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

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Summary

Background We aimed to assess the effect of afatinib on overall survival of patients with *EGFR* mutation-positive lung adenocarcinoma through an analysis of data from two open-label, randomised, phase 3 trials.

Methods Previously untreated patients with *EGFR* mutation-positive stage IIIB or IV lung adenocarcinoma were enrolled in LUX-Lung 3 (n=345) and LUX-Lung 6 (n=364). These patients were randomly assigned in a 2:1 ratio to receive afatinib or chemotherapy (pemetrexed-cisplatin [LUX-Lung 3] or gemcitabine-cisplatin [LUX-Lung 6]), stratified by *EGFR* mutation (exon 19 deletion [del19], Leu858Arg, or other) and ethnic origin (LUX-Lung 3 only). We planned analyses of mature overall survival data in the intention-to-treat population after 209 (LUX-Lung 3) and 237 (LUX-Lung 6) deaths. These ongoing studies are registered with ClinicalTrials.gov, numbers NCT00949650 and NCT01121393.

Findings Median follow-up in LUX-Lung 3 was 41 months (IQR 35–44); 213 (62%) of 345 patients had died. Median follow-up in LUX-Lung 6 was 33 months (IQR 31–37); 246 (68%) of 364 patients had died. In LUX-Lung 3, median overall survival was 28·2 months (95% CI 24·6–33·6) in the afatinib group and 28·2 months (20·7–33·2) in the pemetrexed-cisplatin group (HR 0·88, 95% CI 0·66–1·17, p=0·39). In LUX-Lung 6, median overall survival was 23·1 months (95% CI 20·4–27·3) in the afatinib group and 23·5 months (18·0–25·6) in the gemcitabine-cisplatin group (HR 0·93, 95% CI 0·72–1·22, p=0·61). However, in preplanned analyses, overall survival was significantly longer for patients with del19-positive tumours in the afatinib group than in the chemotherapy group in both trials: in LUX-Lung 3, median overall survival was 33·3 months (95% CI 26·8–41·5) in the afatinib group versus 21·1 months (16·3–30·7) in the chemotherapy group (HR 0·54, 95% CI 0·36–0·79, p=0·0015); in LUX-Lung 6, it was 31·4 months (95% CI 24·2–35·3) versus 18·4 months (14·6–25·6), respectively (HR 0·64, 95% CI 0·44–0·94, p=0·023). By contrast, there were no significant differences by treatment group for patients with *EGFR* Leu858Arg-positive tumours in either trial: in LUX-Lung 3, median overall survival was 27·6 months (19·8–41·7) in the afatinib group versus 40·3 months (24·3–not estimable) in the chemotherapy group (HR 1·30, 95% CI 0·80–2·11, p=0·29); in LUX-Lung 6, it was 19·6 months (95% CI 17·0–22·1) versus 24·3 months (19·0–27·0), respectively (HR 1·22, 95% CI 0·81–1·83, p=0·34). In both trials, the most common afatinib-related grade 3–4 adverse events were rash or acne (37 [16%] of 229 patients in LUX-Lung 3 and 35 [15%] of 239 patients in LUX-Lung 6), diarrhoea (33 [14%] and 13 [5%]), paronychia (26 [11%] in LUX-Lung 3 only), and stomatitis or mucositis (13 [5%] in LUX-Lung 6 only). In LUX-Lung 3, neutropenia (20 [18%] of 111 patients), fatigue (14 [13%]) and leucopenia (nine [8%]) were the most common chemotherapy-related grade 3–4 adverse events, while in LUX-Lung 6, the most common chemotherapy-related grade 3–4 adverse events were neutropenia (30 [27%] of 113 patients), vomiting (22 [19%]), and leucopenia (17 [15%]).

Interpretation Although afatinib did not improve overall survival in the whole population of either trial, overall survival was improved with the drug for patients with del19 *EGFR* mutations. The absence of an effect in patients with Leu858Arg *EGFR* mutations suggests that *EGFR* del19-positive disease might be distinct from Leu858Arg-positive disease and that these subgroups should be analysed separately in future trials.

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Introduction

Patients with lung adenocarcinoma harbouring *EGFR* mutations are highly responsive to treatment with EGFR tyrosine kinase inhibitors such as gefitinib, erlotinib, or afatinib.[1] Findings from seven randomised phase 3 studies done in this genetically selected subset of patients with lung cancer have shown better progression-free survival and responses with gefitinib or erlotinib than

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with platinum-based chemotherapy.[2–8] However, differences in overall survival were not reported in these studies, irrespective of *EGFR* mutation type,[8–15] presumably because most patients randomly assigned to first-line chemotherapy were subsequently treated with EGFR tyrosine kinase inhibitors. Findings from a meta-analysis of 13 randomised studies examining first-line gefitinib or erlotinib (monotherapy or combined with chemotherapy) compared with chemotherapy or placebo in patients with *EGFR* mutation-positive lung cancer showed that overall survival did not differ (hazard ratio [HR] 1·01, 95% CI 0·87–1·18) despite the large progression-free survival advantage among patients receiving EGFR tyrosine kinase inhibitors (HR 0·43, 95% CI 0·38–0·49, p<0·001).[16]

Afatinib, a second-generation irreversible tyrosine kinase inhibitor that inhibits signalling from all homodimers and heterodimers formed by ERBB receptor family members (including EGFR, HER2, ERBB3, and ERBB4), has shown clinical activity in patients with *EGFR* mutation-positive lung adenocarcinoma previously untreated with EGFR tyrosine kinase inhibitors.[17–19] First-line afatinib was compared with standard chemotherapy in two large, randomised phase 3 trials in previously untreated 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 was used in LUX-Lung 3, and gemcitabine-cisplatin in LUX-Lung 6. Findings from both studies showed improved progression-free survival (the primary endpoint), objective responses, and patient-reported outcomes for patients receiving first-line afatinib.[18–20] These studies also demonstrated differences in progression-free survival with afatinib on the basis of *EGFR* mutation type; progression-free survival was most improved in patients with tumours harbouring exon 19 deletion (del19) followed by the exon 21 substitution (Leu858Arg) mutation.[18,19]

Here, we report mature overall survival results from the individual LUX-Lung 3 and LUX-Lung 6 studies. Additionally, to provide more accurate estimates of the overall effect of afatinib treatment in these patients (particularly in prespecified subgroups), we combined individual patient data from the two studies for an exploratory analysis of overall survival.

Methods
Study design and participants
Detailed study designs, inclusion and exclusion criteria, and methods of the primary analyses of both trials have been previously published.[18,19] In brief, each trial was a randomised, open-label, phase 3 study done either globally[18] or in China, South Korea, and Thailand.[19] Eligible patients were aged 18 years or older, had previously untreated stage IIIB or IV lung adenocarcinoma (measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1), an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and a life expectancy of at least 3 months. In addition, tumour tissue had to be *EGFR* mutation-positive at screening based on central laboratory analysis of biopsy tissue with a validated test kit (Therascreen EGFR 29; Qiagen, Manchester, UK).

Exclusion criteria included the presence of any other cancer diagnosed within the past 5 years or at screening (other than non-melanomatous skin cancer and in-situ cervical cancer); active brain metastases; pre-existing interstitial lung disease; clinically significant or recent acute gastrointestinal disorders with diarrhoea as a major symptom; history or presence of clinically relevant cardiovascular abnormalities (eg, uncontrolled hypertension, congestive heart failure of New York Heart Association classification of 3, unstable angina, or poorly controlled arrhythmia) or myocardial infarction within 6 months of randomisation; cardiac left ventricular function with resting ejection fraction of less than 50%; active hepatitis B or C infection or known HIV carrier. Additionally, patients were excluded if they had: an absolute neutrophil count less than 1500 cells per μL, platelet count less than 100 000 cells per μL, creatinine clearance less than 60 mL/min or serum creatinine more than 1·5×upper limit of normal (ULN), bilirubin more than 1·5×ULN, and aspartate aminotransferase or alanine aminotransferase more than 3×ULN (if related to liver metastases, >5×ULN).

Both studies were done 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 centre. Written informed consent was obtained for each patient.

Randomisation
Patients enrolled in LUX-Lung 3 (n=345) and LUX-Lung 6 (n=364) were randomly assigned in a 2:1 ratio to receive afatinib or chemotherapy and stratified by *EGFR* mutation type (del19 *vs* Leu858Arg *vs* other uncommon mutations) and by ethnic origin (Asian *vs* non-Asian; LUX-Lung 3 only); a block size of three was used within each of the strata. Randomisation was done with 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 trials did not have access to the randomisation schedule.

Procedures
Patients received either continuous oral afatinib (40 mg/day) or up to six cycles of intravenous pemetrexed (500 mg/m²) plus cisplatin (75 mg/m²) once every 21 days in LUX-Lung 3 or gemcitabine (1000 mg/m²; days 1 and 8) plus cisplatin (75 mg/m²; day 1) once every

21 days in LUX-Lung 6. Patients receiving afatinib were permitted to increase their dose to 50 mg/day after the first 21 day cycle if they did not have treatment-related adverse events 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 lengthy grade 2 adverse events, 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.

Tumour assessments were done by CT or MRI every 6 weeks for the first 48 weeks, and then every 12 weeks thereafter until disease progression or start of new anticancer therapy. Adverse events 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 about subsequent therapies and survival until patient death, loss to follow-up, or withdrawal of consent.

Outcomes

In both studies, the primary endpoint was progression-free survival, defined as time from randomisation to progression (as determined by independent review). Key secondary endpoints in both studies were objective response (complete response and partial response), disease control (objective response and stable disease), and overall survival; other secondary endpoints included patient-reported outcomes and safety.

Statistical analysis

Each study was powered (90%) at a two-sided 5% significance level to detect a progression-free survival 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] Efficacy endpoints were assessed for the intention-to-treat population, including all patients who met eligibility criteria and were randomly assigned to treatment. Safety was assessed for all randomly assigned patients who received at least one dose of study medication.
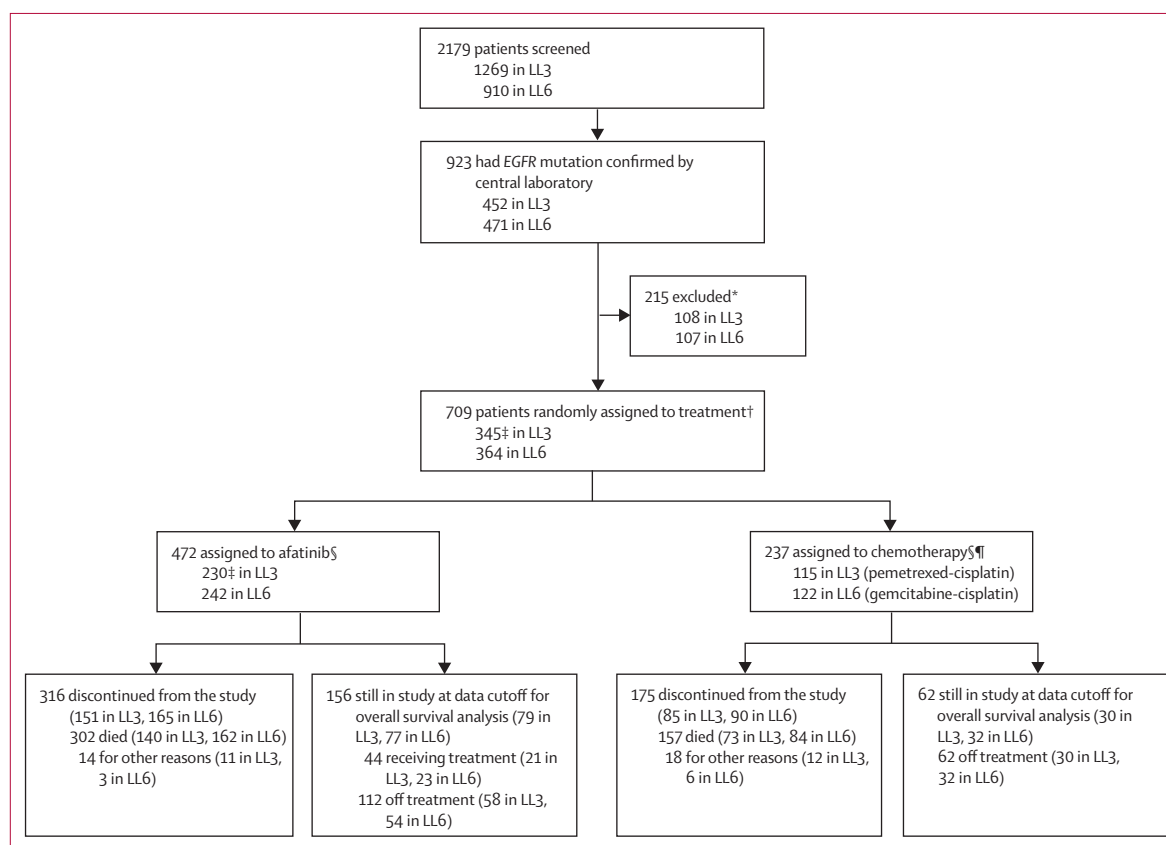
Figure 1: Study profile
LL3=LUX-Lung 3. LL6=LUX-Lung 6. *Reasons for exclusion before randomisation in LUX-Lung 3 included: did not meet inclusion criteria (n=59), withdrew consent (n=24), adverse events (n=5), lost to follow-up (n=5), and other reason (n=15); in LUX-Lung 6 reasons included did not meet inclusion criteria (n=51), withdrew consent (n=38), adverse events (n=1), and other reason (n=17). †Overall survival analyses included all patients randomly assigned to receive study medication. ‡Includes one patient with wild-type *EGFR* randomly assigned in error. §One patient in LUX-Lung 3 and three patients in LUX-Lung 6 did not receive afatinib treatment; four patients in LUX-Lung 3 and nine patients in LUX-Lung 6 did not receive chemotherapy. ¶Cisplatin-pemetrexed in LUX-Lung 3; cisplatin-gemcitabine in LUX-Lung 6.

	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)
Sex						
Men	83 (36%)	38 (33%)	87 (36%)	39 (32%)	170 (36%)	77 (32%)
Women	147 (64%)	77 (67%)	155 (64%)	83 (68%)	302 (64%)	160 (68%)
Age (years)	62 (28–86)	61 (31–83)	58 (29–79)	58 (27–76)	60 (28–86)	59 (27–83)
Ethnic origin						
Asian	166 (72%)	83 (72%)	242 (100%)	122 (100%)	408 (86%)	205 (86%)
Non-Asian	64 (28%)	32 (28%)	0	0	64 (14%)	32 (14%)
Adenocarcinoma stage						
IIIB with pleural effusion	20 (9%)	17 (15%)	16 (7%)	6 (5%)	36 (8%)	23 (10%)
IV	210 (91%)	98 (85%)	226 (93%)	116 (95%)	436 (92%)	214 (90%)
Baseline ECOG performance status						
0	92 (40%)	41 (36%)	48 (20%)	41 (34%)	140 (30%)	82 (35%)
1	138 (60%)	74* (64%)	194 (80%)	81 (66%)	332 (70%)	155* (65%)
EGFR mutation						
Common mutations	203 (88%)	104 (90%)	216 (89%)	108 (89%)	419 (89%)	212 (89%)
Exon 19 deletion	112 (49%)	57 (50%)	124 (51%)	62 (51%)	236 (50%)	119 (50%)
Leu858Arg	91 (40%)	47 (41%)	92 (38%)	46 (38%)	183 (39%)	93 (39%)
Uncommon mutations†	27‡ (12%)	11 (10%)	26 (11%)	14 (11%)	53‡ (11%)	25 (11%)
Smoking status						
Never	155 (67%)	81 (70%)	181 (75%)	99 (81%)	336 (71%)	180 (76%)
Former	70 (30%)	32 (28%)	44 (18%)	13 (11%)	114 (24%)	45 (19%)
Current	5 (2%)	2 (2%)	17 (7%)	10 (8%)	22 (5%)	12 (5%)

Data are n (%) or median (range). ECOG=Eastern Cooperative Oncology Group. *Includes one patient with an ECOG performance status of 2. †Including Thr790Met, exon 20 insertions, Gly719X (Gly719Ser, Gly719Ala, or Gly719Cys), Ser768Ile, and Leu861Gln, alone or as complex mutations in two or more exons. ‡Includes one patient with wild-type _EGFR_ who was randomly assigned in error.

Table 1: Patient demographics and baseline characteristics

Primary and key secondary endpoints were analysed following a hierarchical testing strategy to minimise the overall risk of type I error (5%). Overall survival analyses were planned for two timepoints. The first analysis of overall survival was concurrent with the primary analysis of progression-free survival; a Haybittle-Peto stopping boundary was used (p<0·0001) to preserve the overall 5% type I error. The second overall survival analysis was planned after 209 deaths in LUX-Lung 3 and 237 deaths in LUX-Lung 6, when the investigators estimated that the data would be mature. Neither trial was purposefully designed with sufficient power to detect differences in overall survival because none of the previous studies comparing first-line erlotinib or gefitinib with chemotherapy showed benefits in overall survival.[8–15] Similar to the primary analysis of progression-free survival, stratification by _EGFR_ mutation type (del19, Leu858Arg, or other) and ethnic origin (Asian _vs_ non-Asian; LUX-Lung 3 only) was applied for the overall survival analysis. For each trial, preplanned analyses of subgroups of special interest (sex, age, baseline ECOG performance status, _EGFR_ mutation category [common—ie, del19 and Leu858Arg—and uncommon], smoking history, and

ethnic origin [LUX-Lung 3 only]) were also defined. Because these analyses did not form part of the confirmatory analysis strategy, no adjustment for multiplicity was done, and p values are descriptive in nature. We did a post-hoc exploratory analysis of overall survival based on the combined individual patient data from both trials; heterogeneity was evaluated by testing the study-by-treatment interaction.

For each study, we compared overall survival between treatment groups using a stratified log-rank test, adjusting for _EGFR_ mutation type (both trials) and ethnic origin (LUX-Lung 3 only); the combined analysis of overall survival was adjusted by study (LUX-Lung 3 or LUX-Lung 6) and _EGFR_ mutation type. We used Cox proportional hazard models to derive HRs and 95% CIs comparing the two treatment groups, and to examine 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. We used Kaplan-Meier estimates to construct survival curves and calculate median overall survival. Median follow-up was calculated with the reverse Kaplan-Meier method.[22] We did statistical analyses with SAS (version 9.2).

Role of the funding source

Boehringer Ingelheim was responsible for each of the trial designs, managed the clinical trial database, and coordinated the development of the Article. JC-HY, Y-LW, LVS, and the Boehringer Ingelheim study team were responsible for the collection, analysis, and interpretation of the data, and decided on exploratory analyses. JC-HY had full access to the study data and prepared the Article draft, and all authors participated in the Article development and made the final decision to submit the manuscript for publication.

Results

In LUX-Lung 3, 1269 patients were screened between Aug 17, 2009, and Feb 28, 2011, and 345 patients were randomly assigned to study treatment (figure 1). Of these patients, 340 received at least one dose of study medication. In LUX-Lung 6, 910 patients were screened between April 27, 2010, and Nov 16, 2011, and 364 patients were randomly assigned to study treatment (figure 1). Of these patients, 352 received at least one dose of study medication. Reasons for patient ineligibility for randomisation are shown in figure 1. Reasons for randomly assigned patients not receiving study medication included not meeting eligibility criteria (four [80%] of five patients in LUX-Lung 3; three [25%] of 12 patients in LUX-Lung 6) and refusal to take study medication (one [20%] in LUX-Lung 3; nine [75%] in LUX-Lung 6). All randomly assigned patients were included in the overall survival analyses; randomly assigned patients receiving at least one dose of study medication were included in the safety analyses.

Table 1 shows patient characteristics at baseline. In both studies, most patients were women, never smokers, had stage IV disease, and had an ECOG performance status of 1 (table 1). In LUX-Lung 3, 249 (72%) of 345 patients were Asian. Most patients in each study had tumours harbouring common EGFR mutations (del19 or Leu858Arg); roughly half of patients had EGFR del19-positive tumours (table 1). Because patients with lung adenocarcinoma harbouring uncommon EGFR mutations represent a heterogeneous population with variable responses to treatment, analysis of outcomes in these patients will be reported separately.

At the data cutoff for this analysis (Nov 14, 2013, for LUX-Lung 3 and Dec 27, 2013, for LUX-Lung 6), the median duration of follow-up was 41 months (IQR 35–44) in LUX-Lung 3 and 33 months (IQR 31–37) in LUX-Lung 6; 213 (62%) patients in LUX-Lung 3 and 246 (68%) patients in LUX-Lung 6 had died. Because 21 (9%) of 230 patients in LUX-Lung 3 and 23 (10%) of 242 patients in LUX-Lung 6 were still receiving afatinib at the data cutoff, follow-up for overall survival and data on subsequent therapies are not final.
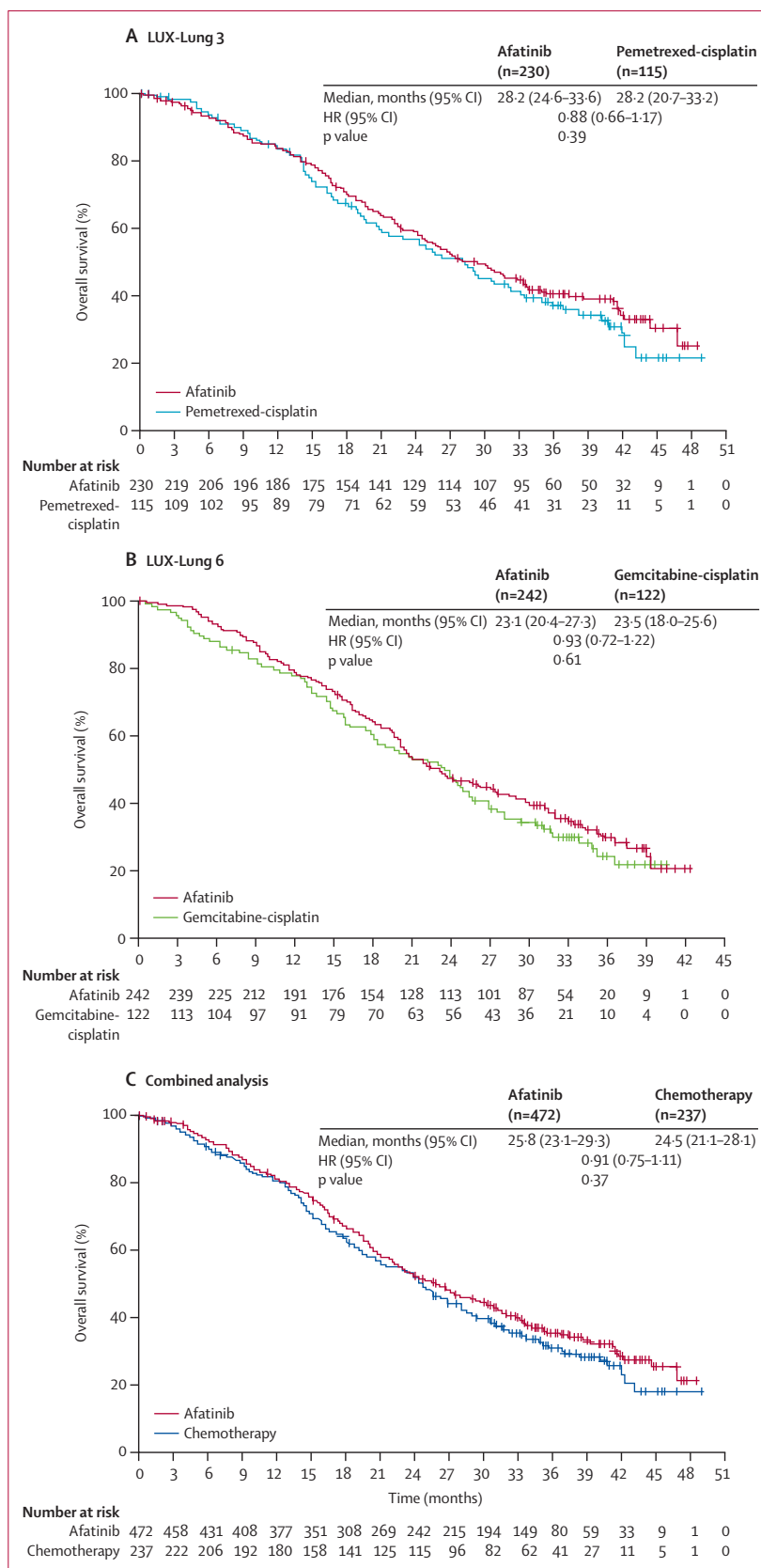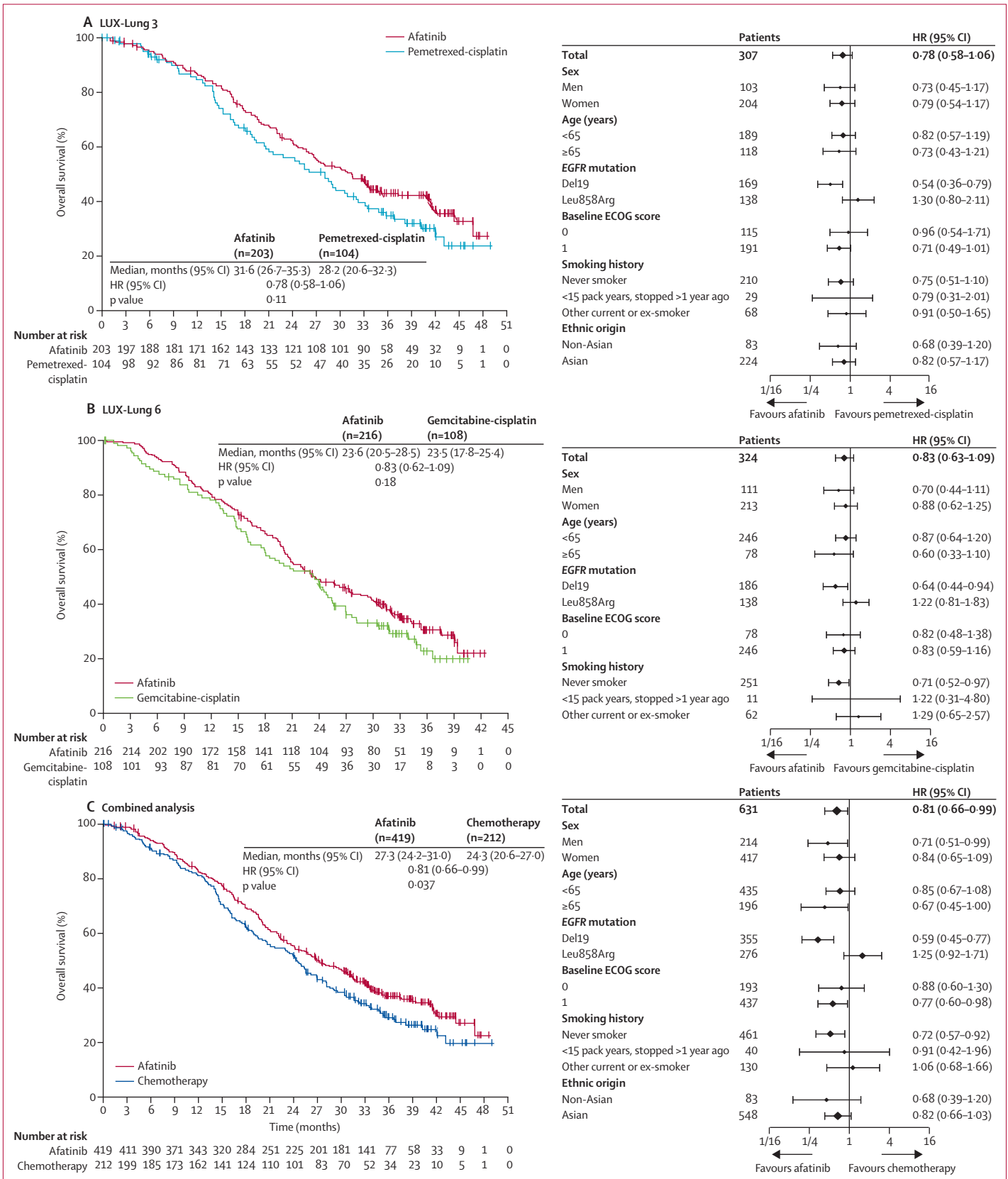

Figure 2: Overall survival in the overall populations of LUX-Lung 3 (A), LUX-Lung 6 (B), and the combined analysis (C)
HR=hazard ratio.

A LUX-Lung 3

— Afatinib
— Pemetrexed-cisplatin

Overall survival (%)

	Afatinib (n=203)	Pemetrexed-cisplatin (n=104)
Median, months (95% CI)	31·6 (26·7–35·3)	28·2 (20·6–32·3)
HR (95% CI)	0·78 (0·58–1·06)	
p value	0·11	

Number at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Afatinib	203	197	188	181	171	162	143	133	121	108	101	90	58	49	32	9	1	0
Pemetrexed-cisplatin	104	98	92	86	81	71	63	55	52	47	40	35	26	20	10	5	1	0

	Patients		HR (95% CI)
Total	307		0·78 (0·58–1·06)
Sex			
Men	103		0·73 (0·45–1·17)
Women	204		0·79 (0·54–1·17)
Age (years)			
<65	189		0·82 (0·57–1·19)
≥65	118		0·73 (0·43–1·21)
EGFR mutation			
Del19	169		0·54 (0·36–0·79)
Leu858Arg	138		1·30 (0·80–2·11)
Baseline ECOG score			
0	115		0·96 (0·54–1·71)
1	191		0·71 (0·49–1·01)
Smoking history			
Never smoker	210		0·75 (0·51–1·10)
<15 pack years, stopped >1 year ago	29		0·79 (0·31–2·01)
Other current or ex-smoker	68		0·91 (0·50–1·65)
Ethnic origin			
Non-Asian	83		0·68 (0·39–1·20)
Asian	224		0·82 (0·57–1·17)

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← Favours afatinib   Favours pemetrexed-cisplatin →

B LUX-Lung 6

	Afatinib (n=216)	Gemcitabine-cisplatin (n=108)
Median, months (95% CI)	23·6 (20·5–28·5)	23·5 (17·8–25·4)
HR (95% CI)	0·83 (0·62–1·09)	
p value	0·18	

Overall survival (%)

— Afatinib
— Gemcitabine-cisplatin

Number at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
Afatinib	216	214	202	190	172	158	141	118	104	93	80	51	19	9	1	0
Gemcitabine-cisplatin	108	101	93	87	81	70	61	55	49	36	30	17	8	3	0	0

	Patients		HR (95% CI)
Total	324		0·83 (0·63–1·09)
Sex			
Men	111		0·70 (0·44–1·11)
Women	213		0·88 (0·62–1·25)
Age (years)			
<65	246		0·87 (0·64–1·20)
≥65	78		0·60 (0·33–1·10)
EGFR mutation			
Del19	186		0·64 (0·44–0·94)
Leu858Arg	138		1·22 (0·81–1·83)
Baseline ECOG score			
0	78		0·82 (0·48–1·38)
1	246		0·83 (0·59–1·16)
Smoking history			
Never smoker	251		0·71 (0·52–0·97)
<15 pack years, stopped >1 year ago	11		1·22 (0·31–4·80)
Other current or ex-smoker	62		1·29 (0·65–2·57)

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← Favours afatinib   Favours gemcitabine-cisplatin →

C Combined analysis

	Afatinib (n=419)	Chemotherapy (n=212)
Median, months (95% CI)	27·3 (24·2–31·0)	24·3 (20·6–27·0)
HR (95% CI)	0·81 (0·66–0·99)	
p value	0·037	

Overall survival (%)

— Afatinib
— Chemotherapy

Time (months)

Number at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Afatinib	419	411	390	371	343	320	284	251	225	201	181	141	77	58	33	9	1	0
Chemotherapy	212	199	185	173	162	141	124	110	101	83	70	52	34	23	10	5	1	0

	Patients		HR (95% CI)
Total	631		0·81 (0·66–0·99)
Sex			
Men	214		0·71 (0·51–0·99)
Women	417		0·84 (0·65–1·09)
Age (years)			
<65	435		0·85 (0·67–1·08)
≥65	196		0·67 (0·45–1·00)
EGFR mutation			
Del19	355		0·59 (0·45–0·77)
Leu858Arg	276		1·25 (0·92–1·71)
Baseline ECOG score			
0	193		0·88 (0·60–1·30)
1	437		0·77 (0·60–0·98)
Smoking history			
Never smoker	461		0·72 (0·57–0·92)
<15 pack years, stopped >1 year ago	40		0·91 (0·42–1·96)
Other current or ex-smoker	130		1·06 (0·68–1·66)
Ethnic origin			
Non-Asian	83		0·68 (0·39–1·20)
Asian	548		0·82 (0·66–1·03)

1/16 1/4 1 4 16
← Favours afatinib   Favours chemotherapy →

Overall survival in both studies did not significantly differ between treatment groups (LUX-Lung 3: HR 0·88, 95% CI 0·66–1·17, p=0·39; LUX-Lung 6: HR 0·93, 95% CI 0·72–1·22, p=0·61; figure 2). Likewise, in patients with tumours harbouring common *EGFR* mutations (del19 and Leu858Arg), overall survival did not differ significantly between treatment groups (LUX-Lung 3: HR 0·78, 95% CI 0·58–1·06, p=0·11; LUX-Lung 6: HR 0·83, 95% CI 0·62–1·09, p=0·18; figure 3). However, in subgroup analyses examining different *EGFR* mutations in both trials, we noted a significant improvement in overall survival with afatinib compared with chemotherapy in patients with tumours harbouring the *EGFR* del19 mutation (LUX-Lung 3: HR 0·54, 95% CI 0·36–0·79, p=0·0015; LUX-Lung 6: HR 0·64, 95% CI 0·44–0·94, p=0·023; figure 4). By contrast, we noted no significant differences in overall survival by treatment group for patients with *EGFR* Leu858Arg-positive tumours in either LUX-Lung 3 (HR 1·30, 95% CI 0·80–2·11, p=0·29) or LUX-Lung 6 (HR 1·22, 95% CI 0·81–1·83, p=0·34; figure 4).

Complete safety analyses—including incidence and severity of adverse events, dose reductions, discontinuations, and fatalities—in both trials have been previously reported (data cutoff for adverse events: Jan 11, 2012, for LUX-Lung 3; Dec 29, 2012, for LUX-Lung 6).[18,19] Briefly, in LUX-Lung 3, the most common treatment-related grade 3 or 4 adverse events were rash or acne (37 [16%] of 229 patients), diarrhoea (33 [14%]), and paronychia (26 [11%]) with afatinib, and neutropenia (20 [18%] of 111 patients), fatigue (14 [13%]), and leucopenia (9 [8%]) with pemetrexed-cisplatin. Treatment-related serious adverse events occurred in 33 (14%) patients in the afatinib group and 16 (14%) patients in the pemetrexed-cisplatin group. In LUX-Lung 6, the most common treatment-related grade 3 or 4 adverse events were rash or acne (35 [15%] of 239 patients), diarrhoea (13 [5%]), and stomatitis or mucositis (13 [5%]) with afatinib, and neutropenia (30 [27%] of 113 patients), vomiting (22 [19%]), and leucopenia (17 [15%]) with gemcitabine-cisplatin. Treatment-related serious adverse events occurred in 15 (6%) patients in the afatinib group and nine (8%) patients in the gemcitabine-cisplatin group. Patients with disease progression or intolerable adverse events discontinued assigned study medication (first-line afatinib or chemotherapy) and received subsequent standard treatment at their physician's discretion. In LUX-Lung 3, drug-related adverse events leading to treatment discontinuation in more than one patient included diarrhoea (three [1%]), paronychia (two [1%]) and interstitial lung disease (two [1%]) in 229 afatinib-treated patients, and fatigue (three [3%]) in
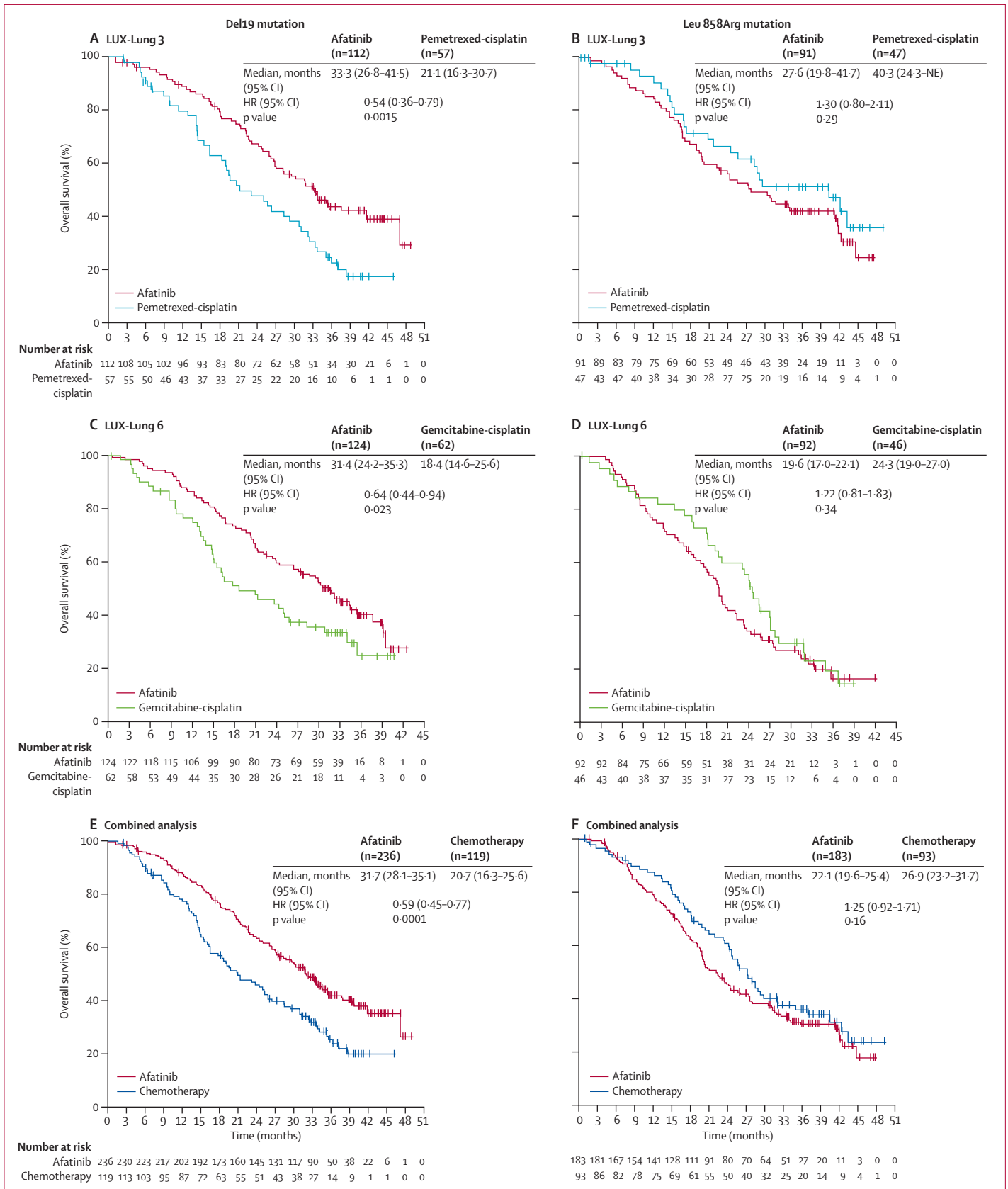
111 pemetrexed-cisplatin-treated patients. Drug-related adverse events leading to discontinuation in LUX-Lung 6 included rash (five [2%]) in 239 afatinib-treated patients, and vomiting (16 [14%]), nausea (11 [10%]), neutropenia (10 [9%]), leucopenia (eight [7%]), adverse events related to platelet and white blood cell count (five [4%]), anaemia (four [4%]), thrombocytopenia (four [4%]), fatigue (four [4%]), abnormal hepatic function (two [2%]), and renal failure (two [2%]) in 113 gemcitabine-cisplatin-treated patients.

Subsequent treatment regimens for the patients with common *EGFR* mutations are shown in table 2. Subsequent treatment with chemotherapy or an EGFR tyrosine kinase inhibitor after first-line therapy was balanced across treatment groups within each study. Among patients who discontinued study medication in LUX-Lung 3, 78 (75%) of 104 chemotherapy-treated patients with tumours harbouring common *EGFR* mutations subsequently received an EGFR tyrosine kinase inhibitor, and 131 (71%) of 184 afatinib-treated patients received subsequent chemotherapy. Among patients who discontinued study medication in LUX-Lung 6, 61 (56%) of 108 chemotherapy-treated patients and 114 (59%) of 194 afatinib-treated patients received subsequent therapy with EGFR tyrosine kinase inhibitors or chemotherapy, respectively. Additionally, we noted no differences in the proportion of patients receiving subsequent treatment with chemotherapy or an EGFR tyrosine kinase inhibitor after first-line therapy by *EGFR* mutation type (table 2). Of note, patients randomly assigned to first-line chemotherapy typically received erlotinib or gefitinib as later-line EGFR tyrosine kinase inhibitor treatment because afatinib was not clinically available at the time.

We combined individual patient data from LUX-Lung 3 and LUX-Lung 6 for exploratory analyses. Because the two studies had very similar designs and were done simultaneously, heterogeneity in this combined analysis was insignificant (p=0·92). Median overall survival in the combined overall population was not significantly different between treatment groups (HR 0·91, 95% CI 0·75–1·11, p=0·37; figure 2). Among patients with tumours harbouring common *EGFR* mutations, overall survival was significantly improved with afatinib compared with chemotherapy (HR 0·81, 95% CI 0·66–0·99, p=0·037; figure 3). Consistent with individual study findings, subgroup analyses suggested that the overall survival benefit of afatinib was driven mainly by patients with *EGFR* del19-positive tumours (HR 0·59, 95% CI 0·45–0·77, p=0·0001; figure 4), whereas in patients with *EGFR* Leu858Arg-positive tumours, there was no difference between groups (HR 1·25, 95% CI 0·92–1·71, p=0·16; figure 4). Of note, HRs favoured afatinib for all but two of the subgroups analysed (figure 3). In the subgroup of non-Asian patients with tumours harbouring common *EGFR* mutations (n=83) in LUX-Lung 3, median overall survival was 28·1 months

Figure 3: Overall survival in patients with common *EGFR* mutations
Common mutations refer to del19 and Leu858Arg combined. (A) LUX-Lung 3. (B) LUX-Lung 6. (C) Both trials combined. HR=hazard ratio. Del19=deletion of exon 19.

A LUX-Lung 3 — Del19 mutation

	Afatinib (n=112)	Pemetrexed-cisplatin (n=57)
Median, months (95% CI)	33·3 (26·8–41·5)	21·1 (16·3–30·7)
HR (95% CI)	0·54 (0·36–0·79)	
p value	0·0015	

Number at risk
Afatinib: 112 108 105 102 96 93 83 80 72 62 58 51 34 30 21 6 1 0
Pemetrexed-cisplatin: 57 55 50 46 43 37 33 27 25 22 20 16 10 6 1 1 0 0

B LUX-Lung 3 — Leu 858Arg mutation

	Afatinib (n=91)	Pemetrexed-cisplatin (n=47)
Median, months (95% CI)	27·6 (19·8–41·7)	40·3 (24·3–NE)
HR (95% CI)	1·30 (0·80–2·11)	
p value	0·29	

Number at risk
91 89 83 79 75 69 60 53 49 46 43 39 24 11 3 0 0
47 43 42 40 38 34 30 28 27 25 20 19 16 14 9 4 1 0

C LUX-Lung 6

	Afatinib (n=124)	Gemcitabine-cisplatin (n=62)
Median, months (95% CI)	31·4 (24·2–35·3)	18·4 (14·6–25·6)
HR (95% CI)	0·64 (0·44–0·94)	
p value	0·023	

Number at risk
Afatinib: 124 122 118 115 106 99 90 80 73 69 59 39 16 8 1 0
Gemcitabine-cisplatin: 62 58 53 49 44 35 30 28 26 21 18 11 4 3 0 0

D LUX-Lung 6

	Afatinib (n=92)	Gemcitabine-cisplatin (n=46)
Median, months (95% CI)	19·6 (17·0–22·1)	24·3 (19·0–27·0)
HR (95% CI)	1·22 (0·81–1·83)	
p value	0·34	

Number at risk
92 92 84 75 66 59 51 38 31 24 21 12 3 1 0 0
46 43 40 38 37 35 31 27 23 15 12 6 4 0 0 0

E Combined analysis

	Afatinib (n=236)	Chemotherapy (n=119)
Median, months (95% CI)	31·7 (28·1–35·1)	20·7 (16·3–25·6)
HR (95% CI)	0·59 (0·45–0·77)	
p value	0·0001	

Number at risk
Afatinib: 236 230 223 217 202 192 173 160 145 131 117 90 50 38 22 6 1 0
Chemotherapy: 119 113 103 95 87 72 63 55 51 43 38 27 14 9 1 1 0 0

F Combined analysis

	Afatinib (n=183)	Chemotherapy (n=93)
Median, months (95% CI)	22·1 (19·6–25·4)	26·9 (23·2–31·7)
HR (95% CI)	1·25 (0·92–1·71)	
p value	0·16	

Number at risk
183 181 167 154 141 128 111 91 80 70 64 51 27 20 11 3 0 0
93 86 82 78 75 69 61 55 50 40 32 25 20 14 9 4 1 0

(22·1 to 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-positive tumours (n=46; 33·6 months [24·6 to not estimable] *vs* 20·0 months [11·2–33·5]; HR 0·45, 95% CI 0·21–0·95, p=0·03) but not Leu858Arg-positive tumours (n=37; 19·8 months [14·5–41·8] *vs* 21·2 months [14·2 to not estimable]; HR 1·22, 95% CI 0·50–2·99, p=0·67).

We also did exploratory combined analyses of patients in both trials treated in countries with or without a universal health-care reimbursement policy to examine whether regional and systematic access to subsequent therapies might affect overall survival in these studies. These results are shown in the appendix.

Discussion

Findings from randomised studies comparing first-line EGFR tyrosine kinase inhibitors with standard chemotherapies suggest that patients with lung adeno-carcinoma harbouring *EGFR* mutations have improved responses, progression-free survival, and quality of life, although no improvements in overall survival have been reported (panel).[2–8,18,19] To our knowledge, our analysis of these two independent phase 3 studies shows for the first time that first-line afatinib significantly improved overall survival compared with chemotherapy, specifically in patients with lung adenocarcinoma harbouring the *EGFR* del19 mutation but not in patients with Leu858Arg-positive tumours or in the *EGFR* mutation-positive patient population overall. Of note, although most patients in LUX-Lung 3 and the entire population of LUX-Lung 6 were Asian, a significant improvement in overall survival with afatinib in the del19 subgroup was also noted in the smaller subpopulation of non-Asian patients in LUX-Lung 3, supporting the applicability of the findings to all patients with *EGFR* mutation-positive disease, irrespective of ethnic origin.

EGFR del19 and Leu858Arg mutations make up around 90% of all *EGFR* mutation-positive lung adeno-carcinomas,[23] and are strongly associated with robust responses to EGFR tyrosine kinase inhibitors.[24] Patients with *EGFR* del19-positive tumours have consistently show improved outcomes with EGFR tyrosine kinase inhibitors compared with patients with Leu858Arg-positive disease.[25–28] The cause of this difference in response to EGFR tyrosine kinase inhibitors by *EGFR* mutation subtype is not known. Within this context, our analysis now suggests that afatinib significantly improves overall survival compared with chemotherapy among patients with *EGFR* del19-positive tumours but not for patients

with Leu858Arg-positive disease, where clinical benefit of afatinib over chemotherapy was demonstrated in terms of progression-free survival and objective response.[18,19] One should note, however, that although subgroups and their analyses were preplanned, no adjustment for multiplicity was done, thus increasing the chance of a false positive finding.

Previous reports of reversible EGFR tyrosine kinase inhibitors erlotinib and gefitinib have not shown an overall survival benefit compared with chemotherapy in overall study populations or by *EGFR* mutation type.[8–15] Because EGFR tyrosine kinase inhibitor sensitivity among *EGFR*-mutant tumours is not adversely affected by chemotherapy pretreatment,[23] any overall survival benefit of first-line EGFR tyrosine kinase inhibitors in these studies was thought to be offset by subsequent treatment with second-line EGFR tyrosine kinase inhibitors after progression on chemotherapy. Because afatinib was not clinically available at the time of the LUX-Lung 3 and LUX-Lung 6 studies, very few patients received afatinib as later-line EGFR tyrosine kinase

See **Online** for appendix

Figure 4: Overall survival in patients with del19-positive disease and Leu858Arg-positive disease
Del19-positive disease in (A) LUX-Lung 3, (C) LUX-Lung 6, and (E) both trials combined. Leu858Arg-positive disease in (B) in LUX-Lung 3, (D) LUX-Lung 6, and (F) both trials combined. HR=hazard ratio. NE=not estimable.

	Del19		Leu858Arg	
	Afatinib	Cisplatin combination	Afatinib	Cisplatin combination
LUX-Lung 3				
Number of patients	112	57	91	47
Discontinued study treatment	100	57	84	47
Received subsequent systemic therapy*	76 (76%)	49 (86%)	68 (81%)	39 (83%)
Chemotherapy	69 (69%)	29 (51%)	62 (74%)	20 (43%)
EGFR TKI therapy	41 (41%)	43 (75%)	40 (48%)	35 (74%)
Erlotinib	32 (32%)	27 (47%)	29 (35%)	19 (40%)
Gefitinib	14 (14%)	26 (46%)	14 (17%)	18 (38%)
Afatinib	1 (1%)	6 (11%)	1 (1%)	1 (2%)
AZD9291	1 (1%)	1 (2%)	1 (1%)	0
Dacomitinib	0	0	0	1 (2%)
EGFR TKI combinations	2 (2%)	8 (14%)	3 (4%)	3 (6%)
Other	2 (2%)	1 (2%)	3 (4%)	1 (2%)
Radiotherapy	18 (18%)	13 (23%)	14 (17%)	8 (17%)
LUX-Lung 6				
Number of patients	124	62	92	46
Discontinued study treatment, n	110	62	84	46
Received subsequent systemic therapy*	79 (72%)	39 (63%)	44 (52%)	31 (67%)
Chemotherapy	72 (65%)	16 (26%)	42 (50%)	13 (28%)
EGFR TKI therapy	36 (33%)	33 (53%)	14 (17%)	28 (61%)
Gefitinib	15 (14%)	19 (31%)	4 (5%)	20 (43%)
Erlotinib	15 (14%)	11 (18%)	6 (7%)	11 (24%)
Icotinib	8 (7%)	3 (5%)	3 (4%)	0
EGFR TKI combinations	4 (4%)	2 (3%)	1 (1%)	1 (2%)
Other	2 (2%)	2 (3%)	1 (1%)	2 (4%)
Radiotherapy	4 (4%)	0	0	0

TKI=tyrosine kinase inhibitor. *Percentages based on the number of patients who discontinued treatment. Collection of data on subsequent therapies is still ongoing.

Table 2: Treatment beyond first-line therapy in patients with common *EGFR* mutations

Panel: Research in context

Systematic review

We did a systematic review of the scientific literature (English only) published up to Sept 30, 2014, using PubMed to identify phase 3, randomised trials assessing first-line EGFR tyrosine kinase inhibitor therapy versus standard platinum-based chemotherapy regimens in previously untreated patients with *EGFR* mutation-positive advanced lung adenocarcinoma. Using the search terms "phase 3", "advanced" or "metastatic lung adenocarcinoma", and "EGFR", we identified seven trials done with the reversible EGFR tyrosine kinase inhibitors gefitinib (four trials[2-4,8-12,15]) and erlotinib (three trials[5-7,13,14]), and two trials done with the second-generation irreversible tyrosine kinase inhibitor afatinib (LUX-Lung 3 and LUX-Lung 6[18,19]). In each of these studies, significant improvements in progression-free survival and objective response were reported with EGFR tyrosine kinase inhibitor therapy versus chemotherapy.[2-8,18,19] None of the studies were designed to detect a difference in overall survival in the overall population or in *EGFR* exon 19 deletion (del19) or Leu858Arg mutation subgroups. In this context, overall survival benefit compared with chemotherapy was not reported in the gefitinib or erlotinib studies.[8-15] Only the IPASS, NEJ002, and EURTAC trials examined overall survival with reversible EGFR tyrosine kinase inhibitors specifically in *EGFR* del19 or Leu858Arg mutation subgroups; no differences in overall survival were reported.[9-11,13]

Interpretation

Results from LUX-Lung 3 and LUX-Lung 6 previously corroborated the findings of other randomised trials in this setting with regards to understanding of *EGFR* mutation-positive lung adenocarcinoma and response to EGFR tyrosine kinase inhibitors based on assessments of tumour response and progression-free survival.[18,19] To our knowledge, this is the first time that an overall survival benefit has been demonstrated in patients with tumours that contain the *EGFR* del19 mutations, although no such benefit was observed in patients with Leu858Arg-positive tumours, or when common *EGFR* mutations were pooled. This finding suggests that among standard first-line EGFR tyrosine kinase inhibitors, afatinib should be the preferred option for patients with *EGFR* del19-positive lung adenocarcinoma. The difference in outcomes for patients with *EGFR* del19 and Leu858Arg-positive disease suggests that these populations should be studied separately in future trials.

inhibitor treatment; the majority received erlotinib or gefitinib after chemotherapy. The clinically meaningful difference in median overall survival observed with afatinib compared with chemotherapy in patients with *EGFR* del19-positive tumours in both studies could be attributed to mechanistic differences between the irreversible ERBB family blocker afatinib and first-generation reversible EGFR tyrosine kinase inhibitors. Further, preclinical studies have shown that *EGFR* del19 and Leu858Arg mutants have distinct biological properties that might affect response to different EGFR tyrosine kinase inhibitors.[29,30]

In LUX-Lung 3, the proportion of patients receiving subsequent therapies after study discontinuation was consistent with reports of similar randomised trials.[5,6,9,11,12] In LUX-Lung 6, fewer patients were followed up at the time of data cutoff (ie, the follow-up was shorter), and the proportion of patients receiving subsequent therapies was lower in both groups, potentially resulting from disparities in access to treatments in different countries. Of note, the group of patients who did not receive subsequent treatments in both studies included those who died early, withdrew consent, or were lost to follow-up. Additionally, we noted no differences in the proportions of patients receiving subsequent therapies in the *EGFR* del19 and Leu858Arg subgroups within each study, suggesting that the overall survival benefit seen with afatinib in del19-positive disease is unlikely to be attributable to follow-up treatment.

In summary, findings from the LUX-Lung 3 and LUX-Lung 6 trials showed no benefit in overall survival for all patients or the Leu858Arg-positive subgroup with the use of afatinib, but the drug did result in significant improvements in overall survival compared with platinum-doublet chemotherapy in patients with *EGFR* del19-positive lung adenocarcinoma. To the best of our knowledge, these are the only two studies to date to suggest an overall survival advantage for *EGFR* del19-positive disease treated with a first-line EGFR tyrosine kinase inhibitor. Further, these findings suggest that patients with lung adenocarcinoma harbouring *EGFR* del19 and Leu858Arg mutations should be stratified and analysed separately in future clinical trials.

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