Effect of afatinib on overall survival of patients with EGFR mutation-positive lung adenocarcinoma: outcomes of the two randomised Phase III trials LUX-Lung 3 and LUX-Lung 6

Authors:

James Chih-Hsin Yang*,†, Yi-Long Wu*,†, Martin Schuler, Martin Sebastian, Sanjay Popat, Nobuyuki Yamamoto, Caicun Zhou, Cheng-Ping Hu, Kenneth O'Byrne, Jifeng Feng, Shun Lu, Yunchao Huang, Sarayut L Geater, Kye Young Lee, Chun-Ming Tsai, Vera Gorbunova, Vera Hirsh, Jaafar Bennouna, Sergey Orlov, Tony Mok, Michael Boyer, Wu-Chou Su, Ki Hyeong Lee, Terufumi Kato, Dan Massey, Mehdi Shahidi, Victoria Zazulina, Lecia V Sequist

Affiliations:

National Taiwan University Hospital and National Taiwan University, Taipei, Taiwan (Prof JC-H Yang MD); Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China (Prof Y-L Wu MD); West German Cancer Center, University Hospital Essen, University Duisburg-Essen, Essen, Germany (Prof M Schuler MD); Johann Wolfgang Goethe University Medical Center, Frankfurt am Main, and University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany (M Sebastian MD); Royal Marsden Hospital, London, UK (S Popat FRCP); Wakayama Medical University, Wakayama, Japan (Prof N Yamamoto MD); Shanghai Pulmonary Hospital, Tongji University, Shanghai, China (Prof C Zhou MD); Xiangya Hospital, Central South University, Changsha, China (Prof C-P Hu MD); Princess Alexandra Hospital and Queensland University of Technology, Australia (Prof K O'Byrne MD); Jiangsu Province Cancer Hospital, Nanjing, Jiangsu, China (Prof J Feng PhD); 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); Prince of Songkla University, Songkhla, Thailand (SL Geater MD); Department of Internal Medicine, Konkuk University Medical Center, Seoul, South Korea (Prof KY Lee MD); Taipei Veterans General Hospital, Taipei, Taiwan (Prof C-M Tsai MD); FSBI "N.N Blokhin Russian Cancer Research Centre", Russian Academy of Medical Sciences, Moscow, Russia (Prof V Gorbunova MD); McGill University, Montreal, Canada (Prof V Hirsh MD); Institut de Cancérologie de l'Ouest-site René Gauducheau, Nantes, France (Prof J Bennouna MD); Pavlov State Medical University, St Petersburg, Russia (Prof S Orlov MD); State Key Laboratory of South China, Hong Kong Cancer Institute, The Chinese University of Hong Kong, Hong Kong, China (Prof T Mok MD); Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia (Prof M Boyer MBBS); National Cheng Kung University Hospital, Tainan, Taiwan (Prof W-C Su MD); Chungbuk National University Hospital, Cheongju, South Korea (Prof KH Lee MD); Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan (T Kato MD); Boehringer Ingelheim Ltd UK, Bracknell, Berkshire, UK (D Massey MSc, M Shahidi MD, V Zazulina MD); Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA (LV Sequist MD)

*These authors contribute equally to this work.

[†]Correspondence to:

James Chih-Hsin Yang

National Taiwan University Hospital, 7 Chung-Shan South Rd, Taipei 100, Taiwan

Phone: +886223123456 ext 67511

Fax: +886223711174

Email: chihyang@ntu.edu.tw

Yi-Long Wu

Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences,106 Zhongshan Er Rd, Guangzhou 510080, China

Phone: +862083877855

Fax: +862083827712

Email: syylwu@live.cn

Previous presentation: Presented in part at the 50th Annual Meeting of the American Society of Clinical Oncology, 30 May–3 June 2014, Chicago, IL, USA.

Summary

Background

Afatinib, an irreversible ErbB family blocker, improved progression-free survival (PFS) versus pemetrexed/cisplatin (LUX-Lung-3 [LL3]) or gemcitabine/cisplatin (LUX-Lung-6 [LL6]) in patients with lung adenocarcinoma harbouring epidermal growth factor receptor (*EGFR*) mutations. Overall survival (OS) was a pre-specified secondary endpoint.

Methods

Treatment-naïve patients with *EGFR* mutation-positive stage IIIB/IV lung adenocarcinoma (LL3=345; LL6=364) were randomised (2:1) to afatinib or chemotherapy, stratified by *EGFR* mutation (Del19/L858R/other) and race (LL3). Mature OS analyses, including pre-specified subgroup analyses, were planned in the intent-to-treat population after 209 (LL3) and 237 (LL6) events. Individual patient data from these studies were also combined for post-hoc exploratory OS analyses. These ongoing (active, not recruiting) studies are registered with ClinicalTrials.gov: NCT00949650 (LL3), NCT01121393 (LL6).

Findings

In LL3 and LL6, median follow-up was 41 and 33 months, respectively, and 213 (62%) of 345 patients and 246 (68%) of 364 patients had died. In each study, a trend towards OS improvement was observed with afatinib versus chemotherapy for all patients and those with tumours harbouring common *EGFR* mutations (Del19/L858R). OS was significantly improved with afatinib versus chemotherapy in patients with Del19 mutation-positive tumours in LL3 (33·3 months [95% CI 26·8–41·5] *vs* 21·1 months [16·3–30·7]; hazard ratio [HR] 0.54 [95% CI 0·36–0·79; p=0·0015]) and LL6 (31·4 months [24·2–35·3] *vs* 18·4 months [14·6–25·6]; HR 0·64 [0·44–0·94; p=0·023]). In combined analyses, OS was improved with afatinib versus chemotherapy in patients with tumours harbouring common *EGFR* mutations

(27·3 months [24·2–31·0] *vs* 24·3 months [20·6–27·0]; HR 0·81 [0·66–0·99; p=0·037]); HRs were 0·59 (0·45–0·77; p=0·0001) for the Del19 subgroup and 1·25 (0·92–1·71; p=0·16) for the L858R subgroup.

Interpretation

LL3 and LL6 independently demonstrated significant improvements in OS with first-line afatinib versus chemotherapy in patients with lung adenocarcinoma harbouring *EGFR* Del19 mutation; no difference was observed in the L858R mutation-positive subgroup. These findings suggest that patients with *EGFR* Del19 and L858R mutation-positive tumours are biologically distinct disease subgroups that should be analysed separately in future trials.

Funding

Boehringer Ingelheim.

Introduction

Lung adenocarcinoma patients with tumours harbouring epidermal growth factor receptor (*EGFR*) mutations are highly responsive to treatment with EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib, erlotinib, or afatinib.[1] Seven randomised phase 3 studies conducted in this genetically-selected subset of lung cancer patients demonstrated superior progression-free survival (PFS) and response rate with gefitinib or erlotinib compared to platinum-based chemotherapy.[2–8] However, overall survival (OS) benefit was not observed in these studies, irrespective of *EGFR* mutation type,[8–15] presumed to be due to the fact that the majority of patients randomised to first-line chemotherapy were subsequently treated with EGFR TKIs. A meta-analysis of 13 randomised studies examining first-line gefitinib or erlotinib (monotherapy or combined with chemotherapy) compared to chemotherapy/placebo in patients with *EGFR* mutation-positive lung cancer concluded there was no difference in OS (hazard ratio [HR] 1·01 [95% confidence interval (CI) 0·87–1·18]) despite the overwhelming PFS advantage among those receiving EGFR TKIs (HR 0·43 [95% CI 0·38–0·49; p<0·001]).[16]

Afatinib, a second-generation irreversible TKI that inhibits signalling from all homodimers and heterodimers formed by ErbB receptor family members (EGFR, HER2, ErbB3, and ErbB4), has demonstrated clinical activity in EGFR TKI-naïve patients with *EGFR* mutation-positive lung adenocarcinoma.[17–19] First-line afatinib versus standard chemotherapy was recently evaluated in two large, randomised phase 3 trials in treatment-naïve patients with *EGFR* mutation-positive advanced lung adenocarcinoma.[18,19] These two studies, designed to meet the regulatory requirements of different regions, were nearly identical in design with the exception of the platinum-based comparator regimen: pemetrexed/cisplatin in LUX-Lung-3 (LL3) and gemcitabine/cisplatin in LUX-Lung-6 (LL6). Both studies showed superior PFS (primary endpoint), objective response rate (ORR) and

patient-reported outcomes for patients receiving first-line afatinib.[18–20] These studies also demonstrated differences in PFS with afatinib based on *EGFR* mutation type; PFS was most improved in patients with tumours harbouring exon 19 deletion (Del19) followed by the exon 21 substitution (L858R) mutation.[18,19]

Here we report mature OS results from the individual LL3 and LL6 studies. Additionally, in order to provide more accurate estimates of the overall treatment effect of afatinib in these patients, particularly in pre-specified subgroups, individual patient data from the LL3 and LL6 studies were combined for an exploratory OS analysis.

Methods

Study design and endpoints

Detailed study designs, inclusion/exclusion criteria, and methods of the primary analyses of LL3 and LL6 have been previously published.[18,19] In brief, eligible patients were aged ≥18 years, had previously untreated stage IIIB/IV lung adenocarcinoma (measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1) and confirmed *EGFR* mutations in the tumour (based on a validated test kit [Therascreen EGFR 29; Qiagen, Manchester, UK]), had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and a life expectancy of at least three months.

Patients enrolled in LL3 (N=345; recruited globally) and LL6 (N=364; recruited in China, Korea, and Thailand) were randomised (2:1) to receive afatinib or chemotherapy, stratified by *EGFR* mutation type (Del19 *vs* L858R *vs* other 'uncommon' mutations) and race (Asian *vs* non-Asian; LL3 only); a block size of 3 was used within each of the strata. Randomisation was performed using a validated random number generating system at Boehringer Ingelheim, verified by a trial-independent statistician, and implemented centrally via an

Interactive Voice/Web Response System; individuals directly involved in the conduct and analysis of the trial did not have access to the randomisation schedule. Patients received either continuous oral afatinib (40 mg/day; Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany) or up to six cycles of intravenous pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) once every 21 days in LL3 or gemcitabine (1000 mg/m^2; day 1 and 8) plus cisplatin (75 mg/m^2; day 1) every 21 days in LL6. Patients receiving afatinib were permitted to dose escalate to 50 mg/day after the first 21-day cycle if they did not experience treatment-related adverse events (AEs) greater than grade 1. Afatinib dose reduction by 10-mg decrements down to 20 mg/day was allowed for treatment-related grade 3 or selected prolonged grade 2 AEs, as previously described.[18,19] Dose reductions for patients receiving chemotherapy were in accordance with guidance provided in the current summary of product characteristics and institutional guidelines.

In both studies, the primary endpoint was PFS, defined as time from randomisation to progression (as determined by independent review). Key secondary endpoints were ORR (complete response and partial response), disease control rate (ORR and stable disease), and OS; other secondary endpoints included patient-reported outcomes and safety. Tumour assessments were performed by computed tomography or magnetic resonance imaging every six weeks for the first 48 weeks and then every 12 weeks thereafter until disease progression or start of new anticancer therapy. AEs were categorised and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. After the last scheduled follow-up visit for the primary endpoint, patients were contacted every 2 months to collect information on subsequent therapies and survival until patient death, loss to follow-up, or withdrawal of consent.

Both studies were conducted in accordance with the Declaration of Helsinki and guidelines on Good Clinical Practice, and the protocols were approved by local ethics committees at

each participating center. Written informed consent was obtained for each patient.

Statistical analyses

Each study was powered (90%) at a two-sided 5% significance level to detect a PFS improvement from 7 months (combination chemotherapy) to 11 months (afatinib) after a minimum of 217 progression events by independent review, with estimated samples sizes of at least 330 patients for each study.[18,19] Primary and key secondary endpoints were analysed following a hierarchical testing strategy to minimise the overall risk of type I error (5%). OS analyses were planned for two time points. The first OS analysis was concurrent with the primary PFS analysis; a Haybittle-Peto stopping boundary was used ($p<0{\cdot}0001$) to preserve the overall 5% type I error. The second OS analysis was planned after 209 deaths in LL3 and 237 deaths in LL6, when it was estimated that the data would be mature. LL3 and LL6 were not purposefully designed with sufficient power to detect OS differences, given that none of the previous studies comparing first-line erlotinib or gefitinib to chemotherapy demonstrated OS benefits.[8–15] Similar to the primary PFS analysis, pre-planned stratification by *EGFR* mutation type (Del19/L858R/other) and race (Asian *vs* non-Asian; LL3 only) was applied for the OS analysis. Pre-planned analyses of additional subgroups of special interest (gender, age, baseline ECOG performance status, *EGFR* mutation category ['common' *vs* 'uncommon'], and smoking history) were also defined. As these did not form part of the confirmatory analysis strategy, no adjustment for multiplicity was performed, and p values can be considered descriptive in nature. A post-hoc exploratory OS analysis based on the combined individual patient data from LL3 and LL6 was performed; heterogeneity was evaluated by testing the study-by-treatment interaction. All efficacy analyses were performed in an intent-to-treat manner, including all patients randomised to treatment.

For each study, the main comparison of OS between treatment arms was performed using a stratified log-rank test adjusting for *EGFR* mutation type (LL3 and LL6) and race (LL3); the

combined OS analysis was adjusted for study (LL3/LL6) and *EGFR* mutation type. Cox proportional-hazard models were used to derive HRs and 95% CIs comparing the two treatment arms, and examining patient subgroups of interest. The proportional hazards assumption was checked via a test for proportionality[21] along with visual checks of the log-cumulative hazard plots. Kaplan-Meier (KM) estimates were used to construct survival curves and calculate median OS. Median follow-up was calculated using the reverse KM method.[22] Statistical analyses were performed with SAS (version 9.2).

Role of the funding source

Boehringer Ingelheim managed the clinical trial database. JC-HY, Y-LW, LVS, and the Boehringer Ingelheim study team analysed the data according to the statistical plan and decided upon exploratory analyses. JC-HY had full access to the study data and prepared the manuscript draft, and all authors participated in the manuscript development and made the final decision to submit the manuscript for publication.

Results

Patients

Patients were randomised between August 2009 and February 2011 in LL3, and between April 2010 and November 2011 in LL6. 345 patients in LL3 and 364 patients in LL6 were randomly assigned to study treatment (figure 1); all randomised patients were included in the OS analysis. Patient baseline characteristics are listed in table 1. In both studies, the majority of patients were females (LL3: 224 [65%] of 345 patients; LL6: 238 [65%] of 364 patients), never smokers (LL3: 236 [68%] of 345 patients; LL6: 280 [77%] of 364 patients), had stage IV disease (LL3: 308 [89%] of 345 patients; LL6: 342 [94%] of 364 patients), and had an ECOG performance status of 1 (LL3: 212 [61%] of 345 patients; LL6: 275 [76%] of 364 patients). In the LL3 study, which recruited globally, 249 (72%) of 345 patients were

Asian. All patients enrolled in LL6 were Asian. The majority of patients in each study had tumours harbouring common *EGFR* mutations (Del19/L858R; LL3: 307 [89%] of 345 patients; LL6: 324 [89%] of 364 patients); approximately half of patients (LL3: 169 [49%] of 345 patients; LL6: 186 [51%] of 364 patients) had *EGFR* Del19 mutation-positive tumours. This analysis focused on clinical outcomes in patients with tumours harbouring common *EGFR* mutations. As patients with lung adenocarcinoma harbouring uncommon *EGFR* mutations represent a heterogeneous population with variable responses to treatment, a dedicated manuscript is in development to detail the outcomes of these patients.

At the data cutoff for this analysis (November 2013 for LL3 and December 2013 for LL6), the median (interquartile range [IQR]) duration of follow-up was 41 (IQR 35–44) months in LL3 and 33 (IQR 31–37) months in LL6; 213 (62%) of 345 patients and 246 (68%) of 364 patients had died. As 21 (9%) of 230 patients in LL3 and 23 (10%) of 242 patients in LL6 were still receiving afatinib treatment at the cutoff, follow-up for OS and data on subsequent therapies are not final.

Individual trial OS analyses

In the overall populations, median OS was 28 months (afatinib: 95% CI 24·6–33·6; pemetrexed/cisplatin: 20·7–33·2) in each treatment arm in LL3 (HR 0·88 [95% CI 0·66–1·17; p=0·39]; figure 2A), and 23 months (afatinib: 20·4–27·3; gemcitabine/cisplatin: 18·0–25·6) in each treatment arm in LL6 (HR 0·93 [95% CI 0·72–1·22; p=0·61]; figure 2B). In patients with tumours harbouring common *EGFR* mutations (Del19 and L858R combined), median OS with afatinib and chemotherapy was 31·6 months (95% CI 26·7–35·3) and 28·2 months (20·6–32·3; HR 0·78 [95% CI 0·58–1·06; p=0·11]) in LL3, and 23·6 months (20·5–28·5) and 23·5 months (17·8–25·4; HR 0·83 [95% CI 0·62–1·09; p=0·18]) in LL6 (figures 3A and 3B).

In subgroup analyses examining *EGFR* mutation type in both LL3 and LL6, a significant

improvement with afatinib compared to chemotherapy was observed in patients with tumours harbouring the *EGFR* Del19 mutation (figure 3D). In LL3, median OS for these patients was 33·3 months (95% CI 26·8–41·5) with afatinib versus 21·1 months (16·3–30·7) with chemotherapy (HR 0·54 [95% CI 0·36–0·79; p=0·0015]; figure 4A). In LL6, median OS for patients with *EGFR* Del19 mutation-positive tumours was 31·4 months (24·2–35·3) with afatinib versus 18·4 months (14·6–25·6) with chemotherapy (HR 0·64 [95% CI 0·44–0·94; p=0·023]; figure 4B). No significant differences were observed by treatment arm for patients with *EGFR* L858R mutation-positive disease in either LL3 (HR 1·30 [95% CI 0·80–2·11; p=0·29]; figure 4D) or LL6 (HR 1·22 [95% CI 0·81–1·83; p=0·34]; figure 4E).

Patients with disease progression or intolerable AEs discontinued assigned study medication (first-line afatinib or chemotherapy) and received subsequent standard treatment at their physician's discretion. In LL3, drug-related AEs leading to treatment discontinuation in >1 patient included diarrhoea (three, 1%), paronychia (two, 1%) and interstitial lung disease (two, 1%) in 229 afatinib-treated patients, and fatigue (three, 3%) in 111 pemetrexed/cisplatin-treated patients. Drug-related AEs leading to discontinuation in LL6 included rash (five, 2%) in 239 afatinib-treated patients, and vomiting (16, 14%), nausea (11, 10%), neutropenia (10, 9%), leukopenia (eight, 7%), AEs related to platelet and white blood cell count (five, 4%), anaemia (four, 4%), thrombocytopenia (four, 4%), fatigue (four, 4%), hepatic function abnormal (two, 2%), and renal failure (two, 2%) in 113 gemcitabine/cisplatin-treated patients. Complete safety analyses, including incidence of AEs, dose reductions, discontinuations and fatalities, in LL3 and LL6 have been previously reported.[18,19]

Subsequent treatment regimens received are summarised by *EGFR* mutation type for each study in table 2. Subsequent treatment with chemotherapy or an EGFR TKI following first-line therapy was balanced across treatment arms within each study. Among patients

who discontinued study medication in LL3, 78 (75%) of 104 chemotherapy-treated patients with tumours harbouring common *EGFR* mutations subsequently received an EGFR TKI, and 131 (71%) of 184 afatinib-treated patients received subsequent chemotherapy. Among patients who discontinued study medication in LL6, 61 (56%) of 108 chemotherapy-treated patients and 114 (59%) of 194 afatinib-treated patients received subsequent EGFR TKI therapy or chemotherapy, respectively. In addition, there were no differences in the proportion of patients receiving subsequent treatment with chemotherapy or an EGFR TKI following first-line therapy by *EGFR* mutation type (table 2). Of note, patients randomised to first-line chemotherapy typically received erlotinib or gefitinib as later-line EGFR TKI treatment because afatinib was not clinically available at the time.

Exploratory combined OS analysis

Individual patient data from LL3 and LL6 were combined for the afatinib (n=472) and chemotherapy (n=237) treatment arms for exploratory analyses. As the two studies had very similar designs and were conducted simultaneously, heterogeneity in this combined analysis was minimal (p=0·92). Median OS in the combined overall population was 25·8 months (95% CI 23·1–29·3) with afatinib and 24·5 months (21·1–28·1) with chemotherapy (HR 0·91 [95% CI 0·75–1·11; p=0·37]; figure 2C). Among patients with tumours harbouring common *EGFR* mutations (afatinib, n=419; chemotherapy, n=212), OS was significantly improved with afatinib compared to chemotherapy (median 27·3 months [24·2–31·0] *vs* 24·3 months [20·6–27·0]; HR 0·81 [95% CI 0·66–0·99; p=0·037]; figure 3C). Consistent with individual study findings, subgroup analyses indicated that the OS benefit of afatinib was driven primarily by patients with *EGFR* Del19 mutation-positive tumours (figure 3D). In these patients, median OS was 31·7 months (28·1–35·1) versus 20·7 months (16·3–25·6; HR 0·59 [95% CI 0·45–0·77; p=0·0001]; figure 4C), while in patients with *EGFR* L858R mutation-positive tumours, median OS was 22·1 months (19·6–25·4) versus 26·9 months (23·2–31·7; HR 1·25 [95% CI 0·92–1·71; p=0·16]; figure 4F). Of note, HRs favoured afatinib

for all but two of the subgroups analysed (figure 3D). In the subgroup of non-Asian patients with tumours harbouring common *EGFR* mutations (n=83) in LL3, median OS was 28·1 months (22·1–not estimable) with afatinib versus 20·7 months (16·7–33·5) with chemotherapy (HR 0·68, [95% CI 0·39–1·20; p=0·18]), with a significant improvement in non-Asian patients harbouring *EGFR* Del19 mutation-positive tumours (n=46; 33·6 months [24·6–not estimable] *vs* 20·0 months [11·2–33·5]; HR 0·45 [95% CI 0·21–0·95; p=0·03]).

In addition to analyses of subsequent treatment received in the individual LL3 and LL6 studies described above, exploratory combined analyses among LL3 and LL6 patients treated in countries with or without a universal healthcare reimbursement policy were conducted to examine whether regional and systematic access to subsequent therapies had an influence on OS in these studies. These results are presented in table S1 and figure S1.

Discussion

Randomised studies comparing first-line EGFR TKIs with standard chemotherapies suggest that patients with lung adenocarcinoma harbouring *EGFR* mutations benefit from first-line EGFR TKI treatment, with improved response, PFS, and quality of life, although no improvements in OS have been reported.[2–8,18,19] To our knowledge, these two independent phase 3 studies have demonstrated for the first time that first-line afatinib significantly improved OS compared to chemotherapy in patients with lung adenocarcinoma harbouring the *EGFR* Del19 mutation; no difference was observed in patients with L858R mutation-positive disease. Importantly, while the majority of patients in LL3 and the entire population of LL6 were Asian, a significant improvement in OS with afatinib in the Del19 subgroup was also observed in the smaller subpopulation of non-Asian patients in LL3, supporting the applicability of the findings to all patients with *EGFR* mutation-positive disease, regardless of race. The recommendation to use EGFR TKIs as first-line therapy in

patients with *EGFR* mutation-positive disease was based solely on PFS improvement over chemotherapy. [2–8,18,19] Based on this report, the evidence to recommend afatinib as first-line therapy in patients with *EGFR* Del19 mutation-positive disease now includes OS benefit.

EGFR Del19 and L858R mutations comprise up to 90% of all *EGFR* mutation-positive lung adenocarcinoma[23] and are strongly associated with response to EGFR TKIs.[24] In retrospective analyses, patients with *EGFR* Del19 mutation-positive tumours consistently demonstrated greater response rates, time to progression, and survival with erlotinib and gefitinib compared to L858R mutation-positive disease.[25–27] In a large prospective registry of patients treated with erlotinib, multivariate analysis showed that *EGFR* L858R mutation was associated with poorer PFS and OS compared with Del19 mutation.[23] Further, in a meta-analysis of six randomised studies comparing EGFR TKIs to chemotherapy in patients with *EGFR* mutation-positive lung adenocarcinoma, Del19 mutation was associated with significantly greater benefit from EGFR TKI therapy compared to chemotherapy than L858R mutation (p=0·001).[28] The etiology of this pervasive difference in outcomes on EGFR TKIs by *EGFR* mutation subtype is not known. Previously reported results of the LL3 and LL6 studies demonstrated PFS benefit with afatinib versus chemotherapy in patients with *EGFR* Del19 mutation-positive tumours *and* those with the L858R mutation, though consistent with prior literature greater benefit was observed in Del19 mutation-positive disease.[18,19] Within this landscape, our analysis now suggests that afatinib significantly improves OS compared to chemotherapy among patients with *EGFR* Del19 mutation-positive tumours that is not observed in L858R mutation-positive disease, where clinical benefit of afatinib over chemotherapy was demonstrated in terms of PFS and ORR.[18,19] Although subgroups and their analyses were pre-planned, no p value adjustment for multiplicity was performed, thus increasing the chance of a false positive finding. However, for the *EGFR* Del19 mutation subgroup, statistical evidence was considerably stronger than p<0·05, particularly for LL3 (p=0·0015); this coupled with the replication of the result across two independent trials is

strong evidence that the effect is genuine.

Previous reports of reversible EGFR TKIs erlotinib and gefitinib have not demonstrated an OS benefit compared to chemotherapy in overall study populations or by *EGFR* mutation type.[8–15] As EGFR TKI sensitivity among *EGFR*-mutant tumours is not adversely affected by chemotherapy pretreatment,[23] any OS benefit of first-line EGFR TKIs in these studies was thought to be offset by subsequent treatment with second-line EGFR TKIs following progression on chemotherapy. Since afatinib was not clinically available at the time of the LL3 and LL6 studies, very few patients received afatinib as later-line EGFR TKI treatment; the majority received erlotinib or gefitinib after chemotherapy. The clinically meaningful difference in median OS observed with afatinib compared to chemotherapy in patients with *EGFR* Del19 mutation-positive tumours in both studies may be attributed to mechanistic differences between the irreversible ErbB family blocker afatinib and first-generation reversible EGFR TKIs. Further, preclinical studies have shown that *EGFR* Del19 and L858R mutants have distinct biological properties that may impact response to different EGFR TKIs.[29,30]

In LL3, the proportion of patients receiving subsequent therapies following study discontinuation was consistent with reports of similar randomised trials.[5,6,9,11,12] In LL6, which had less follow-up at the time of data cutoff, the proportion of patients receiving subsequent therapies was lower in both arms, potentially reflecting reduced access to treatments in certain countries with different healthcare systems. It is also important to note that the group of patients who did not receive subsequent treatments in both LL3 and LL6 included those who experienced early death, withdrew consent, or were lost to follow-up. In exploratory combined analyses among patients in LL3 and LL6 treated in countries with or without a universal healthcare reimbursement policy, more patients received subsequent therapy in countries with a universal reimbursement policy than countries without a universal policy.

Further, greater access to subsequent therapy was associated with improved median OS in both treatment groups, yet the OS benefit with afatinib over chemotherapy was maintained. In addition, no differences were observed in the proportions of patients receiving subsequent therapies in the *EGFR* Del19 and L858R subgroups within each study, indicating that the OS benefit seen with afatinib in Del19 mutation-positive disease is unlikely attributable to follow-up treatment.

The LL3 control arm of pemetrexed/cisplatin is one of the most commonly used regimens for patients with nonsquamous non-small cell lung cancer.[31] At the time of LL3 initiation, pemetrexed maintenance following initial pemetrexed/cisplatin treatment was not standard of care. Recent results from the PARAMOUNT study showed a statistically significant improvement in OS with maintenance pemetrexed therapy compared to placebo; however, only a 2-month difference in OS versus placebo was observed.[32] Bevacizumab was also evaluated in combination with pemetrexed for maintenance therapy following pemetrexed/cisplatin induction therapy in the phase 3 AVAPERL trial.[33] Although the addition of bevacizumab to the combination therapy improved PFS, a significant benefit in OS was not observed. Thus, it is unlikely that the 1-year OS benefit observed with afatinib versus chemotherapy in the current studies would have been impacted by the addition of pemetrexed and/or bevacizumab maintenance therapy to the chemotherapy arm.

In summary, LL3 and LL6 independently demonstrate that afatinib provided significant improvements in OS compared to platinum-doublet chemotherapy in patients with *EGFR* Del19 mutation-positive lung adenocarcinoma, but not the L858R mutation-positive subgroup. These are the only two studies to date that reveal an OS advantage for *EGFR* Del19 mutation-positive disease treated with a first-line EGFR TKI. Further, these findings suggest that patients with lung adenocarcinoma harbouring *EGFR* Del19 and L858R mutations should be stratified and analysed separately in future clinical trials.

Research in context

Systematic Review

A systematic review of the literature using PubMed to identify phase III, randomised trials evaluating first-line EGFR TKI therapy versus standard platinum-based chemotherapy regimens in treatment-naïve patients with *EGFR* mutation-positive advanced lung adenocarcinoma identified seven trials conducted with reversible EGFR TKIs gefitinib (four trials[2–4,8–12,15]) and erlotinib (three trials[5–7,13,14]), and two trials conducted with the second-generation irreversible TKI afatinib (LL3 and LL6[18,19]). In each of these studies, significant improvements in PFS and response rate were observed with EGFR TKI therapy versus chemotherapy.[2–8,18,19] None of the studies were designed to detect a difference in OS in the overall population or in *EGFR* Del19 or L858R mutation subgroups. In this context, OS benefit over chemotherapy was not observed in the gefitinib or erlotinib studies.[8–15] Only the IPASS, NEJ002 and EURTAC trials examined OS with reversible EGFR TKIs specifically in *EGFR* Del19 or L858R mutation subgroups; no differences in OS were observed.[9–11,13]

Interpretation

LL3 and LL6 previously corroborated the findings of other randomised trials in this setting with regards to our understanding of *EGFR* mutation-positive lung adenocarcinoma and response to EGFR TKIs based on assessments of tumour response and PFS.[18,19] To our knowledge, both LL3 and LL6 have independently demonstrated for the first time a survival benefit in patients with lung adenocarcinoma harbouring the *EGFR* Del19 mutation receiving first-line afatinib versus platinum-doublet chemotherapy, whereas no difference was observed in L858R mutation-positive disease. This finding suggests that among standard first-line EGFR TKIs, afatinib should be the preferred option for patients with *EGFR* Del19 mutation-positive lung adenocarcinoma. Of note, the difference in outcomes for patients with *EGFR* Del19 and L858R mutation-positive disease suggests that these populations should be studied separately in future trials.

Acknowledgements

We thank the patients, their families, and all of the investigators who participated in these studies. Medical writing assistance was provided by Katie McClendon, PhD, of GeoMed, part of KnowledgePoint360, an Ashfield Company, and was supported financially by Boehringer Ingelheim during the preparation of this manuscript. SP acknowledges NHS funding to the Royal Marsden Hospital/Institute of Cancer Research NIHR Biomedical Research Centre.

Contributions

JC-HY, Y-LW, KO'B, VH, TM, DM, MSh, and LVS were involved in conception and design of the study. JC-HY was involved in the literature search. MSc was involved in the provision of study material. JC-HY, Y-LW, MSc, MSe, SP, NY, CZ, C-PH, KO'B, JF, SL, YH, SLG, KYL, C-MT, VG, VH, JB, SO, TM, MB, W-CS, KHL, TK and LVS were involved in patient enrolment, recruitment and treatment. JC-HY, Y-LW, MSc, MSe, NY, CZ, C-PH, JF, YH, SLG, KYL, C-MT, VG, VH, JB, SO, TM, MB, W-CS, KHL, TK and VZ were involved in data collection. JC-HY, Y-LW, MSc, MSe, SP, NY, CZ, KO'B, JF, SL, YH, SLG, KYL, C-MT, VH, SO, TM, MB, KHL, DM, MSh, VZ, and LVS were involved in data analysis and interpretation. JC-HY, Y-LW, MSh and LVS were involved in study oversight and supervision. All authors were involved in the drafting and reviewing of the manuscript, and approved the final manuscript for submission.

Declaration of interests

JC-HY has received honoraria for presentations and advisory board participation from Boehringer Ingelheim, AstraZeneca, Roche, Genentech, Pfizer, Novartis, MSD, Merck Serono, Clovis Oncology, and Bayer. MSc has received personal fees from Novartis, AstraZeneca, Pfizer, GlaxoSmithKline and Lilly, and grants from Novartis and Boehringer Ingelheim. MSe has received honoraria for lectures from Boehringer Ingelheim, Pfizer, Roche, Novartis, BMS and Eli Lilly. He reports advisory board participation for Boehringer

Ingelheim, Roche, Novartis, Pfizer, BMS, Eli Lilly and Teva. SP has received reimbursement of travel expenses as a non-compensated consultant from Boehringer Ingelheim Eli Lilly. KO'B has received advisory board and speaker honoraria from Boehringer Ingelheim. SLG has received fees from Boehringer Ingelheim for accommodation and travel to an international congress. VH reports advisory board participation for Boehringer Ingelheim. JB has received honoraria from Boeringher Ingelheim and Roche, and also Novartis for advisory board participation. TM has received personal fees from AstraZeneca, Roche, Lilly, Merck Serono, Eisai, BMS, AVEO, Pfizer, Boehringer Ingelheim, Novartis, GlaxoSmithKline, Clovis Oncology, Amgen, Janssen, BioMarin Pharmaceuticals, and Threshold Pharmaceuticals. MB has received grants from Boehringer Ingelheim and grants and personal fees from Pfizer, and reports non-financial support from Roche. TK has received fees from Boehringer Ingelheim, Eli Lilly, Chugai pharmaceuticals, AstraZeneca, Pfizer, Taiho pharmaceuticals, Takeda pharmaceuticals, Kirin-Kyowa pharmaceuticals, Shionogi and BMS for research funding. He also reports advisory board participation for Eli Lilly, AstraZeneca and Ono pharmaceuticals. DM is an employee of Boehringer Ingelheim. MSh is an employee of Boehringer Ingelheim. VZ is an employee of Boehringer Ingelheim. LVS reports that her institution received funding from Boehringer Ingelheim to support the study and also reports non-compensated consulting for Boehringer Ingelheim, Clovis Oncology, AstraZeneca, Novartis, Merrimack, Taiho and Genentech. All other authors report no conflicts.

References

1 Mok T, Yang JJ, Lam KC. Treating patients with EGFR-sensitizing mutations: first line or second line-is there a difference? *J Clin Oncol* 2013; **31**: 1081–8.

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

3 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**: 2380–8.

4 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**: 121–8.

5 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.

6 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.

7 Wu Y-L, Liam C-K, Zhou C, et al. First-line erlotinib versus cisplatin/gemcitabine (GP) in patients with advanced EGFR mutation-positive non-small-cell lung cancer (NSCLC): Interim analyses from the Phase 3, open-label, ENSURE study. *J Thorac Oncol* 2013; **8**: S603 (abstr).

8 Han JY, Park K, Kim SW, et al. First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. *J Clin Oncol* 2012; **30**: 1122–8.

9 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.

10 Yang J, Wu YL, Saijo S, et al. Advanced NSCLC With Gefitinib (G) vs Carboplatin/paclitaxel (C/P) by Epidermal Growth Factor Receptor (EGFR) Gene-copy Number Score and by Most Common EGFR Mutation Subtypes – Exploratory Data From IPASS. *Eur J Cancer* 2011; S633.

11 Inoue A, Kobayashi K, Maemondo M, et al. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naive non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). *Ann Oncol* 2013; **24**: 54–9.

12 Mitsudomi T, Morita S, Yatabe Y, et al. Updated overall survival results of WJTOG 3405, a randomized phase III trial comparing gefitinib (G) with cisplatin plus docetaxel (CD) as the first-line treatment for patients with non-small cell lung cancer harboring mutations of the epidermal growth factor receptor (EGFR). *J Clin Oncol* 2012; **30**: 7521 (abstr).

13 TARCEVA® (erlotinib) tablets, for oral use [prescribing information] 2014. (Accessed August 14, 2014, at http://www.gene.com/download/pdf/tarceva_prescribing.pdf.)

14 Zhou C, Wu YL, Liu X, et al. Overall survival (OS) results from OPTIMAL (CTONG0802), a phase III trial of erlotinib (E) versus carboplatin plus gemcitabine (GC) as first-line treatment for Chinese patients with EGFR mutation-positive advanced non-small cell

lung cancer (NSCLC). *J Clin Oncol* 2012; **30**: 7520 (abstr).

15 Yoshioka H, Mitsudomi T, Morita S, et al. Final overall survival results of WJTOG 3405, a randomized phase 3 trial comparing gefitinib (G) with cisplatin plus docetaxel (CD) as the first-line treatment for patients with non-small cell lung cancer (NSCLC) harboring mutations of the epidermal growth factor receptor (EGFR). *J Clin Oncol* 2014; **32**: 8117 (abstr).

16 Lee CK, Brown C, Gralla RJ, et al. Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis. *J Natl Cancer Inst* 2013; **105**: 595–605.

17 Yang JC, Shih JY, Su WC, et al. Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial. *Lancet Oncol* 2012; **13**: 539–48.

18 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.

19 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.

20 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/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013; **31**: 3342–50.

21 Collett D. Modelling Survival Data in Medical Research, Second Edition. USA: Chapman & Hall/CRC CRC Press LLC; 2003.

22 Shuster JJ. Median follow-up in clinical trials. *J Clin Oncol* 1991; **9**: 191–2.

23 Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med* 2009; **361**: 958–67.

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

25 Jackman DM, Yeap BY, Sequist LV, et al. Exon 19 deletion mutations of epidermal growth factor receptor are associated with prolonged survival in non-small cell lung cancer patients treated with gefitinib or erlotinib. *Clin Cancer Res* 2006; **12**: 3908–14.

26 Jackman DM, Miller VA, Cioffredi LA, et al. Impact of epidermal growth factor receptor and KRAS mutations on clinical outcomes in previously untreated non-small cell lung cancer patients: results of an online tumor registry of clinical trials. *Clin Cancer Res* 2009; **15**: 5267–73.

27 Riely GJ, Pao W, Pham D, et al. Clinical course of patients with non-small cell lung cancer and epidermal growth factor receptor exon 19 and exon 21 mutations treated with gefitinib or erlotinib. *Clin Cancer Res* 2006; **12**: 839–44.

28 Ding PN, Gralla R, Inoue A, et al. Exon 19 deletions, smoking history and gender as additional predictive factors for treatment benefit with EGFR tyrosine kinase inhibitors in patients harbouring activating EGFR mutations: a meta-analysis of 1432 patients in six randomised trials. *J Thorac Oncol* 2013; **8**: P1.11-003 (abstr).

29 Okabe T, Okamoto I, Tamura K, et al. Differential constitutive activation of the epidermal growth factor receptor in non-small cell lung cancer cells bearing EGFR gene mutation and amplification. *Cancer Res* 2007; **67**: 2046–53.

30 Zhu JQ, Zhong WZ, Zhang GC, et al. Better survival with EGFR exon 19 than exon 21

mutations in gefitinib-treated non-small cell lung cancer patients is due to differential inhibition of downstream signals. *Cancer Lett* 2008; **265**: 307–17.

31 National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology - Breast Cancer, Version 3.2014. (Accessed March 4, 2014, at http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.)

32 Paz-Ares LG, De Marinis F, Dediu M, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol* 2013; **31**: 2895–902.

33 Barlesi F, Scherpereel A, Gorbunova V, et al. Maintenance bevacizumab-pemetrexed after first-line cisplatin-pemetrexed-bevacizumab for advanced nonsquamous nonsmall-cell lung cancer: updated survival analysis of the AVAPERL (MO22089) randomized phase III trial. *Ann Oncol* 2014; **25**: 1044–52.

Tables

Table 1: Patient demographics and baseline characteristics

	LUX-Lung 3		LUX-Lung 6		Combined analysis	
	Afatinib (n=230)	Cisplatin/pemetrexed (n=115)	Afatinib (n=242)	Cisplatin/gemcitabine (n=122)	Afatinib (n=472)	Chemotherapy (n=237)
Gender, n (%)						
Male	83 (36·1)	38 (33·0)	87 (36·0)	39 (32·0)	170 (36·0)	77 (32·5)
Female	147 (63·9)	77 (67·0)	155 (64·0)	83 (68·0)	302 (64·0)	160 (67·5)
Median (range) age, years	62 (28–86)	61 (31–83)	58 (29–79)	58 (27–76)	60 (28–86)	59 (27–83)
Race, n (%)						
Asian	166 (72·2)	83 (72·2)	242 (100·0)	122 (100·0)	408 (86·4)	205 (86·5)
Non-Asian	64 (27·8)	32 (27·8)	0	0	64 (13·6)	32 (13·5)
Adenocarcinoma stage, n (%)						
IIIB with pleural effusion	20 (8·7)	17 (14·8)	16 (6·6)	6 (4·9)	36 (7·6)	23 (9·7)
IV	210 (91·3)	98 (85·2)	226 (93·4)	116 (95·1)	436 (92·4)	214 (90·3)
Baseline ECOG PS						
0	92 (40·0)	41 (35·7)	48 (19·8)	41 (33·6)	140 (29·7)	82 (34·6)
1	138 (60·0)	74 (64·3)*	194 (80·2)	81 (66·4)	332 (70·3)	155 (65·4)*

EGFR mutation, n (%)						
Common mutations	203 (88·3)	104 (90·4)	216 (89·3)	108 (88·5)	419 (88·8)	212 (89·5)
Exon 19 deletion	112 (48·7)	57 (49·6)	124 (51·2)	62 (50·8)	236 (50·0)	119 (50·2)
L858R	91 (39·6)	47 (40·9)	92 (38·0)	46 (37·7)	183 (38·8)	93 (39·2)
Uncommon mutations†	27 (11·7)‡	11 (9·6)	26 (10·7)	14 (11·5)	53 (11·2)‡	25 (10·5)
Smoking status, n (%)						
Never	155 (67·4)	81 (70·4)	181 (74·8)	99 (81·1)	336 (71·2)	180 (75·9)
Former	70 (30·4)	32 (27·8)	44 (18·2)	13 (10·7)	114 (24·2)	45 (19·0)
Current	5 (2·2)	2 (1·7)	17 (7·0)	10 (8·2)	22 (4·7)	12 (5·1)

ECOG PS=Eastern Cooperative Oncology Group performance status. *EGFR*=epidermal growth factor receptor. *Includes one patient with an ECOG PS of 2. †Including T790M, exon 20 insertions, G719X, S768I, and L861Q, alone or as complex mutations in two or more exons. ‡Includes one patient with wild-type *EGFR* who was randomised in error.

Table 2: **Treatment beyond first-line therapy in patients with common *EGFR* mutations (Del19/L858R) in LL3 and LL6**

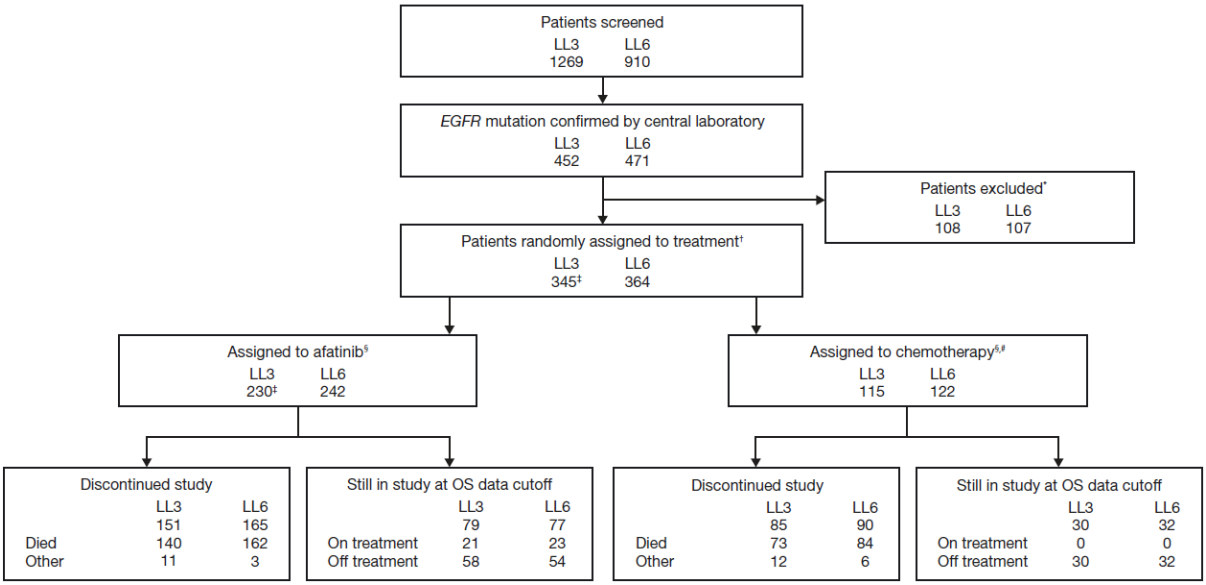
	Del19		L858R	
LUX-Lung 3	Afatinib (n=112)	Cisplatin/ pemetrexed (n=57)	Afatinib (n=91)	Cisplatin/ pemetrexed (n=47)
Discontinued study treatment, n	100	57	84	47
Received subsequent systemic therapy, n (%)*	76 (76·0)	49 (86·0)	68 (81·0)	39 (83·0)
Chemotherapy	69 (69·0)	29 (50·9)	62 (73·8)	20 (42·6)
EGFR TKI therapy	41 (41·0)	43 (75·4)	40 (47·6)	35 (74·5)
Erlotinib	32 (32·0)	27 (47·4)	29 (34·5)	19 (40·4)
Gefitinib	14 (14·0)	26 (45·6)	14 (16·7)	18 (38·3)
Afatinib	1 (1·0)	6 (10·5)	1 (1·2)	1 (2·1)
AZD9291	1 (1·0)	1 (1·8)	1 (1·2)	0 (0)
Dacomitinib	0 (0)	0 (0)	0 (0)	1 (2·1)
EGFR TKI combinations	2 (2·0)	8 (14·0)	3 (3·6)	3 (6·4)
Other	2 (2·0)	1 (1·8)	3 (3·6)	1 (2·1)
Radiotherapy	18 (18·0)	13 (22·8)	14 (16·7)	8 (17·0)
LUX-Lung 6	Afatinib (n=124)	Cisplatin/ gemcitabine (n=62)	Afatinib (n=92)	Cisplatin/ gemcitabine (n=46)
Discontinued study treatment, n	110	62	84	46
Received subsequent systemic therapy, n (%)*	79 (71·8)	39 (62·9)	44 (52·4)	31 (67·4)
Chemotherapy	72 (65·5)	16 (25·8)	42 (50·0)	13 (28·3)
EGFR TKI therapy	36 (32·7)	33 (53·2)	14 (16·7)	28 (60·9)

Gefitinib	15 (13·6)	19 (30·6)	4 (4·8)	20 (43·5)
Erlotinib	15 (13·6)	11 (17·7)	6 (7·1)	11 (23·9)
Icotinib	8 (7·3)	3 (4·8)	3 (3·6)	0 (0)
EGFR TKI combinations	4 (3·6)	2 (3·2)	1 (1·2)	1 (2·2)
Other	2 (1·8)	2 (3·2)	1 (1·2)	2 (4·3)
Radiotherapy	4 (3·6)	0 (0)	0 (0)	0 (0)

EGFR=epidermal growth factor receptor. LL3=LUX-Lung 3. LL6=LUX-Lung 6. TKI=tyrosine kinase inhibitor. *Percentages based on the number of patients who discontinued treatment. Collection of data on subsequent therapies is still ongoing.

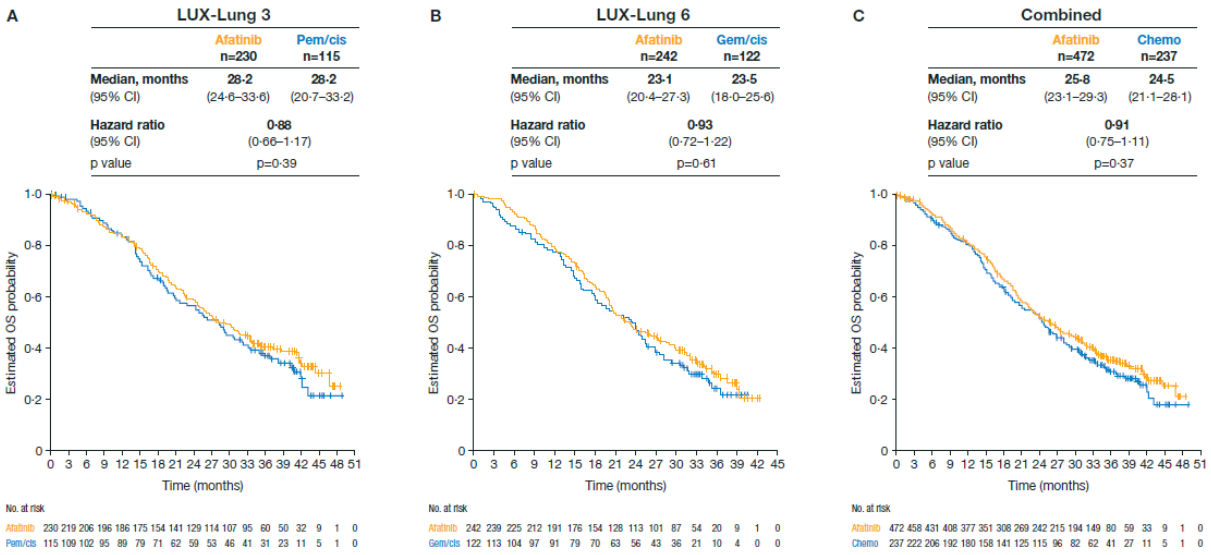
Figures

Figure 1: Patient disposition



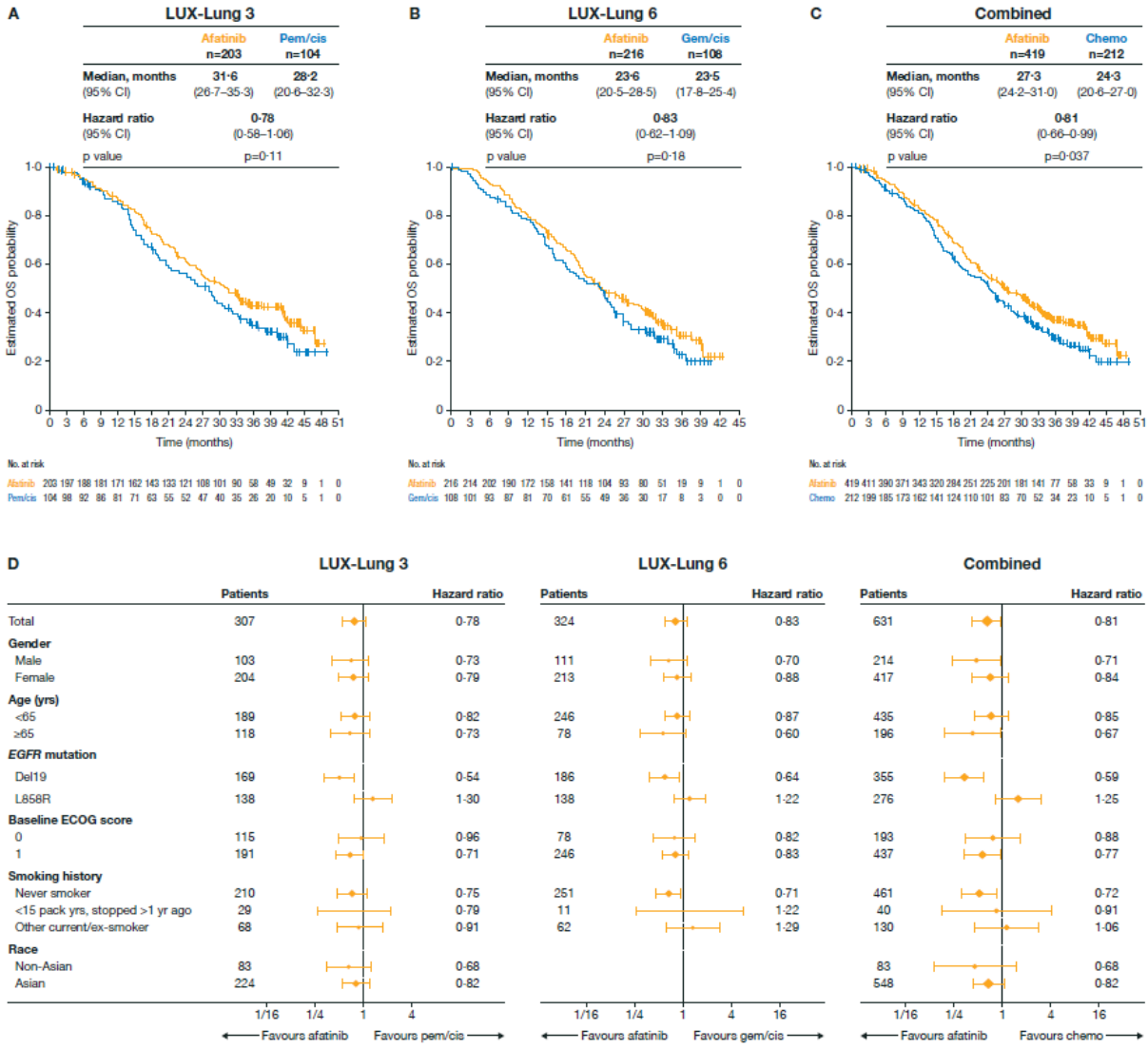
AE=adverse event. *EGFR*=epidermal growth factor receptor. LL3=LUX-Lung 3. LL6=LUX-Lung 6. OS=overall survival. *Reasons for exclusion prior to randomisation in LL3 included: did not meet inclusion criteria (n=59), withdrew consent (n=24), AEs (n=5), lost to follow up (n=5), and other reason (n=15); in LL6 reasons included did not meet inclusion criteria (n=51), withdrew consent (n=38), AEs (n=1), and other reason (n=17). †OS analyses included all patients randomised to receive study medication. ‡Includes one patient with wild-type *EGFR* randomised in error. §One patient in LL3 and three patients in LL6 did not receive afatinib treatment; four patients in LL3 and nine patients in LL6 did not receive chemotherapy. #Cisplatin/pemetrexed in LL3; cisplatin/gemcitabine in LL6.

Figure 2: **Kaplan-Meier curves of overall survival in the overall populations of LL3 (A), LL6 (B), and the combined analysis (C)**



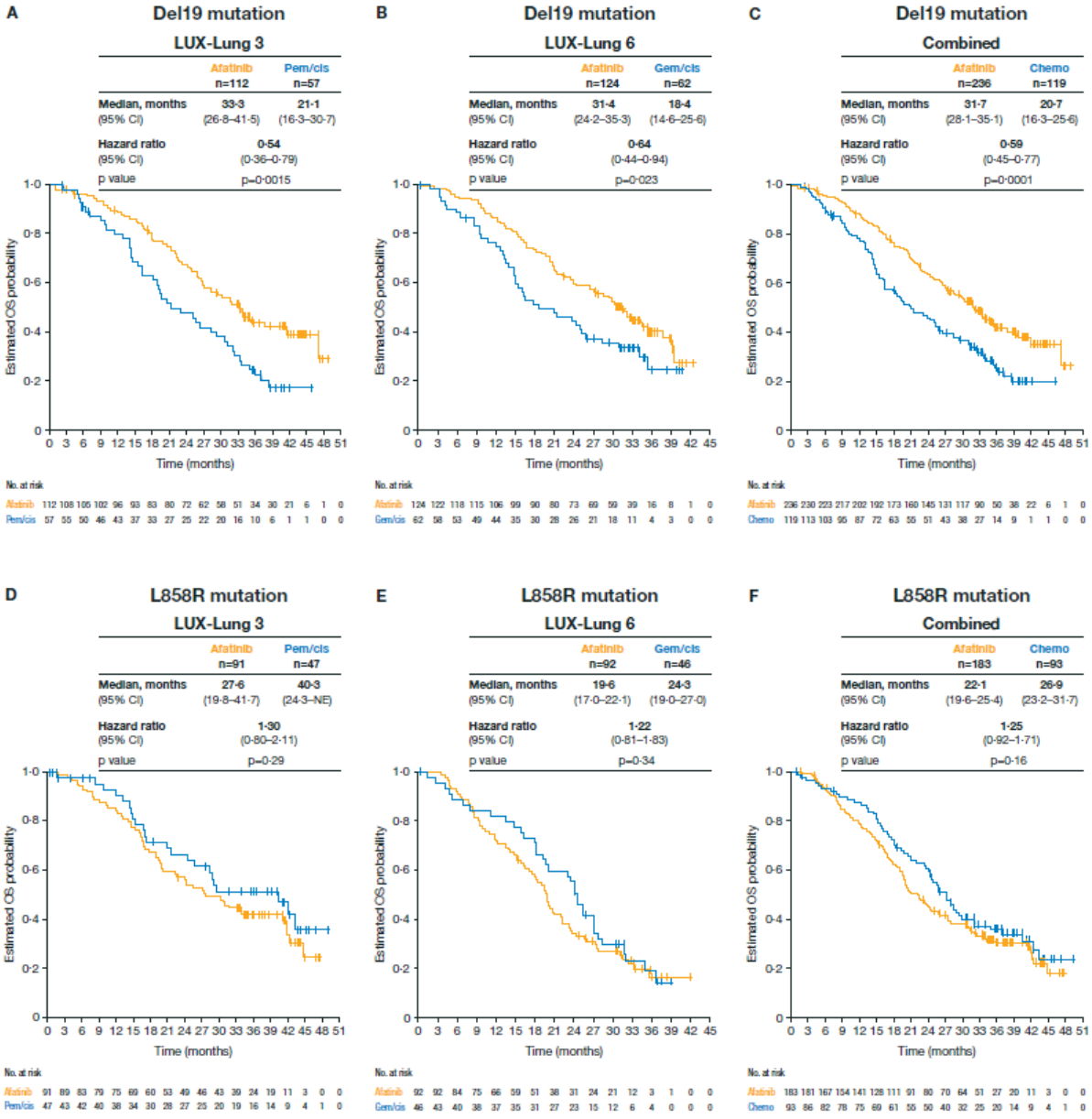
Chemo=chemotherapy. CI=confidence interval. Gem/cis=gemcitabine/cisplatin. LL3=LUX-Lung 3. LL6=LUX-Lung 6. OS=overall survival. Pem/cis=pemetrexed/cisplatin.

Figure 3: **Kaplan-Meier curves (A–C) and subgroup analyses (D) of overall survival in patients with common *EGFR* mutations (Del19/L858R combined) in LL3, LL6, and the combined analysis**



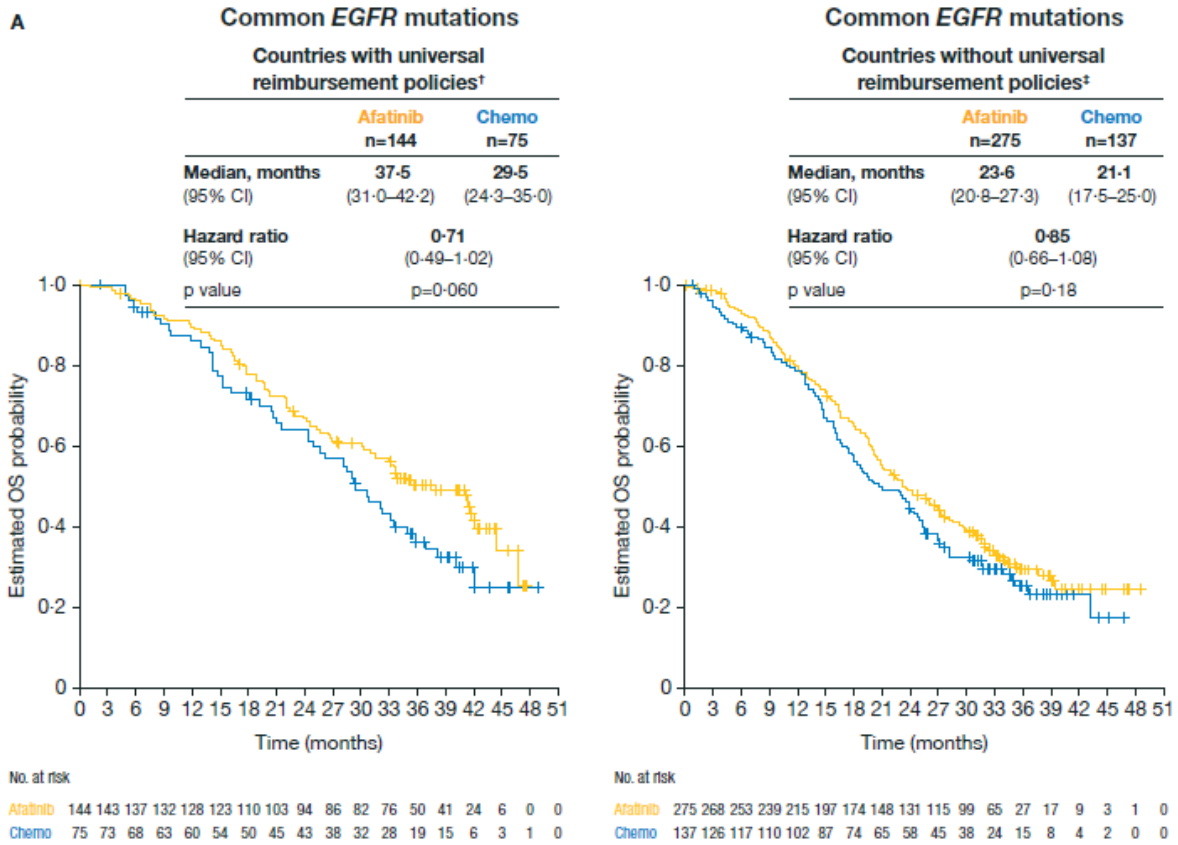
Chemo=chemotherapy. CI=confidence interval. ECOG=Eastern Cooperative Oncology Group. *EGFR*=epidermal growth factor receptor. Gem/cis=gemcitabine/cisplatin. LL3=LUX-Lung 3. LL6=LUX-Lung 6. OS=overall survival. Pem/cis=pemetrexed/cisplatin.

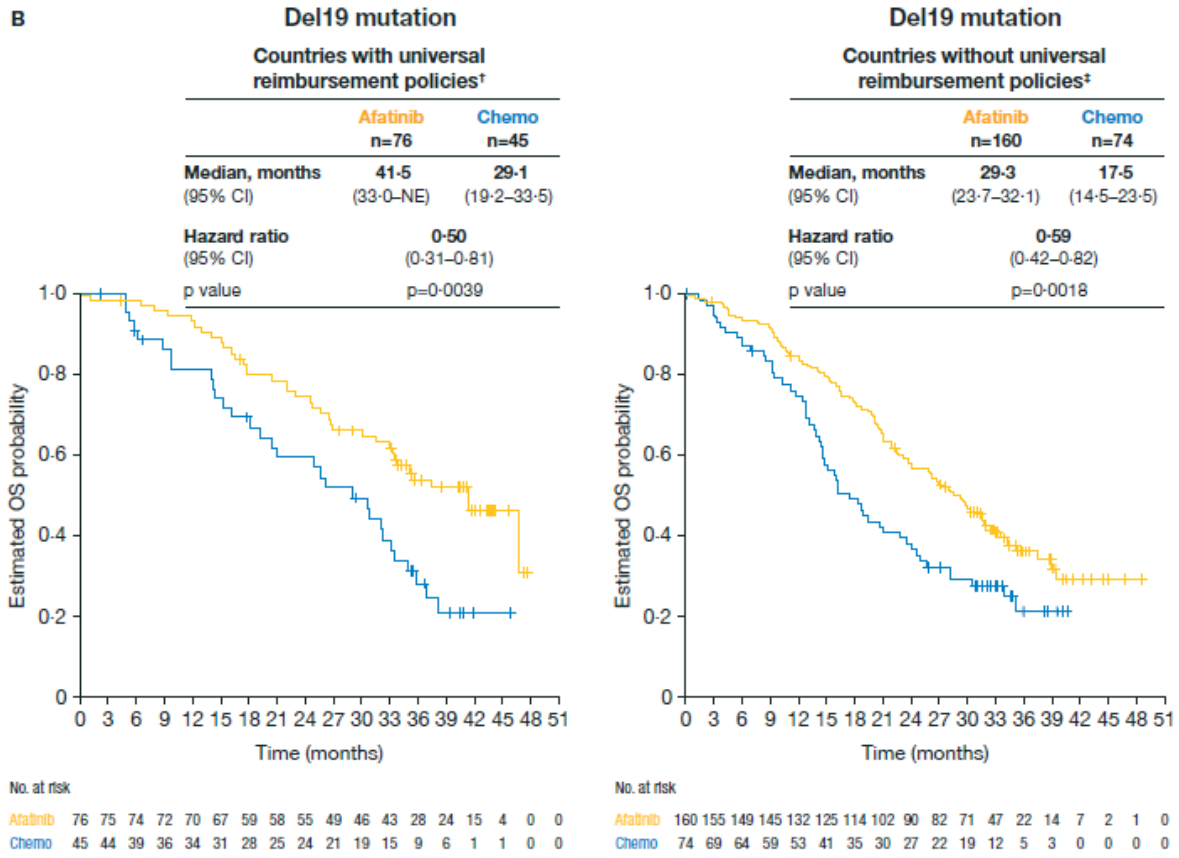
Figure 4: **Kaplan-Meier curves of overall survival in Del19 patients (A–C) and L858R patients (D–F) in LL3, LL6, and the combined analysis**

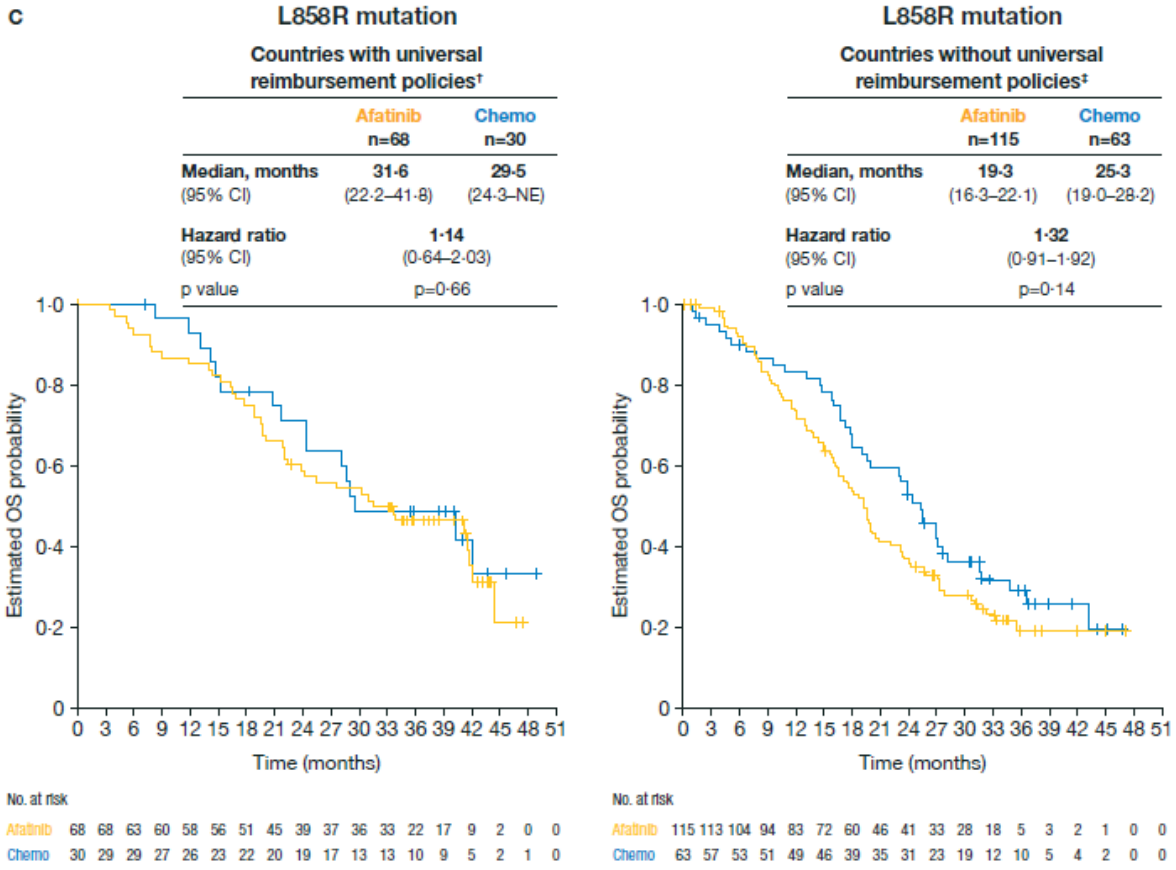


Chemo=chemotherapy. CI=confidence interval. Gem/cis=gemcitabine/cisplatin. LL3=LUX-Lung 3. LL6=LUX-Lung 6. NE=not estimable. OS=overall survival. Pem/cis=pemetrexed/cisplatin.

Figure S1: **Exploratory analysis of overall survival in patients with common *EGFR* mutations (Del19/L858R combined) (A), Del19 patients only (B) and L858R patients only (C) in countries with or without universal reimbursement policies for EGFR TKI therapies*** In those patients with greater access to subsequent therapy, improved median OS was observed in both the afatinib and chemotherapy treatment groups, with an OS benefit observed with afatinib versus chemotherapy. For example, in Japan, all patients assigned to chemotherapy received a subsequent EGFR TKI after progression. Among Japanese patients, the OS benefit of afatinib compared to chemotherapy was more pronounced in patients with tumours harbouring *EGFR* Del19 mutation (HR 0·34) and those with common mutations (HR 0·57) compared to the overall study population.




B
Del19 mutation
Countries with universal reimbursement policies†
Afatinib n=76
Chemo n=45
Median, months (95% CI)
41·5 (33·0–NE)
29·1 (19·2–33·5)
Hazard ratio (95% CI)
0·50 (0·31–0·81)
p value
p=0·0039
Estimated OS probability
1·0
0·8
0·6
0·4
0·2
0
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51
Time (months)
No. at risk
Afatinib 76 75 74 72 70 67 59 58 55 49 46 43 28 24 15 4 0 0
Chemo 45 44 39 36 34 31 28 25 24 21 19 15 9 6 1 1 0 0
Del19 mutation
Countries without universal reimbursement policies‡
Afatinib n=160
Chemo n=74
Median, months (95% CI)
29·3 (23·7–32·1)
17·5 (14·5–23·5)
Hazard ratio (95% CI)
0·59 (0·42–0·82)
p value
p=0·0018
Estimated OS probability
1·0
0·8
0·6
0·4
0·2
0
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51
Time (months)
No. at risk
Afatinib 160 155 149 145 132 125 114 102 90 82 71 47 22 14 7 2 1 0
Chemo 74 69 64 59 53 41 35 30 27 22 19 12 5 3 0 0 0 0



Chemo=chemotherapy. CI=confidence interval. *EGFR*=epidermal growth factor receptor. NE=not estimable. OS=overall survival. TKI=tyrosine kinase inhibitor. *Determined by presence or absence of a national reimbursement policy in effect throughout the period of trial conduct. †Main countries contributing: Japan, Taiwan, Korea, Germany, France, Australia, UK, Belgium, Ireland. ‡Main countries contributing: China, Thailand, Russia, the Philippines, Malaysia.

Table S1: **Subsequent treatments in patients with common *EGFR* mutations (Del19/L858R combined) in countries with or without universal reimbursement policies for EGFR TKI therapies*** More patients received subsequent therapy in countries with a universal reimbursement policy than countries without a universal policy.

	With universal reimbursement policies†		**Without universal reimbursement policies‡**	
	Afatinib (n=144)	Chemotherapy (n=75)	Afatinib (n=275)	Chemotherapy (n=137)
Discontinued study treatment, n	127	75	251	137
Received subsequent systemic therapy, n (%)§	112 (88·2)	69 (92·0)	155 (61·8)	89 (65·0)
Chemotherapy	103 (81·1)	35 (46·7)	142 (56·6)	43 (31·4)
EGFR TKI therapy#	76 (59·8)	68 (90·7)	55 (21·9)	71 (51·8)
Other	5 (3·9)	2 (2·7)	3 (1·2)	4 (2·9)
Radiotherapy	27 (21·3)	18 (24·0)	9 (3·6)	3 (2·2)

EGFR=epidermal growth factor receptor. TKI=tyrosine kinase inhibitor. *Determined by presence or absence of a national reimbursement policy in effect throughout the period of trial conduct. †Main countries contributing: Japan, Taiwan, Korea, Germany, France, Australia, UK, Belgium, Ireland. ‡Main countries contributing: China, Thailand, Russia, the Philippines, Malaysia. §Percentages based on the number of patients who discontinued treatment. Collection of data on subsequent therapies is still ongoing. #Including EGFR TKI-containing combination therapy.

Table S2: **LUX-Lung 3 disposition of patients by country and site of enrollment**

Country	Centre	Investigator	Number of randomised patients
Thailand	3701	Geater	33
Taiwan	3602	Tsai	15
Taiwan	3601	Yang	12
Germany	4305	Schuler	10
Japan	3221	Terufumi	10
Taiwan	3606	Su	10
Russia	5504	Orlov	10
Taiwan	3607	Lin	9
Korea	3304	Lee	9
Thailand	3704	Sirisinha	9
Japan	3202	Takahashi	8
Japan	3214	Yoshioka	8
Philippines	3503	Parra	8
Japan	3205	Nakagawa	7
Japan	3216	Tanaka	7
Japan	3204	Hida	6
Japan	3209	Kiura	6
Japan	3207	Seto	6
Taiwan	3603	Ho	6
Taiwan	3605	Hsia	6
Korea	3301	Kim	6
Hong Kong	3102	Lee	5
Japan	3203	Goto	5
Philippines	3501	Tudtud	5
Australia	2711	Boyer	4
France	4207	Bennouna	4

Japan	3211	Kasahara	4
Japan	3217	Saka	4
Japan	3206	Takeda	4
Malaysia	3403	Chong−Kin	4
Peru	2503	Lopez	4
Russia	5505	Gorbunova	4
Philippines	3502	Caguioa	4
United Kingdom	4807	Shah	4
Belgium	4105	Surmont	3
France	4215	Paganin	3
Ireland	4401	O’Byrne	3
Japan	3219	Katakami	3
Japan	3220	Nogami	3
Malaysia	3402	Muttalif	3
Russia	5506	Khasanov	3
Korea	3303	Lee	3
Thailand	3702	Thongprasert	3
Australia	2707	Hazel	2
Australia	2701	Pavlakis	2
Belgium	4103	Ninane	2
Germany	4306	Dickgreber	2
Germany	4310	Sebastian	2
France	4202	Sibilot	2
Malaysia	3401	Ismail	2
Taiwan	3608	Huang	2
Chile	2303	Gonzalez	2
Chile	2302	Ruiz	2
Korea	3305	Joo Min	2
Ukraine	5601	Bondarenko	2

Ukraine	5604	Vinnnik	2
Austria	5101	Burghuber	1
Australia	2703	Hughes	1
Australia	2706	McLachlan	1
Australia	2702	Parente	1
Belgium	4102	Bosquee	1
Belgium	4101	De Greve	1
Belgium	4107	Vansteenkiste	1
Brazil	2202	Barrios	1
Canada	2903	Hirsh	1
Germany	4308	Griesinger	1
Germany	4311	Wiewrodt	1
France	4210	Daniel	1
France	4201	Perol	1
France	4204	Zalcman	1
Hungary	5302	Papai−Szekely	1
Hong Kong	3101	Mok	1
Japan	3218	Atagi	1
Japan	3215	Oizumi	1
Peru	2505	Lozada	1
Peru	2501	Sanchez	1
Argentina	2112	Carraro	1
Argentina	2110	Fein	1
Argentina	2101	Lerzo	1
Taiwan	3604	Chang	1
Taiwan	3609	Tsai	1
Chile	2301	Diaz	1
Russia	5503	Moiseyenko	1
Russia	5507	Ragulin	1

Romania	5402	Cebotaru	1
Romania	5401	Lungulescu	1
Korea	3302	Kim	1
United Kingdom	4806	Collinson	1
United Kingdom	4803	Middleton	1
United Kingdom	4801	Popat	1
United Kingdom	4808	Toy	1
United States	2606	Chandrasekaran	1

Table S3: **LUX-Lung 6 disposition of patients by country and site of enrollment**

Country	Centre	Investigator	Number of randomised patients
Peoples Republic of China	8601	Wu	41
Thailand	6601	Geater	24
Peoples Republic of China	8603	Zhou	19
Peoples Republic of China	8619	Hu	18
Peoples Republic of China	8611	Feng	17
Peoples Republic of China	8602	Lu	16
Peoples Republic of China	8628	Huang	15
Peoples Republic of China	8615	Li	14
Peoples Republic of China	8617	Hou	14
Peoples Republic of China	8629	Shi	14
Peoples Republic of China	8613	Liu	13
Peoples Republic of China	8614	Liu	13
Peoples Republic of China	8604	Bai	12
Peoples Republic of China	8621	Liang	12
Peoples Republic of China	8622	Huang	12
Peoples Republic of China	8608	Liu	10
Peoples Republic of China	8624	Zhang	9
Peoples Republic of China	8607	Wang	8
Peoples Republic of China	8610	Qin	8
Peoples Republic of China	8620	Luo	8
Peoples Republic of China	8626	Zhu	7
Peoples Republic of China	8630	Chen	7
Peoples Republic of China	8632	Zhu	7
Peoples Republic of China	8605	Li	6
Peoples Republic of China	8616	Yu	6
Peoples Republic of China	8618	Luo	6

Peoples Republic of China	8623	Song	6
Korea	8201	Lee	5
Korea	8205	Lee	5
Peoples Republic of China	8609	Wang	5
Peoples Republic of China	8631	Jianxing	3
Korea	8203	Jang	2
Korea	8202	Lee	1
Peoples Republic of China	8627	Xiu	1