy and safety evidence in a head-to-head comparison. This study showed that afatinib has improved efficacy compared with gefitinib over a range of clinically relevant endpoints including progression-free survival, time-to-treatment failure, and the proportion of patients achieving an objective response. The improvement in efficacy was noted both in patients with exon 19 deletion and Leu858Arg mutations. The adverse event profile was predictable and manageable; the discontinuation rate due to treatment-related adverse events was the same as with gefitinib.

Implications of all the available evidence

LUX-Lung 7 indicates that irreversible ErbB blockade with afatinib could be more effective than reversible EGFR inhibition in the treatment of *EGFR* mutation-positive NSCLC. The results suggest that first-generation and second-generation tyrosine kinase inhibitors are not interchangeable and imply that the broader and irreversible mechanism of action of afatinib compared with gefitinib could have led to better tumour control.

erlotinib, or afatinib, but indicated differences in adverse event profile.[12–14]

There are inherent differences in the method of action of the first-generation EGFR tyrosine kinase inhibitors, gefitinib and erlotinib, which reversibly bind to and inhibit EGFR signalling, and the second-generation ErbB family blocker afatinib, which irreversibly blocks signalling from all relevant homo-dimers and hetero-dimers of the ErbB family of receptors (EGFR/ErbB1, HER2/ErbB2, ErbB3, and ErbB4).[15,16] The broad spectrum of activity and irreversible mechanism of action of afatinib has been postulated to be associated with improved inhibition of EGFR-dependent tumour growth compared with first-generation EGFR tyrosine kinase inhibitors. We aimed to address this question, and to prospectively estimate the effect of a first-generation versus a second-generation EGFR tyrosine kinase inhibitor, by assessing the efficacy and safety of gefitinib and afatinib in patients with NSCLC harbouring common (exon 19 deletions or Leu858Arg) *EGFR* mutations.

Methods

Study design and participants

LUX-Lung 7 was a multicentre, international, randomised, open-label, phase 2B trial, done at 64 sites in 13 countries (appendix pp 4–6). Eligible patients were aged 18 years or older with treatment-naive pathologically confirmed stage IIIB (ineligible for curative intent surgery or local radiotherapy) or IV (recurrent or metastatic) adenocarcinoma of the lung (American Joint Committee on Cancer version 7) with a documented, locally or centrally assessed, common activating *EGFR* mutation (exon 19 deletion or Leu858Arg). Locally identified *EGFR* mutations were retested by a central laboratory upon the provision of mandatory tumour samples; patients could be enrolled on the basis of either central or local test. Locally tested patients could be included without waiting for central confirmation (which was, however, obtained where possible, but at a later date). Patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and adequate organ function defined as: serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) less than or equal to three times the institutional upper limit of normal (ULN), or AST and ALT less than or equal to five times the institutional ULN if liver function abnormalities were due to underlying malignancy; total bilirubin less than or equal to 1·5 times ULN; absolute neutrophil count greater than or equal to 1·5 cells x 10^9/L; platelet count greater than or equal to 75 cells x 10^9/L; and creatinine clearance greater than 45 mL/min. Key exclusion criteria were: previous

systemic chemotherapy or EGFR-targeted drugs for advanced disease; major surgery within 4 weeks of study randomisation; active brain metastases (ie, symptomatic and/or requiring treatment at the time of screening); leptomeningeal disease; previous or concomitant malignancies at other sites; pre-existing interstitial lung disease; any history or presence of poorly controlled gastrointestinal disorders; clinically relevant cardio-vascular abnormalities; cardiac left ventricular function with resting ejection fraction of less than institutional lower limit of normal; any history of or concomitant condition that, in the opinion of the investigator would compromise the patient's ability to comply with the study or interfere with the evaluation of the efficacy and safety of the test drug; active hepatitis B infection, active hepatitis C infection, and/or known HIV infection; any contraindications for therapy with gefitinib; known hypersensitivity to afatinib or the excipients of any of the trial drugs; and use of any investigational drug within 4 weeks of randomisation. The complete eligibility criteria are provided in the appendix (p 1).

The study protocol was approved by an institutional review board or ethics committee at each participating centre. The study was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines as defined by the International Conference on Harmonization. All patients provided written informed consent for trial participation.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to receive afatinib or gefitinib, stratified by *EGFR* mutation type (exon 19 deletion *vs* Leu858Arg) and baseline brain metastases (presence *vs* absence). Permuted blocks of size four were created with a validated random number generating system at Boehringer Ingelheim, verified by a trial-independent statistician, and implemented centrally via an interactive voice or web-based response system. Clinicians and patients were not masked to treatment allocation; independent review of tumour response was done in a blinded manner. Individuals directly involved in the conduct and analysis of the trial did not have access to the randomisation schedule.

Procedures

Patients in the afatinib group received afatinib 40 mg orally once daily. Dose escalation to 50 mg was allowed after 4 weeks of treatment for patients who did not experience rash, diarrhoea, mucositis, or any other drug-related adverse event (National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 [NCI CTCAE 3.0]) of more than grade 1. If patients had any grade 3 or higher drug-related adverse event, or grade 2 diarrhoea lasting 2 days or more, or nausea or vomiting for 7 days consecutively or more despite best supportive care, then the study drug was paused for no more than 14 days until recovery to at least grade 1. After treatment

interruption and recovery to grade 1 or less (or grade present at baseline), the afatinib dose was reduced by 10 mg decrements to a minimum dose of 20 mg. Treatment was permanently discontinued in patients who did not recover to grade 1 or less, or baseline grade, within 14 days.

Patients in the gefitinib group received the approved daily dose of 250 mg. Modifications in administration of gefitinib were allowed according to the summary of product characteristics or prescribing information or institutional guidelines. Treatment interruptions of up to 14 days were allowed but no dose reduction schemes were specified according to the summary of product characteristics or prescribing information because gefitinib is only available in one dose formulation.

In both treatment groups, treatment was continued until disease progression, intolerable adverse events as judged by the investigator, or other reasons necessitating withdrawal; treatment beyond radiological progression was allowed in the case of continued clinical benefit as judged by the investigator.

Tumours were assessed by CT (preferred) or MRI scan after 4 and 8 weeks of treatment, then every 8 weeks until week 64 and every 12 weeks thereafter until permanent discontinuation of study treatment. Patients who discontinued study treatment but did not have progressive disease were imaged until progression or initiation of new anticancer therapy. Adverse events were assessed according to NCI CTCAE 3.0. Safety laboratory assessments (haematology, serum biochemistry, and coagulation) were done at screening, on the first visit of each treatment cycle, at the end of treatment, and first follow-up; urinalysis was only assessed at baseline.

Patient-reported quality-of-life outcomes were measured with the EuroQoL-5D (EQ-5D) health status self-assessment questionnaire that assessed the following five dimensions of health: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. For each patient, utility scores (ranging from 0 [worst health] to 1 [full health]) were calculated from the five item scores with UK preference weights. EQ-5D also comprised the EuroQoL EQ visual analogue scale (EQ-VAS), which recorded respondents' self-rated health status on a vertical (0–100) visual analogue scale. Questionnaires were completed before seeing the investigator at baseline and then every 8 weeks, at the end of treatment visit, and at the first follow-up visit.

Outcomes

Three coprimary endpoints were selected: progression-free survival (defined as the time from randomisation to the time of progression or death, whichever occurred first) by independent central review; time-to-treatment failure (defined as time from randomisation to the time of treatment discontinuation for any reason including disease progression, treatment toxicity, and death); and overall survival (defined as the time from randomisation to the time of death). Secondary endpoints included:

the proportion of patients with an objective response (defined as complete response plus partial response); time to, and duration of, objective response; the proportion of patients who achieved disease control (defined as objective response plus stable disease); duration of disease control; tumour shrinkage (defined as the maximum decrease from baseline in the sum of diameters of target lesions); and longitudinal change from baseline in health-related quality of life.

Statistical analysis

At the time of trial concept and initiation, insufficient data were available to construct a formal testing strategy regarding differences in effect of afatinib and gefitinib in this treatment setting. Therefore the study was set up as an exploratory phase 2B trial with sufficient patient numbers to broadly explore the differences between the two compounds. The main aim of this study was to estimate the effect of afatinib relative to gefitinib on the three endpoints of interest: progression-free survival, time-to-treatment failure, and overall survival. In view of the treatment setting, progression-free survival was considered as the most sensitive clinical endpoint. No formal hypotheses were defined and the sample size was based on controlling the width of the CI for the hazard ratio (HR) of progression-free survival. About 158 patients per treatment group were planned to be recruited to provide roughly 250 progression-free survival

events and restrict the half-width of the 95% CI for the logged HR to 0·25 in both directions. Three analysis timepoints were planned: primary progression-free survival or time-to-treatment failure analysis after 250 progression-free survival events; primary overall survival analysis after roughly 213 overall survival events and a follow-up period of at least 32 months for those patients still alive; and final analysis at study completion (when all patients had completed treatment or 5 years since the last patient was entered, whichever occurred first). The results of the first analysis, at the time of mature progression-free survival, are presented here. After recruitment commenced, but before completion of recruitment and any unblinded efficacy analysis had been done, the protocol was updated to change the designation of endpoints. Originally, the primary outcomes were progression-free survival and disease control at 12 months. On March 6, 2013, the protocol was updated to include time-to-treatment failure and overall survival in the primary outcomes. Disease control became a secondary endpoint. The change was made to distinguish the endpoints considered to be of most clinical importance from the other less important secondary endpoints. The amendment also mandated the balancing of recruitment in Asian versus non-Asian countries, which increased the planned sample size to 316. Another protocol amendment (Dec 16, 2013) provided clarification on the timing of a mature overall survival analysis.

All randomised patients were included in the primary assessment of efficacy (the intention-to-treat population). Safety analyses included all treated patients (randomised patients receiving at least one dose of study drug). Assessment of tumour response was done by both the investigator and an independent central imaging review group blinded to treatment (appendix p 10), with independent assessment considered as primary due to the open-label design. A log-rank test, stratified by *EGFR* mutation type and presence of baseline brain metastases, was used to assess progression-free survival, time-to-treatment failure, and overall survival. A Cox proportional hazards model, stratified by *EGFR* mutation type and baseline brain metastases was used to calculate HRs and 95% CIs. Kaplan-Meier estimates and 95% CIs were calculated at planned imaging timepoints and were used to estimate median and quartiles values (95% CIs). Sensitivity analysis of progression-free survival was also done with a restricted mean survival time approach that did not assume the proportional hazards model, as outlined by Anderson and colleagues.[17] Prespecified subgroups included *EGFR* mutation type (exon 19 deletion *vs* Leu858Arg), baseline brain metastases (presence *vs* absence), ECOG PS (0 *vs* 1), sex, age (<65 years *vs* ≥65 years), ethnic origin (Asian *vs* non-Asian), and smoking history. For patients continuing on study treatment after RECIST (version 1.1) progression, descriptive summaries of the duration of treatment (overall and from the time of initial RECIST
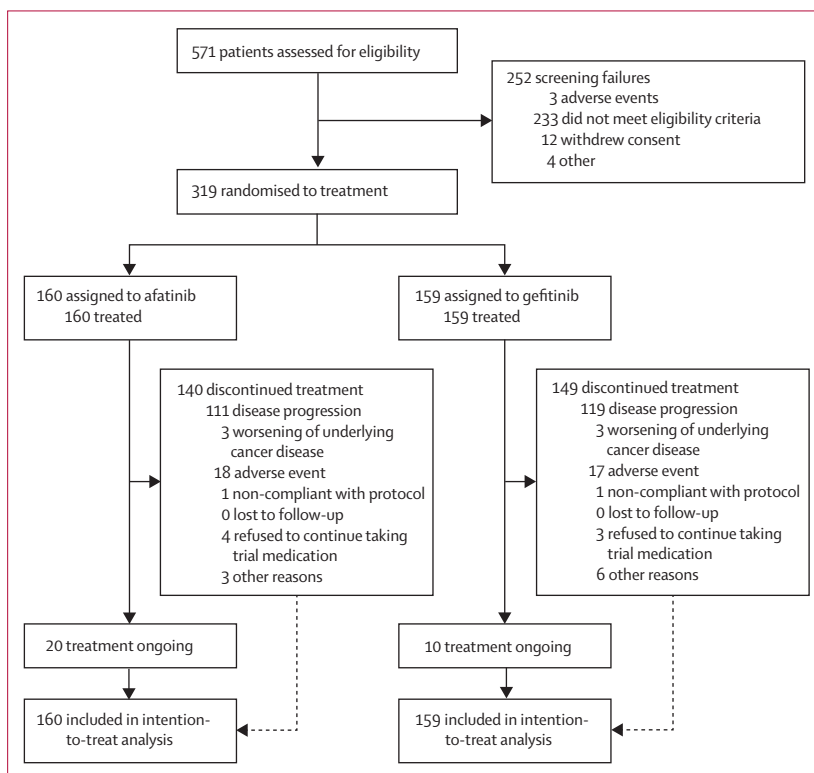

Figure 1: Trial profile

progression) were done. The proportions of patients achieving an objective response or disease control were compared with a logistic regression model adjusted for the covariates of *EGFR* mutation type and baseline brain metastases. An analysis of covariance was used to analyse tumour shrinkage, measured as the difference between the minimum post-baseline sum of the longest diameters of target lesions and the baseline sum of the same lesions. Median progression-free survival follow-up was calculated with the reverse Kaplan-Meier method.[18] For patient-reported outcomes, changes in scores over time were assessed with longitudinal mixed-effects growth curve models with the average profile over time for each endpoint described by a piecewise linear model adjusted for the fixed-effects *EGFR* mutation group and presence of baseline brain metastases. Model estimates of mean EQ-5D utility scores and mean EQ-VAS scores were plotted over time. The treatment effect was estimated as the average difference between the treatment group mean scores, together with a 95% CI and associated p value based on a *t* statistic with degrees of freedom calculated using the Kenward-Roger method.

All statistical testing was two-sided at the nominal 5% significance level, with no adjustment for multiplicity. All patients who received at least one afatinib or gefitinib dose were included in the safety analysis. A data-monitoring committee was appointed to assess the trial data periodically to ensure patient safety and the integrity of the trial.

Data were analysed with SAS version 9.4. This study is ongoing and is registered with ClinicalTrials.gov, number NCT01466660.

Role of the funding source
The funder designed the trial in collaboration with the LUX-Lung 7 steering committee (KP, E-HT, LZ, VH, KO'B, MB, JC-HY, TM, LP-A). Data were collected by the investigators and were analysed jointly with the funder. The funder and all authors were responsible for data interpretation and the development of the Article, and approved the final version. The Article was written by the corresponding author in collaboration with the coauthors, with independent medical writing assistance, supported financially by the funder. The steering committee had access to the raw data. All authors made the final decision to submit the report for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Between Dec 13, 2011, and Aug 8, 2013, 571 patients were screened and 319 were randomly assigned and treated with afatinib (n=160) or gefitinib (n=159; figure 1). Baseline demographics and disease characteristics were similar between the treatment group, except for a slight imbalance in sex (table 1).

Median duration of treatment was 13·7 months (IQR 7·4–24·3) for afatinib and 11·5 months (6·2–18·8) for gefitinib. Nine (6%) of 160 patients had afatinib dose escalations to 50 mg per day, 63 (39%) patients had dose reductions to 30 mg, of whom 21 (13%) patients had further reductions to 20 mg. At the time of primary analysis (Aug 21, 2015), 111 (69%) of 160 patients treated with afatinib and 119 (75%) of 159 of patients treated with gefitinib had discontinued due to progressive disease; 18 (11%) patients had discontinued due to all-cause adverse events in the afatinib group and 17 (11%) patients

	Afatinib (n=160)	Gefitinib (n=159)
Sex		
Men	69 (43%)	53 (33%)
Women	91 (57%)	106 (67%)
Age	63 (30–86)	63 (32–89)
Ethnic origin		
Asian	94 (59%)	88 (55%)
Black/African American	1 (1%)	0
White	48 (30%)	54 (34%)
Missing*	17 (11%)	17 (11%)
Smoking status		
Never smoked	106 (66%)	106 (67%)
Light ex-smoker†	21 (13%)	19 (12%)
Other current or ex-smokers	33 (21%)	34 (21%)
Baseline ECOG PS		
0	51 (32%)	47 (30%)
1	109 (68%)	112 (70%)
Histological classification		
Adenocarcinoma	159 (99%)	158 (99%)
Mixed	1 (1%)	1 (1%)
Clinical stage at screening		
IIIb	8 (5%)	3 (2%)
IV	152 (95%)	156 (98%)
***EGFR* mutation category**		
Leu858Arg	67 (42%)	66 (42%)
Leu858Arg alone	67 (42%)	65 (41%)
Leu858Arg+exon 19 deletion	0	1 (1%)
Exon 19 deletion‡	93 (58%)	93 (58%)
Metastases at screening		
Adrenal glands	12 (8%)	16 (10%)
Bone	80 (50%)	73 (46%)
Brain	26 (16%)	24 (15%)
Liver	16 (10%)	24 (15%)
Lung ipsilateral	86 (54%)	88 (55%)
Lung contralateral	65 (41%)	73 (46%)
Other	100 (63%)	104 (65%)

Data are n (%) or median (range). ECOG PS=Eastern Cooperative Oncology Group performance status. *Patients recruited in French sites did not have their ethnic origin recorded. †Less than 15 pack-years and stopped more than 1 year before diagnosis. ‡One patient in the afatinib group with wild-type *EGFR* was erroneously included in the trial and was reported as exon 19 deletion at the time of randomisation by the investigator.

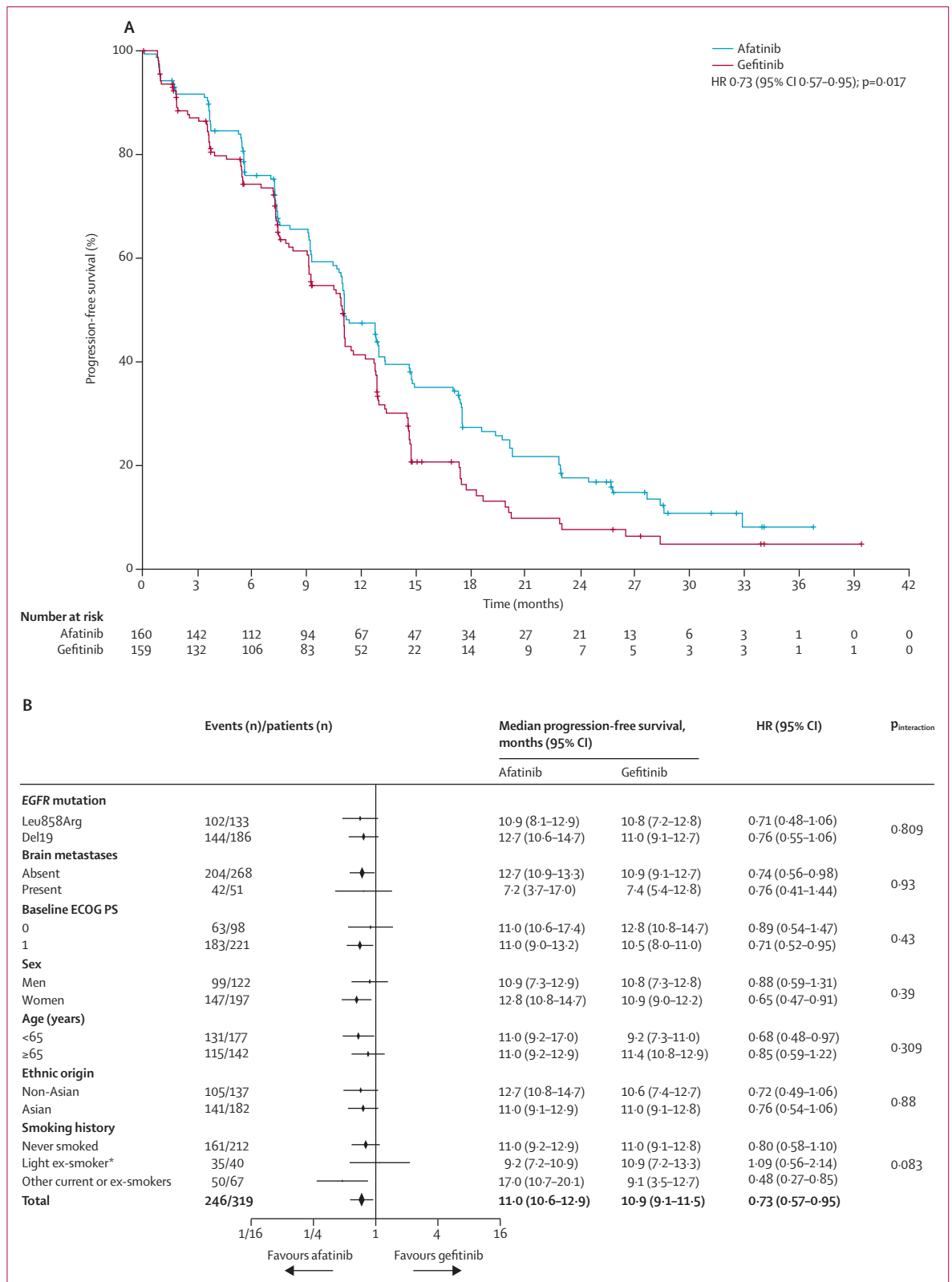*Table 1:* Baseline demographics and disease characteristics

***Figure 2*: Progression-free survival by independent review**
Kaplan-Meier curve (A) and forest plot of prespecified subgroup analyses (B). ECOG PS=Eastern Cooperative Oncology Group performance status. HR=hazard ratio.
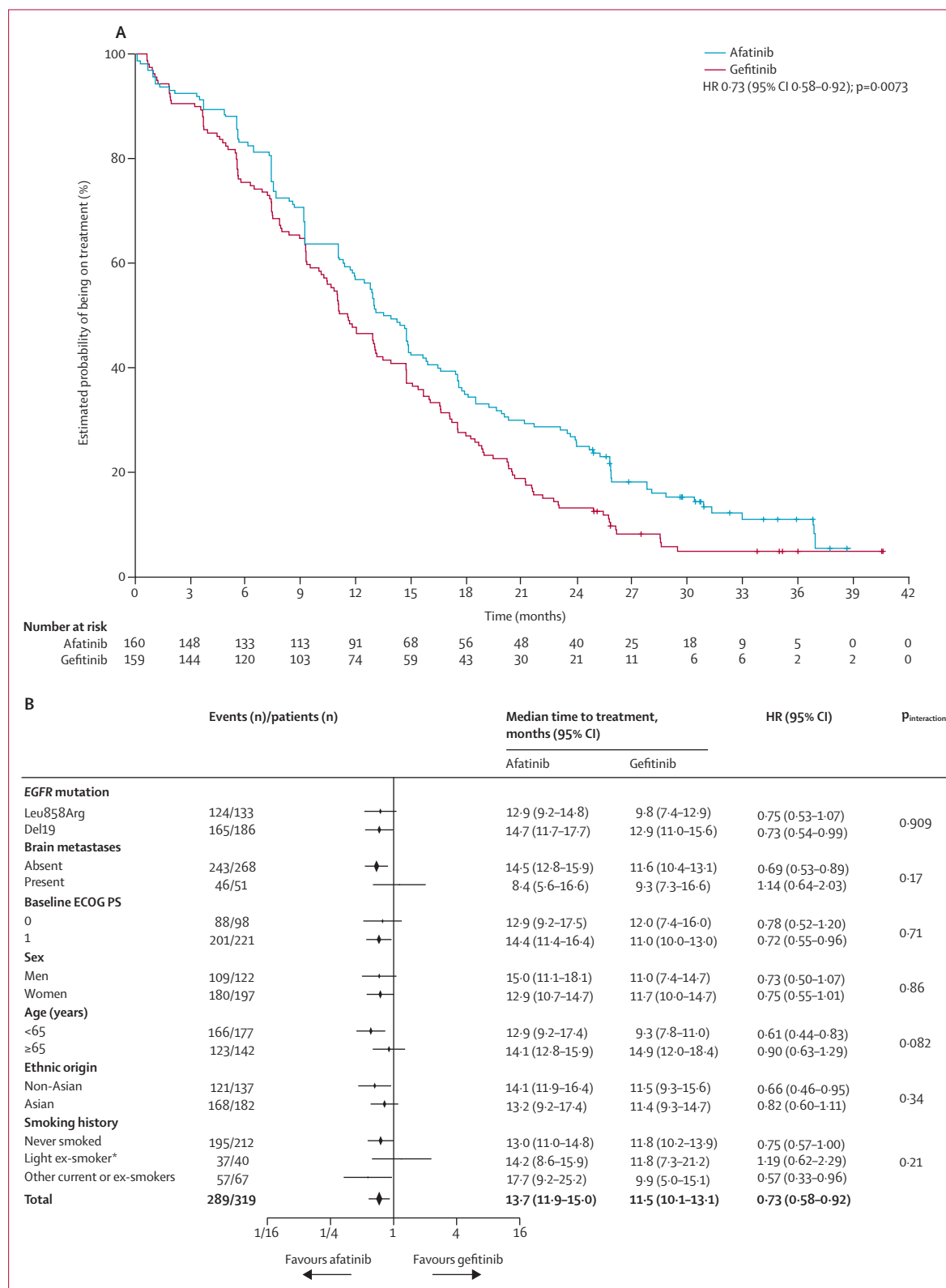*Less than 15 pack-years and stopped more than 1 year before diagnosis.

A

Estimated probability of being on treatment (%)

— Afatinib
— Gefitinib
HR 0·73 (95% CI 0·58–0·92); p=0·0073

Time (months)

Number at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Afatinib	160	148	133	113	91	68	56	48	40	25	18	9	5	0	0
Gefitinib	159	144	120	103	74	59	43	30	21	11	6	6	2	2	0

B

	Events (n)/patients (n)		Median time to treatment, months (95% CI)		HR (95% CI)	P_interaction
			Afatinib	Gefitinib		
EGFR mutation						
Leu858Arg	124/133		12·9 (9·2–14·8)	9·8 (7·4–12·9)	0·75 (0·53–1·07)	0·909
Del19	165/186		14·7 (11·7–17·7)	12·9 (11·0–15·6)	0·73 (0·54–0·99)	
Brain metastases						
Absent	243/268		14·5 (12·8–15·9)	11·6 (10·4–13·1)	0·69 (0·53–0·89)	0·17
Present	46/51		8·4 (5·6–16·6)	9·3 (7·3–16·6)	1·14 (0·64–2·03)	
Baseline ECOG PS						
0	88/98		12·9 (9·2–17·5)	12·0 (7·4–16·0)	0·78 (0·52–1·20)	0·71
1	201/221		14·4 (11·4–16·4)	11·0 (10·0–13·0)	0·72 (0·55–0·96)	
Sex						
Men	109/122		15·0 (11·1–18·1)	11·0 (7·4–14·7)	0·73 (0·50–1·07)	0·86
Women	180/197		12·9 (10·7–14·7)	11·7 (10·0–14·7)	0·75 (0·55–1·01)	
Age (years)						
<65	166/177		12·9 (9·2–17·4)	9·3 (7·8–11·0)	0·61 (0·44–0·83)	0·082
≥65	123/142		14·1 (12·8–15·9)	14·9 (12·0–18·4)	0·90 (0·63–1·29)	
Ethnic origin						
Non-Asian	121/137		14·1 (11·9–16·4)	11·5 (9·3–15·6)	0·66 (0·46–0·95)	0·34
Asian	168/182		13·2 (9·2–17·4)	11·4 (9·3–14·7)	0·82 (0·60–1·11)	
Smoking history						
Never smoked	195/212		13·0 (11·0–14·8)	11·8 (10·2–13·9)	0·75 (0·57–1·00)	
Light ex-smoker*	37/40		14·2 (8·6–15·9)	11·8 (7·3–21·2)	1·19 (0·62–2·29)	0·21
Other current or ex-smokers	57/67		17·7 (9·2–25·2)	9·9 (5·0–15·1)	0·57 (0·33–0·96)	
Total	**289/319**		**13·7 (11·9–15·0)**	**11·5 (10·1–13·1)**	**0·73 (0·58–0·92)**	

1/16 1/4 1 4 16

Favours afatinib   Favours gefitinib

Figure 3: **Time-to-treatment failure**
Kaplan-Meier curve (A) and forest plot of prespecified subgroup analyses (B). HR=hazard ratio. ECOG PS=Eastern Cooperative Oncology Group performance status.
*Less than 15 pack-years and stopped more than 1 year before diagnosis.

in the gefitinib group. 20 (13%) patients were still on treatment with afatinib and ten (6%) with gefitinib (figure 1).

The median duration of follow-up for progression-free survival was 27·3 months (IQR 15·3–33·9). At this time, 124 progression-free survival events had occurred in the afatinib group and 122 had occurred in the gefitinib group. Progression-free survival by blinded independent assessment was significantly longer with afatinib versus gefitinib with an HR of 0·73 (95% CI 0·57–0·95; p=0·017); median progression-free survival was 11·0 months (95% CI 10·6–12·9) in the afatinib group versus 10·9 months (95% CI 9·1–11·5) in the gefitinib group (figure 2A). A sensitivity analysis of progression-free survival was done with a restricted mean survival time approach that did not assume proportional hazards; this analysis also showed that afatinib significantly improved progression-free survival versus gefitinib (appendix p 2). Exploratory Kaplan-Meier estimates of progression-free survival at 12 months (47·4% [95% CI 39·2–55·2] vs 41·3% [95% CI 33·0–49·5]), 18 months (27·3% [95% CI 20·2–34·9] vs 15·2% [95% CI 9·3–22·5]), and 24 months (17·6% [95% CI 11·7–24·6] vs 7·6% [95% CI 3·5–13·8]) were all higher with afatinib than with gefitinib (figure 2A). Progression-free survival according to investigator assessment was also significantly improved with afatinib versus gefitinib (HR 0·78 [95% CI 0·61–0·99]; p=0·042; appendix p 11). Prespecified subgroup analysis of progression-free survival is shown in figure 2. Analysis of progression-free survival according to mutation type (exon 19 deletions or Leu858Arg) are shown in the appendix (p 12).

Analysis of time-to-treatment failure showed that patients remained on treatment for significantly longer with afatinib than gefitinib with an HR of 0·73 (95% CI 0·58–0·92; p=0·0073); median time-to-treatment failure was 13·7 months (95% CI 11·9–15·0) versus 11·5 months (10·1–13·1; figure 3A). Overall, 56 (35%) of 160 patients and 47 (30%) of 159 patients continued treatment beyond investigator-assessed radiological progression with afatinib and gefitinib, respectively. The median duration

of treatment beyond progression for afatinib was 2·7 months (95% CI 1·94–4·3) and 2·0 months for gefitinib (1·5–3·0). Prespecified subgroup analyses of time-to-treatment failure are shown in figure 3.

Overall survival data were immature at the time of this primary analysis with 93 events in the afatinib group and 101 events in the gefitinib group. Median overall survival was 27·9 months (95% CI 25·1–32·2) with afatinib versus 25·0 months (20·6–29·3) with gefitinib (HR 0·87 [95% CI 0·66–1·15]; p=0·33). 105 (75%) of 140 patients who discontinued afatinib and 120 (81%) of 149 patients who discontinued gefitinib received at least one subsequent cancer treatment; of these, 60 (43%) and 78 (52%), respectively, received a subsequent EGFR tyrosine kinase inhibitor, with 12 (9%) and 13 (9%), respectively, receiving a third-generation EGFR tyrosine kinase inhibitor.

The proportion of patients who achieved an objective tumour response was significantly higher with afatinib than with gefitinib by independent review (112 [70%] of 160 patients given afatinib vs 89 [56%] of 159 patients given gefitinib; odds ratio 1·87 [95% CI 1·18–2·99]; p=0·0083; table 2) with a longer median duration of response for patients treated with afatinib than gefitinib (10·1 months [IQR 5·6–16·8] vs 8·4 months [6·2–13·1], respectively). Of those patients with a response, most occurred within the first 16 weeks of treatment (92 [82%] of 112 patients for afatinib and 73 [82%] of 89 patients for gefitinib). The proportion of patients achieving disease control was similar for both groups (146 [91%] given afatinib vs 139 [87%] given gefitinib; odds ratio 1·55 [95% CI 0·75–3·22]; p=0·24; table 2); the median duration of disease control was 12·7 months (IQR 7·3–20·2) in the afatinib group and 11·1 months (7·4–14·7) in the gefitinib group. A substantial proportion of patients in both treatment groups had tumour shrinkage, with a higher proportion of afatinib patients showing 50% or greater reductions in tumour size (appendix pp 7, 13). The proportion of patients achieving an objective responses according to EGFR mutation type was 44 (66%) of 67 Leu858Arg patients with afatinib and 28 (42%) of 66 Leu858Arg patients with gefitinib; and 68 (73%) of 93 exon 19 deletion patients with afatinib and 61 (66%) of 93 exon 19 deletion patients with gefitinib (figure 4). Similar improvements from baseline in EQ-5D utility and EQ-VAS scores were seen in both groups (table 3).

Overall, the frequency and severity of all-cause adverse events were similar with afatinib and gefitinib (any grade: 158 [99%] of 160 in the afatinib group and 159 [100%] of 159 in the gefitinib group; grade ≥3: 91 [57%] in the afatinib group and 83 [52%] in the gefitinib group). The most frequent drug-related grade 3 or worse adverse events in pateints given afatinib were diarrhoea (20 [13%]), rash or acne (15 [9%)], and fatigue (nine [6%]); and in patients given gefitinib were increased ALT/AST concentrations (14 [9%]) and rash or acne (five [3%];

	Afatinib (n=160)	Gefitinib (n=159)	p value*
Objective response	112 (70%)	89 (56%)	0·0083
Complete response	1 (1%)	1 (1%)	..
Partial response	111 (69%)	88 (55%)	..
Stable disease	34 (21%)	50 (31%)	..
Progressive disease	9 (6%)	17 (11%)	..
Not evaluable	5 (3%)	3 (2%)	..
Disease control	146 (91%)	139 (87%)	0·24

Data are n (%). *From a logistic regression model adjusted for the covariates of EGFR mutation type and baseline brain metastases.

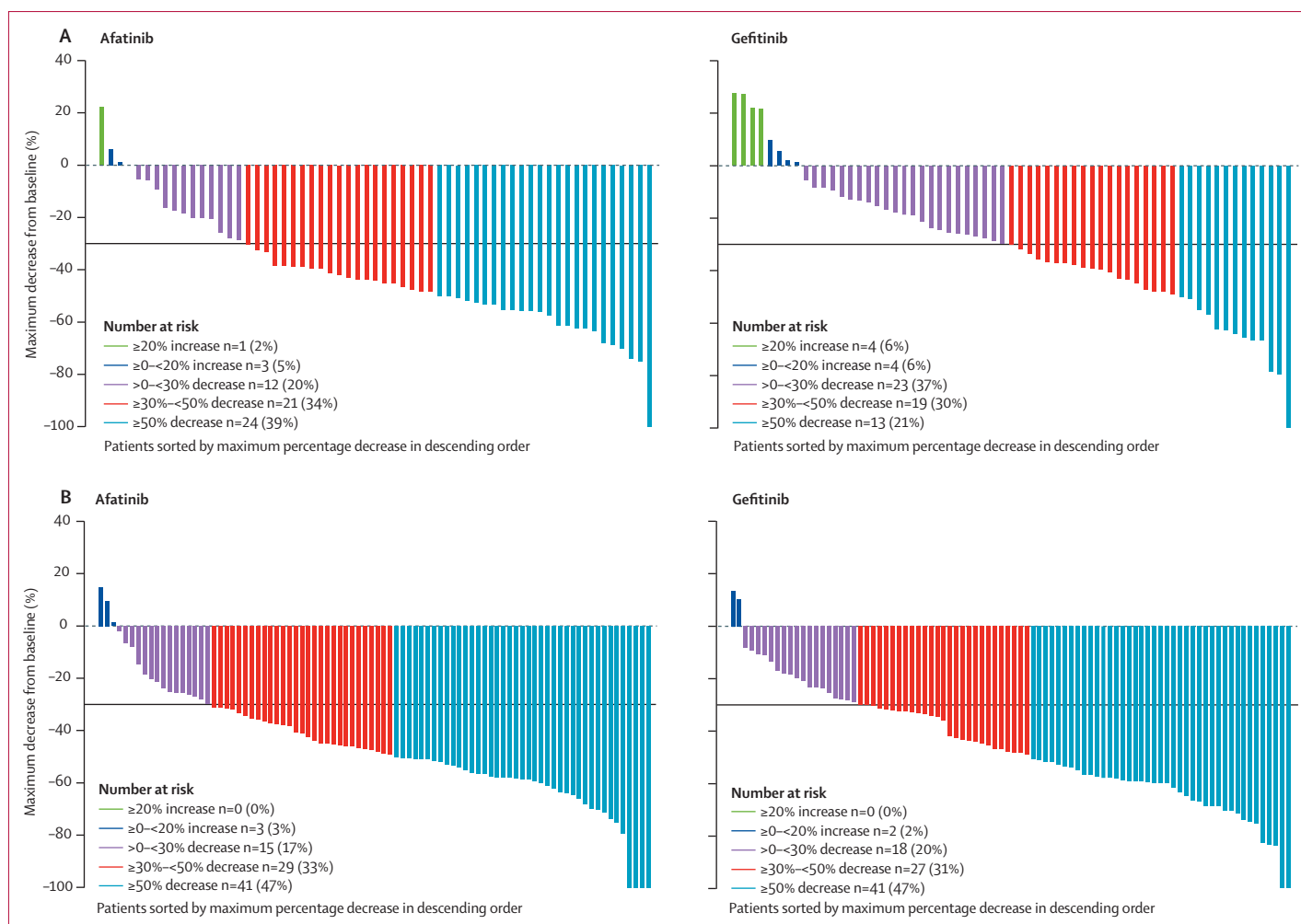Table 2: Best objective tumour response by independent review

Figure 4: Maximum percentage decrease from baseline in the sum of target lesion diameters by independent review
EGFR stratification factor Leu858Arg (A) and *EGFR* stratification factor exon 19 deletion (B).

table 4). Serious drug-related adverse events were reported in 17 (11%) patients given afatinib and seven (4%) patients given gefitinib; the most frequent were diarrhoea (10 [6%] patients given afatinib *vs* one [1%] patient given gefitinib) and interstitial lung disease (four [3%] patients given gefitinib *vs* no patients given afatinib).

Dose reductions due to adverse events were undertaken mostly with afatinib (67 [42%] of 160 patients) rather than gefitinib (three [2%] of 159 patients), but it should be noted that gefitinib only has one dose strength (250 mg) and no dose reduction scheme was specified in the summary of product characteristics or prescribing information. Ten (6%) patients discontinued due to drug-related adverse events in each treatment group (appendix p 8). The most frequent drug-related adverse events leading to discontinuation were diarrhoea (five [3%]) in the afatinib group, and increase in ALT/AST concentrations (five [3%]) and interstitial lung disease (four [3%]) in the gefitinib group. 15 (9%) deaths occurred

	Afatinib (n=160)	Gefitinib (n=159)	p value
EQ-5D			
Baseline mean (SD)	0·72 (0·26)	0·73 (0·25)	..
Post-baseline adjusted mean (SE)*	0·77 (0·01)	0·80 (0·01)	0·14
EQ-VAS			
Baseline mean (SD)	69·7 (19·3)	71·2 (17·0)	..
Post-baseline adjusted mean (SE)*	74·5 (1·1)	76·0 (1·1)	0·203

Utility scores range from 0=worst health to 1=full health. Visual analogue scale scores range from 0=worst imaginable health state to 100=best imaginable health state. EQ-VAS=EuroQoL EQ visual analogue scale. EQ-5D=EuroQoL-5D health status self-assessment questionnaire. *From mixed-effects growth curve models adjusted for *EGFR* mutation group and presence of brain metastases, mean score up to median follow-up of 56 weeks.

Table 3: Change in EQ-5D utility and EQ-VAS scores over time

in the afatinib group (four from malignant neoplasm progression, one from pneumonia, one from metastases to meninges, one from ischaemic stroke, one from acute respiratory failure, one from interstitial lung disease or

respiratory distress, one from pneumonia aspiration, one from respiratory failure, one from hepatic haemorrhage, one from multiorgan failure, one from wound), and one from death from an unknown cause and ten (6%) in the gefitinib group (two from metastases to meninges, one from lung infection, one from malignant neoplasm

	Afatinib (n=160)				Gefitinib (n=159)			
	Grades 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5
Total	106 (66%)	47 (29%)	3 (2%)	0	124 (78%)	26 (16%)	2 (1%)	1 (1%)
Diarrhoea	124 (78%)	19 (12%)	1 (1%)	0	95 (60%)	2 (1%)	0	0
Rash or acne*	127 (79%)	15 (9%)	0	0	124 (78%)	5 (3%)	0	0
Stomatitis†	96 (60%)	7 (4%)	0	0	38 (24%)	0	0	0
Paronychia‡	86 (54%)	3 (2%)	0	0	26 (16%)	1 (1%)	0	0
Dry skin	52 (33%)	0	0	0	59 (37%)	0	0	0
Pruritus	37 (23%)	0	0	0	36 (23%)	0	0	0
Fatigue§	24 (15%)	9 (6%)	0	0	23 (14%)	0	0	0
Decreased appetite	25 (16%)	1 (1%)	0	0	19 (12%)	0	0	0
Nausea	24 (15%)	2 (1%)	0	0	22 (14%)	0	0	0
Alopecia	17 (11%)	0	0	0	24 (15%)	0	0	0
Vomiting	17 (11%)	0	0	0	5 (3%)	1 (1%)	0	0
Increased ALT/AST	16 (10%)	0	0	0	25 (16%)	13 (8%)	1 (1%)	0
Nasal dryness	10 (6%)	1 (1%)	0	0	0	0	0	0
Conjunctivitis¶	7 (4%)	0	0	0	9 (6%)	1 (1%)	0	0
Hand-foot syndrome	5 (3%)	1 (1%)	0	0	3 (2%)	0	0	0
Weight decreased	5 (3%)	1 (1%)	0	0	0	0	0	0
Hypokalaemia	4 (3%)	3 (2%)	0	0	1 (1%)	0	0	0
Neutropenia	2 (1%)	0	1 (1%)	0	1 (1%)	0	0	0
Increased aminotransferases	2 (1%)	0	0	0	0	1 (1%)	0	0
Toxic skin eruption	2 (1%)	1 (1%)	0	0	0	0	0	0
Dehydration	1 (1%)	3 (2%)	0	0	0	0	0	0
Pneumonia	1 (1%)	1 (1%)	0	0	0	0	0	0
Confusional state	1 (1%)	1 (1%)	0	0	0	0	0	0
Hypercreatinaemia	0	0	1 (1%)	0	0	0	0	0
Acute kidney injury	0	1 (1%)	1 (1%)	0	0	0	0	0
Skin bacterial infection	0	1 (1%)	0	0	0	0	0	0
Acidosis	0	1 (1%)	0	0	0	0	0	0
Hypoalbuminaemia	0	1 (1%)	0	0	0	0	0	0
Paraneoplastic encephalomyelitis	0	1 (1%)	0	0	0	0	0	0
Flushing	0	1 (1%)	0	0	2 (1%)	0	0	0
Gastrointestinal pain	0	1 (1%)	0	0	0	0	0	0
Blood bicarbonate decreased	0	1 (1%)	0	0	0	0	0	0
Intertrigo	0	1 (1%)	0	0	1 (1%)	0	0	0
Scab	0	1 (1%)	0	0	1 (1%)	0	0	0
Renal failure	1 (1%)	0	0	0	0	0	0	1 (1%)
Interstitial lung disease	0	0	0	0	1 (1%)	2 (1%)	1 (1%)	0
Anal haemorrhage	0	0	0	0	0	1 (1%)	0	0
Bone marrow failure	0	0	0	0	0	1 (1%)	0	0
Hepatic failure	0	0	0	0	0	0	0	1 (1%)
Hepatitis	0	0	0	0	0	0	1 (1%)	0

There was one drug-related fatal adverse event; a case of hepatic and renal failure with gefitinib treatment. ALT=alanine aminotransferase. AST=aspartate aminotransferase. *Grouped term including the following reported preferred terms: acne, blister, dermatitis, dermatitis acneiform, dermatitis bullous, drug eruption, eczema, erythema, exfoliative rash, folliculitis, rash, rash erythematous, rash follicular, rash macular, rash maculopapular, rash pruritic, rash pustular, skin erosion, skin exfoliation, skin fissures, skin lesion, skin reaction, skin toxicity, and skin ulcer. †Grouped term including the following reported preferred terms: aphthous stomatitis, mucosal erosion, mucosal inflammation, mouth ulceration, and stomatitis. ‡Grouped term including the following reported preferred terms: nail bed infection, nail infection, and paronychia. §Grouped term including the following reported preferred terms: asthenia, fatigue, and lethargy. ¶Grouped term including the following reported preferred terms: conjunctival irritation and conjunctivitis.

Table 4: Drug-related adverse events (≥10% of patients in either treatment group with grade 1–2 and all grade ≥3 adverse events; NCI CTCAE 3.0)

progression, one from cerebral haemorrhage, one from pneumonia aspiration, one from respiratory failure, one from renal or hepatic failure, one from multiorgan failure, and one from general health deterioration. All but one of these deaths was considered unrelated to treatment; one patient in the gefitinib group died from drug-related hepatic and renal failure.

Discussion

To the best of our knowledge, LUX-Lung 7 is the first prospective head-to-head trial to assess an irreversible ErbB family blocker, afatinib, and a reversible EGFR tyrosine kinase inhibitor, gefitinib, as first-line treatment of patients with *EGFR* mutation-positive NSCLC in both Asians and non-Asian patients. Afatinib significantly improved progression-free survival and time-to-treatment failure. The proportion of patients treated with afatinib who achieved an objective response was also significantly greater with afatinib than gefitinib. Overall, both treatment regimens were well tolerated with predictable adverse event profiles and low rates of discontinuation.

The progression-free survival curves separated more substantially with time, commencing at the median. This finding might reflect the broader and more durable inhibitory profile of afatinib and its potential to delay possible resistance mechanisms when compared with gefitinib. For example, both ErbB2 and ErbB3, whose signalling is inhibited by afatinib, have been implicated in the acquired resistance to first-generation tyrosine kinase inhibitors.[19–21] Furthermore, preclinical evidence indicates that afatinib is active against EGFR harbouring the T790M gatekeeper mutation[15,16] and several previous studies have shown that afatinib has modest activity in patients with acquired resistance to first-generation tyrosine kinase inhibitors.[22–24]

The coprimary endpoint time-to-treatment failure was chosen to reflect real-world clinical practice and treatment guidelines; many patients continue on treatment with tyrosine kinase inhibitors beyond radiological progression in the absence of clinical deterioration. Time-to-treatment failure was significantly improved with afatinib versus gefitinib, indicating that afatinib might confer additional clinical benefit in patients who continued treatment beyond radiological progression. Improved time-to-treatment failure with afatinib also testifies to its general tolerability and manageability of adverse events and acceptance by patients and physicians to remain on therapy beyond progression despite possible accompanying adverse events.

The improved antitumour activity with afatinib noted in this trial might reflect its more potent and irreversible inhibition of EGFR signalling.[15,16] The objective responses recorded with afatinib (70%) in this study were consistent with the LUX-Lung 3 and LUX-Lung 6 trials (61% and 67%, respectively in patients with common *EGFR* mutations).[8,9] The proportion of patients achieving an objective response with gefitinib (56%) was similar with

the reported response rates by independent review (50% to 67%) but somewhat lower than those noted in previous phase 3 trials (62% to 74%) based on investigator review.[4–6,25,26]

The differences in progression-free survival, time-to-treatment failure, and objective responses with afatinib and gefitinib noted in this study were largely unaffected by mutation type. Previous studies have implied that mutation subgroups should be considered as distinct biological and clinical entities.[27–29] Our data, however, support the use of afatinib as a treatment option in both patients with Leu858Arg or exon 19 deletion mutations.

The adverse event profiles with afatinib and gefitinib were as expected; drug-related adverse events of diarrhoea and rash were more frequent with afatinib, and elevated liver enzymes and interstitial lung disease were associated with gefitinib. No difference in the frequency of discontinuations due to adverse events was noted between afatinib and gefitinib, indicating that both drugs are similarly well tolerated, and adverse event profiles are effectively managed through use of predefined dose modification schemes. The contrast in the rate of dose reductions reflects the difference in the recommended dose modification schemes for the two drugs; several dose reduction steps are defined for afatinib and none are defined for gefitinib. The outcome of health-related quality-of-life measures in this study, although limited in scope, showed that both drugs had similar improvements in patient-reported outcomes.

The data reported herein have several limitations. First, LUX-Lung 7 was an exploratory phase 2B trial with no formal predefined hypothesis and had three coprimary endpoints with no adjustment for multiple testing, with the aim of broadly exploring any differences between afatinib and gefitinib. Notwithstanding its exploratory nature, LUX-Lung 7 was larger than many previous randomised phase 3 trials in this setting and assessed multiple clinically relevant, independently assessed, endpoints in a multicentre, multiethnic patient population. Moreover, the results were internally consistent, favouring afatinib across most endpoints and patient subgroups. Second, at the time of the present analysis, the coprimary endpoint of overall survival was not sufficiently mature to allow a simultaneous assessment of all three coprimary endpoints. This was not surprising given the first-line treatment setting and the increasing availability of effective second-line treatment options, including the development of third-generation EGFR tyrosine kinase inhibitors,[30–32] and was the reason for preplanning a subsequent mature overall survival analysis. Notably, recent data have indicated that the emergence of the *EGFR* Thr790Met-acquired resistance mutation is as prevalent in patients treated with afatinib as it is in patients treated with erlotinib or gefitinib.[33] As such, osimertinib or other third-generation inhibitors in development, could prove to be effective second-line treatment options in many

patients initially treated with afatinib. Finally, the open-label trial design could have potentially introduced bias to some endpoints. For example, improved time-to-treatment failure with afatinib might partly reflect the desire of patients or physicians to remain on a new treatment. However, the open-label design of the trial could not affect the progression-free survival and objective response endpoints, because imaging data were reviewed independently in a blinded manner.

In summary, although an exploratory trial, the totality of data reported herein indicates that afatinib might offer improved efficacy compared with gefitinib, while conferring a predictable tolerability profile. Our findings suggest that first-generation and second-generation EGFR targeted drugs might not be interchangeable. We believe that these data provide additional evidence to help to inform decision making when choosing a first-line treatment for patients with *EGFR* mutation-positive NSCLC.

Contributors

KP, KO'B, MB, TM, VH, JC-HY, MS, MK, DM, VZ, and LP-A contributed towards study conception and design. KP, KO'B, LZ, MB, KHL, SL, YS, S-WK, JL, D-WK, CDA, KK, C-MT, and LP-A contributed towards patient recruitment. KP, LZ, TM, VH, JC-HY, KHL, SL, YS, S-WK, D-WK, KK, SAL, C-MT, and LP-A contributed towards data collection. KP, E-HT, KO'B, LZ, MB, TM, VH, JC-HY, KHL, SL, YS, S-WK, JL, D-WK, CDA, SAL, C-MT, MS, MK, DM, VZ, and LP-A contributed towards data analysis and interpretation. KO'B, VH, and MK contributed towards the literature search. All authors drafted and reviewed the report, and approved the final version for submission.

Declaration of interests

KP reports personal fees for advisory roles from AstraZeneca, Boehringer Ingelheim, Clovis, Eli Lilly, Hanmi, Kyowa Hakko Kirin, Ono, Novartis, and Roche; and grants from AstraZeneca. KO'B reports writing assistance from Boehringer Ingelheim, Pfizer, and BMS; honoraria for advisory board and speaker bureau work, and travel, accommodation, and registration expenses for meetings/conferences from Boehringer Ingelheim, Merck Sharp & Dohme, Lilly Oncology, AstraZeneca, Roche, Pfizer, and BMS; and honoraria for advisory board work only, from Novartis. LZ reports advisory board participation for AstraZeneca and Roche, and corporate-sponsored research for Pfizer. MB reports grants from Boehringer Ingelheim, per patient payments for the clinical trial; grants from AstraZeneca and Pfizer; and advisory board participation for AstraZeneca. TM reports personal fees from AstraZeneca, Roche/Genentech, Lilly, Merck Serono, ACEA Biosciences, BMS, AVEO & Biodesix, Pfizer, Boehringer Ingelheim, Novartis Pharmaceuticals, GlaxoSmithKline, Clovis Oncology, Amgen, Janssen, BioMarin Pharmaceuticals, SFJ Pharmaceuticals, MSD, Vertex Pharmaceuticals, Prime Oncology, geneDecode, and Sanomics Ltd. VH reports advisory board participation for Boehringer Ingelheim. JC-HY reports grants from Boehringer Ingelheim; personal fees for advisory board participation and presentations from Boehringer Ingelheim, Eli Lilly, Roche/Genentech/Chugai, and MSD; personal fees for presentations only from Bayer; and personal fees for advisory board participation only from Pfizer, Clovis Oncology, Merck Serono, Astelllas, Novartis, and Celgene. JL reports grants paid to her institution from Boehringer Ingelheim Canada and AstraZeneca; and personal fees for educational talks from Pfizer Canada and Boehringer Ingelheim Canada. SAL reports fees to his institution for the conduct of this trial, and honoraria, from Boehringer Ingelheim. C-MT reports consulting fees and honoraria from Pfizer, Roche, Eli Lilly, Boehringer Ingelheim and AstraZeneca. MS, MK, DM, and VZ report employment by Boehringer Ingelheim. LP-A reports personal fees for scientific advice from Boehringer Ingelheim, Pfizer, Roche, Clovis, and AstraZeneca. All other authors declare no competing interests.

References

1   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.

2   Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004; **304:** 1497–500.

3   Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. *Nat Rev Cancer* 2007; **7:** 169–81.

4   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.

5   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.

6   Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; **361:** 947–57.

7   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.

8   Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013; **31:** 3327–34.

9   Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol* 2014; **15:** 213–22.

10 Wu YL, Zhou C, Liam CK, et al. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. *Ann Oncol* 2015; **26:** 1883–89.

11 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.

12 Haaland B, Tan PS, de Castro G Jr, Lopes G. Meta-analysis of first-line therapies in advanced non-small-cell lung cancer harboring EGFR-activating mutations 8. *J Thorac Oncol* 2014; **9:** 805–11.

13 Haspinger ER, Agustoni F, Torri V, et al. Is there evidence for different effects among EGFR-TKIs? Systematic review and meta-analysis of EGFR tyrosine kinase inhibitors (TKIs) versus chemotherapy as first-line treatment for patients harboring EGFR mutations. *Crit Rev Oncol Hematol* 2015; **94:** 213–27.

14 Popat S, Mok T, Yang JC, et al. Afatinib in the treatment of EGFR mutation-positive NSCLC--a network meta-analysis. *Lung Cancer* 2014; **85:** 230–38.

15 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.

16 Solca F, Dahl G, Zoephel A, et al. Target binding properties and cellular activity of afatinib (BIBW 2992), an irreversible ErbB family blocker. *J Pharmacol Exp Ther* 2012; **343:** 342–50.

17 Andersen PK, Hansen MG, Klein JP. Regression analysis of restricted mean survival time based on pseudo-observations. *Lifetime Data Anal* 2004; **10:** 335–50.

18 Shuster JJ. Median follow-up in clinical trials. *J Clin Oncol* 1991; **9:** 191–92.

19 Yonesaka K, Kudo K, Nishida S, et al. The pan-HER family tyrosine kinase inhibitor afatinib overcomes HER3 ligand heregulin-mediated resistance to EGFR inhibitors in non-small cell lung cancer. *Oncotarget* 2015; **6:** 33602–11.

20 Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res* 2013; **19:** 2240–47.

21 Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* 2007; **316:** 1039–43.

22 Katakami N, Atagi S, Goto K, et al. LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. *J Clin Oncol* 2013; **31:** 3335–41.

23 Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol* 2012; **13:** 528–38.

24 Schuler M, Yang JC, Park K, et al. Afatinib beyond progression in patients with non-small-cell lung cancer following chemotherapy, erlotinib/gefitinib and afatinib: phase III randomized LUX-Lung 5 trial. *Ann Oncol* 2015; **27:** 417–23.

25 Douillard JY, Ostoros G, Cobo M, et al. First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: a phase-IV, open-label, single-arm study. *Br J Cancer* 2014; **110:** 55–62.

26 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.

27 Kuan FC, Kuo LT, Chen MC, et al. Overall survival benefits of first-line EGFR tyrosine kinase inhibitors in EGFR-mutated non-small-cell lung cancers: a systematic review and meta-analysis. *Br J Cancer* 2015; **113:** 1519–28.

28 Yang JC, Wu YL, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol* 2015; **16:** 141–51.

29 Lee CK, Wu YL, Ding PN, et al. Impact of specific epidermal growth factor receptor (EGFR) mutations and clinical characteristics on outcomes after treatment with EGFR tyrosine kinase inhibitors versus chemotherapy in EGFR-mutant lung cancer: a meta-analysis. *J Clin Oncol* 2015; **33:** 1958–65.

30 Janne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med* 2015; **372:** 1689–99.

31 Park K, Lee JS, Lee KH, et al. Updated safety and efficacy results from phase I/II study of HM61713 in patients (pts) with EGFR mutation positive non small cell lung cancer (NSCLC) who failed previous EGFR-tyrosine kinase inhibitor (TKI). *Proc Soc Am Clin Oncol* 2015; **33:** abstr 8084.

32 Sequist LV, Soria JC, Goldman JW, et al. Rociletinib in EGFR-mutated non-small-cell lung cancer. *N Engl J Med* 2015; **372:** 1700–09.

33 Wu SG, Liu YN, Tsai MF, et al. The mechanism of acquired resistance to irreversible EGFR tyrosine kinase inhibitor-afatinib in lung adenocarcinoma patients. *Oncotarget* 2016; published online Feb 4. DOI:10.18632/oncotarget.7189.