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Reprint

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Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial

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Summary

Background There is a major unmet need for effective treatments in patients with squamous cell carcinoma of the lung. LUX-Lung 8 compared afatinib (an irreversible ErbB family blocker) with erlotinib (a reversible EGFR tyrosine kinase inhibitor), as second-line treatment for patients with advanced squamous cell carcinoma of the lung.

Methods We did this open-label, phase 3 randomised controlled trial at 183 cancer centres in 23 countries worldwide. We enrolled adults with stage IIIB or IV squamous cell carcinoma of the lung who had progressed after at least four cycles of platinum-based-chemotherapy. Participants were randomly assigned (1:1) to receive afatinib (40 mg per day) or erlotinib (150 mg per day) until disease progression. The randomisation was done centrally with an interactive voice or web-based response system and stratified by ethnic origin (eastern Asian *vs* non-eastern Asian). Clinicians and patients were not masked to treatment allocation. The primary endpoint was progression-free survival assessed by independent central review (intention-to-treat population). The key secondary endpoint was overall survival. This trial is registered with ClinicalTrials.gov, NCT01523587.

Findings 795 eligible patients were randomly assigned (398 to afatinib, 397 to erlotinib). Median follow-up at the time of the primary analysis of progression-free survival was 6·7 months (IQR 3·1–10·2), at which point enrolment was not complete. Progression free-survival at the primary analysis was significantly longer with afatinib than with erlotinib (median 2·4 months [95% CI 1·9–2·9] *vs* 1·9 months [1·9–2·2]; hazard ratio [HR] 0·82 [95% CI 0·68–1·00], p=0·0427). At the time of the primary analysis of overall survival (median follow-up 18·4 months [IQR 13·8–22·4]), overall survival was significantly greater in the afatinib group than in the erloinib group (median 7·9 months [95% CI 7·2–8·7] *vs* 6·8 months [5·9–7·8]; HR 0·81 [95% CI 0·69–0·95], p=0·0077), as were progression-free survival (median 2·6 months [95% CI 2·0–2·9] *vs* 1·9 months [1·9–2·1]; HR 0·81 [95% CI 0·69–0·96], p=0·0103) and disease control (201 [51%] of 398 patients *vs* 157 [40%] of 397; p=0·0020). The proportion of patients with an objective response did not differ significantly between groups (22 [6%] *vs* 11 [3%]; p=0·0551). Tumour shrinkage occurred in 103 (26%) of 398 patients versus 90 (23%) of 397 patients. Adverse event profiles were similar in each group: 224 (57%) of 392 patients in the afatinib group versus 227 (57%) of 395 in the erlotinib group had grade 3 or higher adverse events. We recorded higher incidences of treatment-related grade 3 diarrhoea with afatinib (39 [10%] *vs* nine [2%]), of grade 3 stomatitis with afatinib (16 [4%] *vs* none), and of grade 3 rash or acne with erlotinib (23 [6%] *vs* 41 [10%]).

Interpretation The significant improvements in progression-free survival and overall survival with afatinib compared with erlotinib, along with a manageable safety profile and the convenience of oral administration suggest that afatinib could be an additional option for the treatment of patients with squamous cell carcinoma of the lung.

Funding Boehringer Ingelheim.

Introduction

Few treatment options are available for advanced squamous cell carcinoma of the lung, which accounts for 20–30% of cases of non-small-cell lung cancer,[1] especially after failure of first-line platinum-based doublet chemotherapy.[2] Despite the identification of specific molecular aberrations (eg, *FGFR1* amplification, *PIK3K3* abnormalities, *DDR2* mutations),[3] progress in squamous cell carcinoma lags behind adenocarcinoma, particularly with regard to approved drugs targeting oncogenic drivers. Furthermore, drugs approved for the treatment of adenocarcinoma are contraindicated in patients with squamous cell carcinoma either because of safety concerns (bevacizumab)[4] or reduced efficacy (pemetrexed).[5] Consequently, until recently, erlotinib (an EGFR tyrosine kinase inhibitor) and docetaxel were the only approved second-line treatments for squamous cell carcinoma.[2] In December, 2014, the US Food and Drug Administration approved ramucirumab, an anti-VEGFR-2 antibody, in combination with docetaxel, for the treatment of metastatic

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Research in context

Evidence before this study

We systematically reviewed PubMed up to March 17, 2015, and trials presented as abstracts at the American Society of Clinical Oncology and the European Society for Medical Oncology annual meetings. We used the search terms "phase 2" or "phase 3" and "squamous cell carcinoma" and "lung", and reviewed reports and presentations of phase 2 and 3 trials investigating anti-cancer drugs (chemotherapy or targeted therapies) that included patients with squamous cell carcinoma of the lung who had progressed on or after platinum treatment. Based on this review, we confirmed that there is an unmet medical need for patients in this setting, with few (although increasing) efficacious treatment options. At the time the trial was started, only two drugs had been approved in this setting: erlotinib and docetaxel. During the trial, ramucirumab (plus docetaxel) and nivolumab were approved.

Added value of this study

This study shows that afatinib has clinical efficacy as second-line treatment for patients with squamous cell carcinoma of the lung. Afatinib reduced the risk of death compared with erlotinib and also improved progression-free survival, health-related quality-of-life outcomes, and symptom control.

Implications of all the available evidence

These data support the addition of afatinib to the armamentarium of treatments for this difficult-to-treat population. Further research is needed to define the role of afatinib in squamous cell carcinoma of the lung in relation to nivolumab, ramucirumab, and other emerging treatments. In this context, afatinib has the advantage of oral administration as monotherapy and a well-defined manageable adverse event profile. Further ongoing biomarker analysis might identify subgroups of patients with squamous cell carcinoma of the lung who are most likely to benefit from afatinib treatment.

non-small-cell lung cancer and in March, 2015, approved nivolumab, an immune checkpoint inhibitor, for treatment of patients with metastatic squamous non-small-cell lung cancer, who progressed during or after platinum-based chemotherapy. Although the trial that led to the approval of ramucirumab enrolled patients with non-squamous and squamous histology,[6] the nivolumab trials enrolled only patients with squamous cell carcinoma.[7,8]

Molecular data suggest a role for overexpression or gene amplification of *EGFR* in the pathobiology of squamous cell carcinoma. Several studies[9,10] suggest that *EGFR* overexpression is more common in squamous tumours (up to 82% of cases) than in adenocarcinomas. Although EGFR expression does not seem to be a reliable predictor of responsiveness to EGFR inhibitors in non-small-cell lung cancer (all histological subtypes),[11] this feature might explain the sensitivity of some patients with squamous cell carcinoma of the lung to EGFR-targeted treatments despite having few (<5%) *EGFR*-activating mutations.[12] For example, second-line treatment with erlotinib significantly improves survival compared with placebo in patients with squamous cell carcinoma of the lung.[13,14] This observation, along with the lack of myelosuppression, positions erlotinib as a viable treatment option for a population that has many comorbidities. The rationale for targeting EGFR in patients with squamous cell carcinoma of the lung is supported by trials[15,16] showing an improvement in overall survival when the anti-EGFR monoclonal antibodies cetuximab or necitumumab were added to first-line platinum doublet chemotherapy compared with doublet chemotherapy only. In addition to EGFR, other members of the ErbB family, including HER2,[17–19] HER3,[20] and HER4,[20] as well as their cognate ligand NRG1,[21] have been implicated in the pathogenesis of squamous cell carcinoma.

See Online for appendix

Afatinib is an irreversible ErbB-family inhibitor that, by contrast with EGFR tyrosine kinase inhibitors, selectively blocks signalling from all homodimers and heterodimers formed by EGFR, HER2, HER3, and HER4.[22] It improved first-line progression-free survival compared with chemotherapy in two large phase 3 trials in patients with *EGFR* mutation-positive advanced lung adenocarcinoma, as well as improving overall survival in patients with the *EGFR* del19 mutation.[23–25] Afatinib has a well-defined safety profile and is associated with class-related gastrointestinal (diarrhoea, stomatitis) and cutaneous (rash or acne) adverse events.[23,24,26] These adverse events are generally manageable, with 6–8% of patients in phase 3 trials discontinuing treatment because of adverse events.[23,24,26] We hypothesised that, on the basis of its broader mechanism of action and encouraging activity in patients with squamous histology cancers,[27,28] afatinib would improve efficacy compared with erlotinib (the only tyrosine kinase inhibitor approved in this setting) in a randomised trial of pretreated patients with squamous cell carcinoma of the lung.

Methods

Study design and participants

LUX-Lung 8 was a randomised controlled phase 3 trial done at 183 cancer centres in 23 countries worldwide (appendix). Eligible patients were aged 18 years or older with a diagnosis of stage IIIB or IV non-small-cell lung cancer (American Joint Committee on Cancer version 7) of squamous (including mixed) histology. Participants had to have received at least four cycles of platinum-based doublet chemotherapy as first-line treatment with subsequent disease progression according to the investigator, and had to be eligible for second-line treatment. Left untreated, these patients have a life

expectancy of roughly 4 months.[13] Other inclusion criteria were: an Eastern Cooperative Oncology Group performance status of 0 or 1, measurable disease using Response Evaluation Criteria in Solid Tumors (version 1.1), and adequate organ function defined as: left ventricular ejection fraction of greater than 50% or within institution normal values; absolute neutrophil count greater than 1500 cells per μL; platelet count greater than 75 000 cells per μL; estimated creatinine clearance greater than 45 mL/min; and total bilirubin less than 1·5 times institutional upper limit of normal (ULN); and aspartate aminotransferase or alanine aminotransferase less than three times the institutional ULN. Archived tumour tissue had to be available for all patients for exploratory biomarker analysis. Exclusion criteria were: previous treatment with EGFR-targeted tyrosine kinase inhibitors or antibodies; active brain metastases; radiotherapy within 4 weeks before randomisation; any other present malignancy or malignancy diagnosed within the past 3 years; pre-existing interstitial lung disease; significant or recent acute gastrointestinal disorders with diarrhoea as a major symptom; history or presence of clinically relevant cardiovascular abnormalities; any other concomitant serious illness or organ system dysfunction that in the opinion of the investigator would either compromise patient safety or interfere with the assessment of the safety of afatinib; inability to comply with the protocol in the opinion of the investigator; active hepatitis B or C infection; HIV infection; any contraindications for treatment with afatinib or erlotinib; hypersensitivity to erlotinib, afatinib, or the excipients of any of the trial drugs; major surgery within 4 weeks of starting study treatment; previous participation in a clinical study of afatinib; use of any investigational drug within 4 weeks of randomisation; and patients without progressive disease. The appendix includes the complete eligibility criteria.

The study protocol, designed in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guideline for Good Clinical Practice, and applicable region-specific regulatory requirements, was approved by independent ethics committees at each centre. All patients provided written informed consent for trial participation.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to receive either afatinib or erlotinib. Despite the rarity of *EGFR* mutations in squamous cell carcinoma,[12] we stratified randomisation by ethnic origin (eastern Asian *vs* non-eastern Asian) to eliminate any potential bias in *EGFR* mutation frequency across groups. 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 or web-based response system; individuals directly involved in the conduct and analysis of the trials did not have access to the randomisation schedule. Clinicians and patients were not masked to treatment assignment.

Procedures

Patients in the afatinib group received afatinib 40 mg orally once daily. After the first 28-day cycle, the dose of afatinib could be escalated from 40 mg to 50 mg once daily for patients who did not have rash, diarrhoea, mucositis, or any other drug-related adverse event of more than grade 1. If patients had any grade 3 or higher drug-related adverse events, or grade 2 diarrhoea lasting 2 days or more, or nausea or vomiting for 7 consecutive days or more despite best supportive care, then study drug was paused for no more than 14 days. After treatment interruption and recovery to grade 1 or less (or grade present at baseline), afatinib dose was reduced by 10 mg decrements to a minimum dose of 20 mg. Treatment was permanently discontinued in patients who did not recover to grade 1 or less or baseline grade.

Patients in the erlotinib group received the approved daily oral dose of 150 mg. In the event of adverse events, dose reduction of erlotinib was permitted according to approved label instructions. Smoking induces CYP enzymes, which can affect trough plasma concentrations of erlotinib in patients who continue to smoke.[29] However, dose escalation for smokers in this study was not implemented because it is not a global regulatory standard and it does not improve efficacy.[30] In both groups, treatment was continued until disease progression, unacceptable adverse events preventing continuation, or any other reason necessitating withdrawal.

Tumour assessments were done by CT or MRI of no more than five target lesions at baseline and then at weeks 8, 12, 16, and every 8 weeks thereafter until confirmed progression or withdrawal for another reason. Scans were reviewed by an independent central imaging group masked to treatment assignments. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (version 3.0). Safety laboratory assessments (urinanalysis, biochemistry, and haematology) were done at screening, on the first visit of each treatment cycle, and at the end of treatment.

Patient-reported outcomes were assessed at the first visit of each treatment course and measured with the European Organisation for the Research and Treatment of Cancer core cancer questionnaire (QLQ-C30) and its lung cancer specific module (QLQ-LC13). We analysed percentage of patients improved, time to deterioration, and changes over time for prespecified lung cancer symptoms (cough, dyspnoea, and pain), and the results will be reported separately in the future. Exploratory biomarker analyses will also be reported separately; biomarker methods and preliminary results are briefly described in the appendix. An independent data and safety monitoring committee did regular assessments of efficacy and safety data.

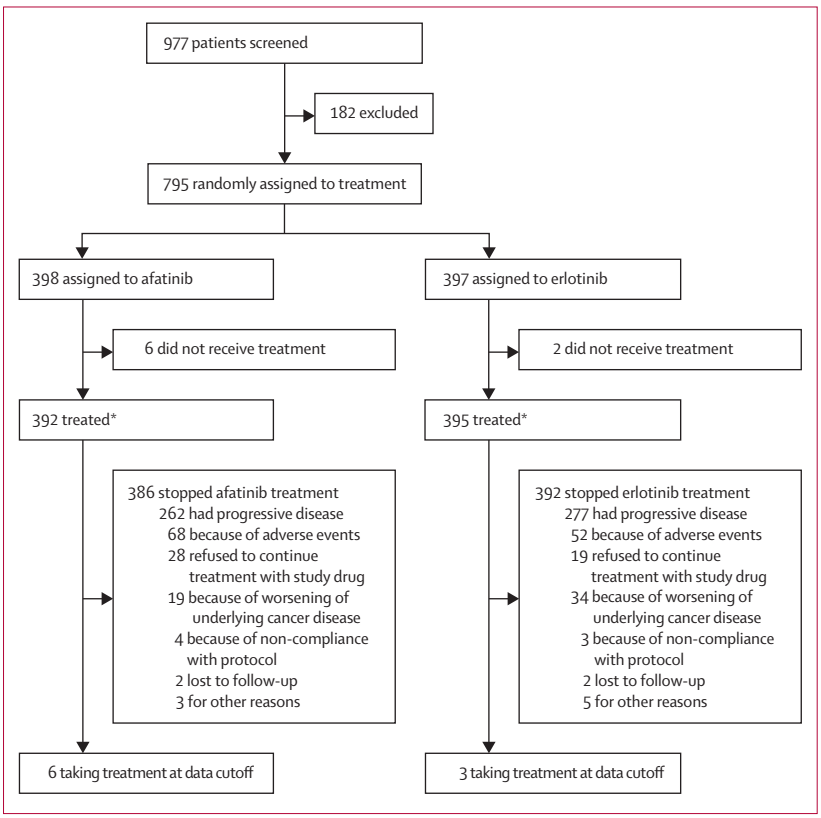


Figure 1: **Trial profile**
*Received at least one dose of study drug.

Outcomes

The primary endpoint was progression-free survival, defined as the time from randomisation to progression or death, whichever occurred first. Progression-free survival was assessed by a central independent review committee according to RECIST (version 1.1). The key secondary endpoint was overall survival, defined as the time from randomisation to death. Other secondary endpoints were the proportion of patients with an objective response (defined as complete response [CR] or partial response [PR]), the proportion of patients who achieved disease control (defined as CR, PR, stable disease [SD], or non-CR and non-progressive disease [NN; stable non-target disease in the absence of baseline target disease]), tumour shrinkage (maximum decrease from baseline in the sum of target lesion diameters), and patient-reported outcomes. We also did a post-hoc analysis of disease control rate excluding patients with NN.

Statistical analysis

An estimated 372 progression-free survival events would be needed to provide 90% power for a log-rank test, assuming a hazard ratio (HR) of 0·714 for afatinib relative to erlotinib (corresponding to a median progression-free survival of 3·2 months *vs* 2·3 months), with a two-sided α of 0·05. Primary analysis of overall survival was planned for when 632 deaths had occurred and was only to be tested if progression-free survival was statistically significant. This number of deaths would provide 80% power for the log-rank test, assuming an HR of 0·80 for afatinib relative to erlotinib (corresponding to a median overall survival of 8·8 months *vs* 7·0 months), with a two-sided α of 0·05.

A prespecified interim analysis was done after 130 patients of the first 176 patients had had progressive disease or death, as determined by assessment at the study sites. The analysis was done by a contract research organisation for the data and safety monitoring committee, which reviewed the results to assess whether to: (1) continue accrual until 800 patients had been randomised, as planned; (2) partly curtail accrual to the 500 patients required for the analysis of progression-free survival; or (3) stop accrual. The trial was not stopped and was allowed to continue to full accrual. Boehringer Ingelheim and the trial team remained masked to treatment allocation throughout this process and were notified only of the data and safety monitoring committee's final recommendation. A Haybittle-Peto boundary ($p<0·0001$) was used for this interim analysis to preserve the 0·05 α for the primary analyses.

The log-rank test (stratified by ethnic origin) was used to compare survival in the afatinib and erlotinib groups with a two-sided α of 0·05. A Cox proportional hazard model was used to estimate the HRs and corresponding 95% CIs for survival; Kaplan-Meier estimates and 95% CIs were calculated with Greenwood's standard error estimate. Logistic regression models, also stratified by ethnic origin, were used to compare the proportions of patients with an overall response and disease control between groups. HRs for longitudinal and time-to-deterioration analyses of patient-reported outcomes were derived by proportional hazards regression. Two-sided p values, stratified by ethnic origin, were calculated with the log-rank test. All efficacy analyses were done in the randomised (intention-to-treat) population. Safety analyses included all patients receiving at least one dose of trial drug. All analyses of adverse events were descriptive. The statistical analyses were done with SAS (version 9.2).

This study is registered with ClinicalTrials.gov, NCT01523587.

Role of the funding source

The trial was designed by the LUX-Lung 8 steering committee (J-CS, EF, SL, VG, AA, SMG, VKC, GDG) in collaboration with the funder. The funder also managed the clinical trial database, analysed the data according to the statistical plan, and decided on exploratory analyses in accordance with the trial steering committee. Members of the steering committee had access to the raw data. All authors made the final decision to submit the report for publication. The corresponding author had

full access to all of the data and the final responsibility to submit for publication.

Results

Between March 30, 2012, and Jan 30, 2014, 977 patients were screened and 795 patients were enrolled: 398 assigned to the afatinib group and 397 assigned to the erlotinib group (figure 1). Baseline characteristics were generally well balanced (table 1). Median age was 64 years, 666 patients were men, 172 were eastern Asian, and 751 were ever-smokers.

As planned, the primary analysis of progression-free survival was done when the requisite number of events judged by central independent review was reached (Oct 7, 2013); at this time recruitment was ongoing. Median follow-up was 6·7 months (IQR 3·1–10·2); treatment with afatinib led to a significant improvement in progression free-survival compared with erlotinib (median 2·4 months [95% CI 1·9–2·9] *vs* 1·9 months [1·9–2·2]; HR 0·82 [95% CI 0·68–1·00]; p=0·0427; appendix).

Progression-free survival was reassessed at the time of the primary overall survival analysis, including all randomly assigned patients, when 307 deaths had occurred in the afatinib group and 325 in the erlotinib group (database lock: March 2, 2015). At this time, 299 progression-free survival events had occurred in the afatinib group and 306 had occurred in the erlotinib group. Median progression-free survival was 2·6 months (95% CI 2·0–2·9) with afatinib and 1·9 months (1·9–2·1) with erlotinib (HR 0·81 [95% CI 0·69–0·96]; p=0·0103; figure 2A). Prespecified subgroup analyses favoured patients treated with afatinib (figure 2B). Investigator-reviewed progression-free survival assessed at the time of the primary overall survival analysis yielded similar results (median 2·7 months [95% CI 2·0–3·3] *vs* 1·9 months [1·9–2·0]; HR 0·79 [95% CI 0·68–0·91]; p=0·0012).

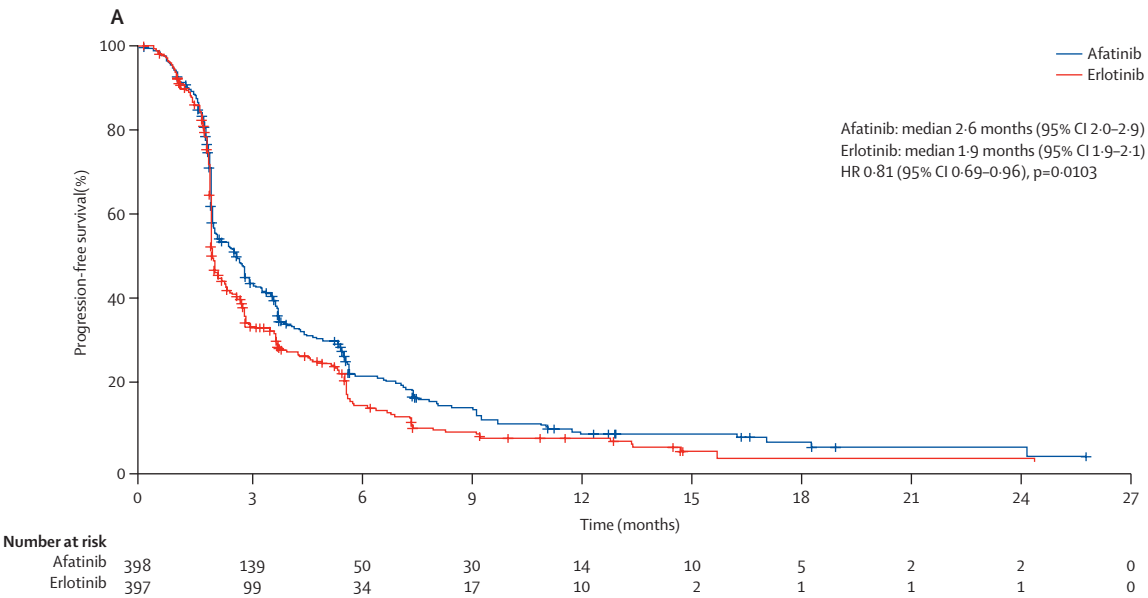
After a median follow-up of 18·4 months (IQR 13·8–22·4), overall survival was significantly improved with afatinib versus erlotinib; median overall survival was 7·9 months (95% CI 7·2–8·7) in the afatinib group and 6·8 months (5·9–7·8) in the erlotinib group (HR 0·81 [95% CI 0·69–0·95]; p=0·0077; figure 3A). Kaplan-Meier estimates of survival at 6 months (63·6% [95% CI 58·6–68·2] *vs* 54·6% [49·5–59·4]; p=0·0099), 12 months (36·4% [95% CI 31·6–41·2] *vs* 28·2% [23·8–32·9]; p=0·0155), and 18 months (22·0% [95% CI 17·6–26·7] *vs* 14·4% [10·7–18·6]; p=0·0132), were all significantly better with afatinib than with erlotinib. The effect of afatinib on overall survival was consistent across subgroups (figure 3B). 182 (46%) of 392 treated patients in the afatinib group and 192 (49%) of 395 in the erlotinib group received at least one line of subsequent treatment. The most common post-progression treatments were docetaxel (93 [24%] *vs* 103 [26%]) and gemcitabine (41 [10%] *vs* 43 [11%]; appendix).

	Afatinib (n=398)	Erlotinib (n=397)
Sex		
Male	335 (84%)	331 (83%)
Female	63 (16%)	66 (17%)
Median age (years, range)	65·0 (36–84)	64·0 (35–88)
Age group		
<65 years	189 (47%)	210 (53%)
≥65 years	209 (53%)	187 (47%)
Baseline ECOG PS		
0	126 (32%)	134 (34%)
1	269 (68%)	262 (66%)
2*	3 (<1%)	1 (<1%)
Ethnic origin		
Non-eastern Asian	312 (78%)	311 (78%)
Eastern Asian	86 (22%)	86 (22%)
Smoking status		
Never smoker	26 (7%)	18 (5%)
Light ex-smoker†	11 (3%)	12 (3%)
Current and other ex-smoker‡	361 (91%)	367 (92%)
Median time since diagnosis (years, range)	0·8 (0·2–9·3)	0·7 (0·2–13·5)
Tumour histology§		
Squamous	381 (96%)	382 (96%)
Mixed	17 (4%)	15 (4%)
Previous platinum doublet		
Carboplatin-based	249 (63%)	229 (58%)
Cisplatin-based	163 (41%)	198 (50%)
Other	5 (1%)	8 (2%)
Clinical stage at screening		
IIIA	1 (<1%)	4 (1%)
IIIB	48 (12%)	48 (12%)
IV	349 (88%)	345 (87%)
Best response to chemotherapy¶		
CR or PR	186 (47%)	185 (47%)
SD	161 (40%)	167 (42%)
Unknown	47 (12%)	42 (11%)

Data are n (%), unless stated otherwise. ECOG PS=Eastern Cooperative Oncology Group performance status. CR=complete response. PR=partial response. SD=stable disease. *Protocol violations. †<15 pack-years and stopped >1 year before diagnosis. ‡71 (18%) versus 85 (21%) were current smokers. §Three patients in the erlotinib group had undifferentiated tumour histology but were considered to be squamous by the treating investigator. ¶Seven patients (four in the afatinib group and three in the erlotinib group) had a best response of progressive disease on chemotherapy.

Table 1: **Baseline characteristics**

More patients in the afatinib group than in the erlotinib group had an objective response according to independent review (table 2). Disease control was significantly improved in the afatinib group versus in the erlotinib group (table 2). Median duration of objective response was 7·3 months (95% CI 3·7–16·5) in the afatinib group versus 3·7 months (2·6–10·2) in the erlotinib group. Maximum percentage decrease from baseline in the sum of target lesions did not differ

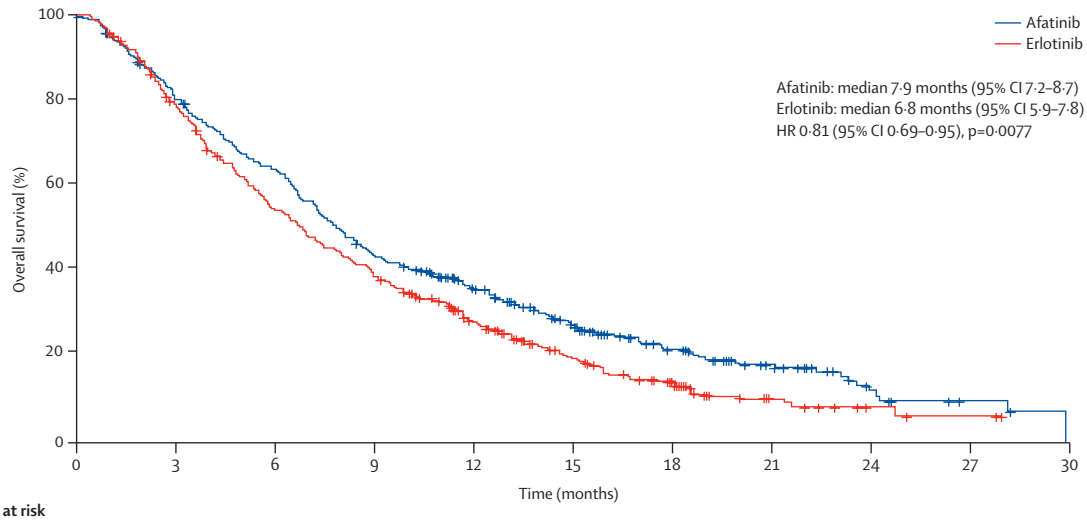


B

	Events/patients	Median progression-free survival, months (95% CI)		HR (95% CI)	$p_{interaction}$
		Afatinib	Erlotinib		
Total	605/795	2·6 (2·0–2·9)	1·9 (1·9–2·1)	0·81 (0·69–0·96)	
Ethnic origin					
Non-eastern Asian	487/623	2·5 (2·0–2·9)	2·0 (1·9–2·2)	0·90 (0·75–1·07)	0·0122
Eastern Asian	118/172	2·8 (1·9–7·4)	1·9 (1·9–2·8)	0·54 (0·37–0·79)	
Sex					
Male	512/666	2·6 (2·0–2·9)	2·0 (1·9–2·3)	0·83 (0·70–0·99)	0·3863
Female	93/129	2·7 (1·9–3·8)	1·9 (1·8–2·1)	0·74 (0·49–1·11)	
Best response to first-line chemotherapy					
CR or PR	287/371	2·7 (2·0–3·1)	1·9 (1·9–2·3)	0·87 (0·69–1·10)	0·2815
SD	246/328	2·6 (1·9–3·3)	2·0 (1·9–2·7)	0·83 (0·64–1·06)	
Unknown	65/89	2·8 (1·9–5·6)	1·9 (1·8–2·8)	0·54 (0·33–0·90)	
Interval between end of first-line and beginning of second-line					
<16 weeks	340/436	1·9 (1·9–2·4)	1·9 (1·9–2·0)	0·87 (0·71–1·08)	0·5556
≥16 weeks	265/359	3·3 (2·7–3·7)	2·2 (1·9–2·8)	0·77 (0·60–0·98)	
Histology					
Squamous histology	579/763	2·6 (2·0–2·9)	1·9 (1·9–2·1)	0·82 (0·70–0·97)	0·1955
Mixed squamous histology	26/32	1·9 (0·9–5·3)	1·6 (0·4–2·8)	0·61 (0·28–1·33)	
Smoking history					
Never smoker	32/44	2·8 (1·9–7·4)	1·8 (1·5–5·5)	0·55 (0·27–1·11)	0·1506
Light ex-smoker*	14/23	5·6 (1·0–NR)	1·9 (1·6–6·3)	0·44 (0·14–1·37)	
Current and other ex-smoker	559/728	2·6 (2·0–2·8)	1·9 (1·9–2·2)	0·85 (0·72–1·01)	
ECOG PS at baseline					
0	207/260	3·0 (2·0–4·3)	1·9 (1·9–2·4)	0·68 (0·51–0·89)	0·2488
1	395/531	2·5 (1·9–2·8)	1·9 (1·9–2·3)	0·87 (0·72–1·06)	
Age					
<65 years	301/399	2·0 (1·9–2·7)	1·9 (1·9–2·1)	0·81 (0·65–1·02)	0·7657
≥65 years	304/396	2·8 (2·4–3·7)	2·0 (1·9–2·4)	0·83 (0·66–1·04)	
Maintenance therapy received					
No	566/750	2·6 (2·0–2·9)	1·9 (1·9–2·2)	0·81 (0·68–0·95)	0·7159
Yes	39/45	2·0 (1·7–4·3)	1·9 (1·3–3·0)	0·88 (0·47–1·68)	

Figure 2: **Progression-free survival**
(A) According to independent review of all randomly assigned patients (primary endpoint). (B) Subgroup analysis by independent review. HR=hazard ratio. CR=complete response. PR=partial response. SD=stable disease. ECOG PS=Eastern Cooperative Oncology Group performance status. NR=not reached. *<15 pack-years and stopped >1 year before diagnosis.

A



Number at risk

Afatinib	398	316	249	170	124	82	47	28	10	4	0
Erlotinib	397	305	210	150	94	54	30	11	4	2	0

B

	Events/patients	Median overall survival, months (95% CI)		HR (95% CI)	$p_{interaction}$
		Afatinib	Erlotinib		
Total	632/795	7·9 (7·2–8·7)	6·8 (5·9–7·8)	0·81 (0·69–0·95)	
Ethnic origin					
Non-eastern Asian	500/623	7·5 (6·7–8·4)	6·7 (5·8–7·8)	0·87 (0·73–1·03)	0·1101
Eastern Asian	132/172	9·6 (7·3–14·1)	7·2 (4·9–8·9)	0·62 (0·44–0·88)	
Sex					
Male	533/666	8·1 (7·2–9·0)	6·9 (5·9–8·0)	0·82 (0·69–0·97)	0·7032
Female	99/129	7·3 (5·4–10·9)	5·8 (4·6–8·2)	0·77 (0·51–1·14)	
Best response to first-line chemotherapy					
CR or PR	285/371	8·5 (7·3–10·7)	8·4 (6·9–10·2)	0·91 (0·72–1·15)	0·2584
SD	271/328	7·4 (6·5–8·7)	5·8 (4·7–6·9)	0·71 (0·56–0·90)	
Unknown	69/89	8·3 (6·3–10·9)	5·8 (3·7–9·4)	0·72 (0·44–1·17)	
Interval between end of first-line and beginning of second-line					
<16 weeks	366/436	6·6 (5·6–7·7)	5·6 (4·9–6·4)	0·78 (0·63–0·96)	0·4493
≥16 weeks	266/359	9·2 (7·9–11·6)	8·9 (7·8–10·1)	0·88 (0·69–1·12)	
Histology					
Squamous histology	602/763	8·0 (7·2–8·8)	6·9 (6·2–8·0)	0·82 (0·70–0·96)	0·1997
Mixed squamous histology	30/32	7·4 (0·9–16·5)	3·6 (1·4–5·3)	0·55 (0·26–1·17)	
Smoking history					
Never smoker	34/44	7·6 (3·2–15·4)	6·8 (1·8–13·2)	0·77 (0·37–1·57)	0·8177
Light ex-smoker*	19/23	12·4 (4·9–17·0)	8·2 (3·5–10·8)	0·43 (0·16–1·12)	
Current and other ex-smoker	579/728	7·8 (7·1–8·7)	6·8 (5·9–7·8)	0·81 (0·69–0·96)	
ECOG PS at baseline					
0	197/260	12·0 (8·0–14·1)	9·6 (7·4–11·6)	0·76 (0·51–1·01)	0·9088
1	431/531	6·7 (6·1–8·1)	5·7 (5·1–6·7)	0·80 (0·66–0·97)	
Age					
<65 years	327/399	8·4 (7·2–11·2)	6·1 (5·3–7·3)	0·68 (0·55–0·85)	0·0498
≥65 years	305/396	7·4 (6·4–8·6)	7·7 (6·4–8·8)	0·95 (0·76–1·19)	
Maintenance therapy received					
No	599/750	7·8 (7·2–8·7)	6·8 (5·8–7·8)	0·79 (0·68–0·93)	0·4135
Yes	33/45	8·4 (6·5–13·8)	7·0 (2·1–24·7)	1·07 (0·52–2·17)	

Figure 3: **Overall survival**
(A) All randomly assigned patients (key secondary endpoint). (B) Subgroup analysis. HR=hazard ratio. CR=complete response. PR=partial response. SD=stable disease. ECOG PS=Eastern Cooperative Oncology Group performance status. *<15 pack-years and stopped >1 year before diagnosis.

	Afatinib (n=398)	Erlotinib (n=397)	p value
Disease control	201 (51%)	157 (40%)	0·0020
Excluding patients with NN*	146 (37%)	114 (29%)	0·0170
Objective response	22 (6%)	11 (3%)	0·0551
CR	1 (<1%)	0 (0%)	..
PR	21 (5%)	11 (3%)	..
SD†	124 (31%)	103 (26%)	..
NN*†	55 (14%)	43 (11%)	..
PD	133 (33%)	169 (43%)	..
NE	64 (16%)	71 (18%)	..

Data are n (%) unless stated otherwise. CR=complete response. PR=partial response. SD=stable disease. PD=progressive disease. NN=non-CR and non-PD (stable non-target disease in the absence of baseline target disease). NE=not evaluable. *Post-hoc analysis. †≥42 days from randomisation.

Table 2: **Best overall tumour response by central independent review irrespective of confirmation**

significantly between groups, although values were greater with afatinib (appendix). Tumour shrinkage occurred in 103 (26%) of 398 patients in the afatinib group and 90 (23%) of 397 patients in the erlotinib group (appendix). According to investigator review, both the proportion of patients with an objective response (43 [11%] *vs* 16 [4%], p=0·0005) and disease control (203 [51%] *vs* 156 [39%], p=0·0009) were significantly improved with afatinib compared with erlotinib.

More patients had improved overall health-related quality-of-life with afatinib than with erlotinib (121 [36%] of 339 *vs* 96 [28%] of 339; p=0·041). Significantly more patients had an improvement in cough with afatinib than with erlotinib (147 [43%] of 339 *vs* 120 [35%] of 341; p=0·029). Differences in the proportion of patients with improved dyspnoea (174 [51%] of 339 *vs* 150 [44%] of 340; p=0·061) and pain (138 [40%] of 343 *vs* 134 [39%] of 342; p=0·775) were not significant for afatinib versus erlotinib. Afatinib significantly delayed time to deterioration of dyspnoea compared with erlotinib (median 2·6 months [95% CI 2·0–2·9] *vs* 1·9 months [1·9–2·3]; HR 0·79 [95% CI 0·66–0·94]; p=0·0078). Time to deterioration of pain was similar for afatinib versus erlotinib (median 2·5 months [95% CI 2·0–2·8] *vs* 2·4 months [1·9–2·8]; HR 0·99 [95% CI 0·82–1·18]; p=0·8690) and cough (median 4·5 months [95% CI 2·9–4·9] *vs* 3·7 months [2·8–4·7]; HR 0·89 [95% CI 0·72–1·09]; p=0·2562).

At the time of database lock, the mean time on treatment was 121 days (range 2–840) in the afatinib group and 97 days (range 4–619) in the erlotinib group. 39 (10%) of 392 patients in the afatinib group received the escalated dose of 50 mg with a mean exposure of 106 days (range 4–588).

A similar proportion of patients had adverse events in each group: 390 (99%) of 392 in the afatinib group versus 385 (97%) of 395 in the erlotinib group. The severity of adverse events was also much the same in each group (grade ≥3: 224 [57%] *vs* 227 [57%]; appendix). 366 (93%) of 392 patients in the afatinib group and 321 (81%) of 395 patients in the erlotinib group had drug-related adverse events. 99 (25%) of patients in the afatinib group versus 64 (16%) in the erlotinib group had grade 3 drug-related adverse events, and five (1%) versus two (<1%) had grade 4 events. The most common adverse events were diarrhoea, rash or acne, fatigue, and stomatitis in the afatinib group and rash or acne, diarrhoea, fatigue, and pruritus in the erlotinib group. The incidences of treatment-related grade 3 diarrhoea and of grade 3 stomatitis were higher with afatinib and the incidence of grade 3 rash or acne was higher with erlotinib (table 3).

Serious adverse events (all-cause) were similar in the two groups (173 [44%] of 392 patients in the afatinib group *vs* 174 [44%] of 395 patients in the erlotinib group); 47 (12%) versus 22 (6%) were attributable to study drug. The most common treatment-related serious adverse events (>two patients) were diarrhoea (15 [4%]), dehydration (seven [2%]), and acute renal failure (four [1%]) in the afatinib group and diarrhoea (six [2%]) in the erlotinib group.

104 (27%) of 392 patients in the afatinib group versus 56 (14%) of 395 in the erlotinib group had dose reductions because of adverse events. 79 (20%) versus 67 (17%) discontinued treatment because of adverse events. Discontinuations because of diarrhoea were rare (16 [4%] patients in the afatinib group *vs* six [2%] in the erlotinib group), as were discontinuations because of rash or acne (ten [3%] *vs* eight [2%]). Six patients died in the afatinib group as a result of adverse events considered to be treatment-related by the investigator (two from interstitial lung disease, one each from respiratory failure, pneumonia, acute renal failure, and general physical health deterioration) compared with five in the erlotinib group (pneumonia, peritonitis, interstitial lung disease, pneumonitis, and intestinal obstruction).

Discussion

To date, LUX-Lung 8 is the largest prospective trial comparing two established tyrosine kinase inhibitors for second-line treatment of patients with squamous cell carcinoma of the lung. The trial achieved its primary endpoint of progression-free survival and key secondary endpoint of overall survival. To the best of our knowledge, afatinib is the first agent to show a significant survival benefit in the second-line treatment setting for patients with squamous histology non-small-cell lung cancer compared with an approved EGFR tyrosine kinase inhibitor. Whether the 1·1 month improvement in median overall survival noted with afatinib is clinically significant could be debated, but it was encouraging that longer-term survival at 12 months and 18 months was significantly improved with afatinib. In one of the most genetically complex and difficult-to-treat human cancers, these improvements can be clinically important. Afatinib was also associated with modest improvements in objective response, disease

	Afatinib (n=392)				Erlotinib (n=395)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea	165 (42%)	68 (17%)	39 (10%)	2 (<1%)	94 (24%)	28 (7%)	9 (2%)	1 (<1%)
Rash or acne*	157 (40%)	83 (21%)	23 (6%)	0 (0%)	142 (36%)	83 (21%)	41 (10%)	0 (0%)
Stomatitis*	65 (17%)	32 (8%)	16 (4%)	0 (0%)	21 (5%)	13 (3%)	0 (0%)	0 (0%)
Fatigue*	33 (8%)	20 (5%)	6 (2%)	0 (0%)	24 (6%)	17 (4%)	7 (2%)	0 (0%)
Nausea	35 (9%)	13 (3%)	4 (1%)	0 (0%)	20 (5%)	5 (1%)	3 (<1%)	0 (0%)
Decreased appetite	31 (8%)	16 (4%)	3 (<1%)	0 (0%)	24 (6%)	15 (4%)	2 (<1%)	0 (0%)
Paronychia*	28 (7%)	11 (3%)	2 (<1%)	0 (0%)	9 (2%)	7 (2%)	1 (<1%)	0 (0%)
Dry skin	28 (7%)	4 (1%)	2 (<1%)	0 (0%)	34 (9%)	7 (2%)	0 (0%)	0 (0%)
Pruritus	22 (6%)	9 (2%)	1 (<1%)	0 (0%)	37 (9%)	10 (3%)	0 (0%)	0 (0%)
Vomiting	20 (5%)	8 (2%)	3 (<1%)	0 (0%)	7 (2%)	4 (1%)	2 (<1%)	0 (0%)
Dehydration	2 (<1%)	5 (1%)	3 (<1%)	4 (1%)	0 (0%)	0 (0%)	3 (<1%)	0 (0%)

Includes events that occurred in >10% of patients with grade 1–2 adverse events, or >1% patients with grade 3–5 adverse events in any treatment group. *Group term.

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

control, patient-reported outcomes, and disease-related symptoms compared with erlotinib. The pattern of adverse events was similar between treatments and consistent with their mechanistic and safety profile. Adverse events were predictable and manageable.

Based on available clinical data and its similar route of administration, we used erlotinib rather than docetaxel as the comparator. A meta-analysis of trials that assessed second-line treatment with EGFR tyrosine kinase inhibitors versus chemotherapy demonstrated better tolerability in the EGFR tyrosine kinase group and confirmed comparable overall survival between groups, both in unselected patients with non-small-cell lung cancer and in an EGFR wild-type population.[31] Furthermore, subgroup analysis of the phase 3 BR.21 trial[13] showed that erlotinib improves progression-free survival and overall survival in patients with lung cancers of squamous histology, compared with placebo (HR 0·66, p=0·009), with similar benefits to docetaxel.[32] Although results of the phase 3 TAILOR trial[33] suggested that second-line docetaxel is superior to erlotinib in patients with non-small-cell lung cancer and wild-type EGFR, this benefit seemed to be driven by patients with adenocarcinoma histology; overall survival in patients with squamous histology did not differ between groups (HR 0·9, 95% CI 0·49–1·65).

Because EGFR mutations are rare (<5%) in squamous cell carcinoma of the lung,[12,20] routine molecular testing of squamous tumours is not generally undertaken as standard clinical practice. Thus, EGFR testing was not mandated in this study. However, post-hoc next-generation sequencing analysis of archival tissue (as part of an ongoing wider analysis of potential biomarkers) were consistent with previous studies; in a subgroup of 238 of patients selected on the basis of clinical benefit achieved with afatinib or erlotinib (progression-free suvival >2 months [presumed treatment benefit; n=144] plus a control group with progression-free survival ≤2 months [treatment refractory; n=94]), the overall proportion of patients with EGFR mutation was low (14 [6%]). Furthermore, EGFR amplification was present in only 15 patients (6%; nine on afatinib and six on erlotinib). Based on these preliminary findings, it is unlikely that the improved survival outcomes we detected with afatinib in this study were driven by molecular aberrations of EGFR. These improvements might be a result of afatinib's higher potency and broader irreversible ErbB blockade in this setting compared with EGFR inhibition alone. Indeed, these receptors have been implicated in the pathobiology of squamous cell carcinoma of the lung. Up to 20% of squamous cell carcinoma express HER2, with substantial overexpression in roughly 5% of cases,[17–19] and roughly 30% of squamous cell carcinomas overexpress HER3.[34] Furthermore, a comprehensive analysis[20] of squamous cell tumours identified genetic aberrations in *HER2* (4%) and *HER3* (2%), in several signalling molecules downstream of the ErbB receptors: *KRAS* (3%), *HRAS* (3%), *BRAF* (4%), *RASA1* (4%), and *NF1* (11%), and in *NRG1*. Based on these findings, we postulated that afatinib inactivates multiple aberrant signalling cascades downstream of ErbB receptors in patients with squamous cell carcinoma of the lung, possibly via its ability to inhibit dimerisation.[35]

Several other drugs have shown promising activity in patients with squamous cell carcinoma of the lung, particularly immunotherapeutic drugs such as nivolumab and pembrolizumab.[7,36] In a phase 2 single-group study,[7] 15% of patients given nivolumab, a PD-1 inhibitor, had an objective response, with a median progression-free survival of 1·9 months (95% CI 1·8–3·2), and median overall survival of 8·2 months (6·1–10·9). This study included 117 heavily pretreated patients (≥two previous treatments) with advanced squamous cell carcinoma of the lung. CheckMate-017, a phase 3 trial[8] comparing second-line nivolumab (n=135)

with docetaxel (n=137) in patients with squamous cell carcinoma of the lung, was stopped early because its primary endpoint of overall survival was met (median 9·2 *vs* 6·0 months; HR 0·59, 95% CI 0·44–0·79; p<0·001). Based on these data, nivolumab was approved by the US Food and Drug Administration for patients with metastatic squamous non-small cell carcinoma of the lung with progression during or after platinum-based chemotherapy. Median overall survival achieved with docetaxel in CheckMate-017 was lower than that previously reported in patients with squamous cell carcinoma of the lung (roughly 7·5 months).[5] Ongoing biomarker analysis in CheckMate-017 might help identify which drug is most suitable for individual patients.

Ramucirumab (an anti-VEGFR-2 antibody) plus docetaxel has also been approved for non-small-cell lung cancer including squamous cell carcinoma. In a subanalysis of the phase 3 REVEL trial,[6] median overall survival in 171 patients with squamous cell carcinoma was 9·5 months (95% CI 4·4–17·6) with ramucirumab plus docetaxel and 8·2 months (95% CI 3·6–14·9, HR 0·88 [95% CI 0·69–1·13]) with docetaxel alone.[6] However, this study was not powered for subgroup analysis.

The safety of afatinib has been well characterised based on an extensive clinical trial programme involving nearly 6600 patients, and post-marketing data. The adverse event profile of afatinib in LUX-Lung 8 was consistent with previous studies with no unexpected safety concerns.[23,24,26,37] The most common adverse events were class-related gastrointestinal and dermatological events. The few discontinuations because of adverse events, including the common class-related adverse events of diarrhoea and rash or acne, suggest that the recommended dose reduction scheme and supportive care measures were generally sufficient to enable patients to remain on afatinib treatment for as long as they had clinical benefit. Based on our findings, afatinib could be an additional option for the treatment of squamous cell carcinoma of the lung.

Contributors

J-CS, EF, SL, KS, VG, WL, AA, SMG, BW, VKC, and GDG designed the study. J-CS, EF, MC, SL, KS, KHL, EG, VG, WL, DI, SZG, AM, YJM, AA, SMG, and GDG recruited participants. EF, SL, KS, KHL, EG, WL, DI, SZG, and SMG collected data. J-CS, EF, SL, KHL, WL, DI, AM, YJM, AA, SMG, BW, VKC, and GDG analysed and interpreted data. All authors drafted and reviewed of the report, and approved the final version for submission.

Declaration of interests

J-CS has received personal fees for advisory boards from Boehringer Ingelheim and Roche. EF has received consulting fees from Eli Lilly, Pfizer, Roche, and Boehringer Ingelheim, and fees for speaker's bureaus from AstraZeneca and Novartis. SL has received consulting fees from Boehringer Ingelheim. AM has received personal fees from Roche, AstraZeneca, Boehringer Ingelheim, Pfizer, and Bayer. AA has received honoraria and consultation fees from Boehringer Ingelheim, Eli Lilly, Bristol-Myers Squibb, and MSD. SMG has received fees for advisory board participation from Boehringer Ingelheim. BW is an employee of Boehringer Ingelheim. VKC is an employee of Boehringer Ingelheim. The other authors declare no competing interests.

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References

1 Travis WD. Pathology of lung cancer. *Clin Chest Med* 2011; **32:** 669–92.

2 Reck M, Popat S, Reinmuth N, De Ruysscher D, Kerr KM, Peters S. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014; **25** (suppl 3)**:** iii27–iii39.

3 Drilon A, Rekhtman N, Ladanyi M, Paik P. Squamous-cell carcinomas of the lung: emerging biology, controversies, and the promise of targeted therapy. *Lancet Oncol* 2012; **13:** e418–26.

4 Scagliotti GV, Novello S, Rapetti S, Papotti M. Current state-of-the-art therapy for advanced squamous cell lung cancer. *Am Soc Clin Oncol Educ Book* 2013; 354–58.

5 Scagliotti G, Brodowicz T, Shepherd FA, et al. Treatment-by-histology interaction analyses in three phase III trials show superiority of pemetrexed in nonsquamous non-small cell lung cancer. *J Thorac Oncol* 2011; **6:** 64–70.

6 Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet* 2014; **384:** 665–73.

7 Rizvi NA, Mazieres J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. *Lancet Oncol* 2015; **16:** 257–65.

8 Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015; published online May 31. DOI:10.1056/NEJMoa1504627.

9 Hirsch FR, Varella-Garcia M, Bunn PA Jr, et al. Epidermal growth factor receptor in non-small-cell lung carcinomas: correlation between gene copy number and protein expression and impact on prognosis. *J Clin Oncol* 2003; **21:** 3798–807.

10 Lopez-Malpartida AV, Ludena MD, Varela G, Garcia PJ. Differential ErbB receptor expression and intracellular signaling activity in lung adenocarcinomas and squamous cell carcinomas. *Lung Cancer* 2009; **65:** 25–33.

11 Tsao MS, Sakurada A, Cutz JC, et al. Erlotinib in lung cancer—molecular and clinical predictors of outcome. *N Engl J Med* 2005; **353:** 133–44.

12 Dearden S, Stevens J, Wu YL, Blowers D. Mutation incidence and coincidence in non small-cell lung cancer: meta-analyses by ethnicity and histology (mutMap). *Ann Oncol* 2013; **24:** 2371–76.

13 Clark GM, Zborowski DM, Santabarbara P, et al. Smoking history and epidermal growth factor receptor expression as predictors of survival benefit from erlotinib for patients with non-small-cell lung cancer in the National Cancer Institute of Canada Clinical Trials Group study BR.21. *Clin Lung Cancer* 2006; **7:** 389–94.

14 Wojtowicz-Praga S, Leon L. Comparative efficacy and safety of erlotinib in non-small cell lung cancer (NSCLC) of squamous cell and adenocarcinoma histology in the phase III NCIC CTG BR.21 and saturn (BO18192) trials. *Ann Oncol* 2012; **23** (suppl 9)**:** ix419. abstr 1277P.

15 Pirker R, Pereira JR, von Pawel J, et al. EGFR expression as a predictor of survival for first-line chemotherapy plus cetuximab in patients with advanced non-small-cell lung cancer: analysis of data from the phase 3 FLEX study. *Lancet Oncol* 2012; **13:** 33–42.

16 Thatcher N, Hirsch FR, Luft AV, et al. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial. *Lancet Oncol* 2015; **16:** 763–74.

17 Heinmoller P, Gross C, Beyser K, et al. HER2 status in non-small cell lung cancer: results from patient screening for enrollment to a phase II study of herceptin. *Clin Cancer Res* 2003; **9:** 5238–43.

18 Hirsch FR, Franklin WA, Veve R, Varella-Garcia M, Bunn PA Jr. HER2/neu expression in malignant lung tumors. *Semin Oncol* 2002; **29** (suppl 4)**:** 51–58.

19 Ugocsai K, Mandoky L, Tiszlavicz L, Molnar J. Investigation of HER2 overexpression in non-small cell lung cancer. *Anticancer Res* 2005; **25:** 3061–66.

20 Cancer Genome Atlas Research Network. Comprehensive genomic characterization of squamous cell lung cancers. *Nature* 2012; **489:** 519–25.

21 Dhanasekaran SM, Alejandro BO, Chen G, et al. Transcriptome meta-analysis of lung cancer reveals recurrent aberrations in NRG1 and Hippo pathway genes. *Nat Commun* 2014; **5:** 5893.

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

23 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.

24 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.

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

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

27 Machiels J, Haddad R, Fayette J, et al. Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomised phase 3 trial. *Lancet Oncol* 2015; **16:** 583–94.

28 Kim JH, Grossi F, De Marinis F, et al. Afatinib monotherapy in patients with metastatic squamous cell carcinoma of the lung progressing after erlotinib/gefitinib (E/G) and chemotherapy: interim subset analysis from a phase III trial. *Proc Am Soc Clin Oncol* 2012; **30** (suppl 15)**:** abstr 7558.

29 Hamilton M, Wolf JL, Rusk J, et al. Effects of smoking on the pharmacokinetics of erlotinib. *Clin Cancer Res* 2006; **12:** 2166–71.

30 Smit EF, Gervais R, Zhou C, et al. Efficacy and safety results from CurrentS, a double-blind, randomized, phase III study of second-line erlotinib (150 mg versus 300 mg) in current smokers with advanced non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 2014; **32** (suppl 5)**:** abstr 8046.

31 Li N, Yang L, Ou W, Zhang L, Zhang SL, Wang SY. Meta-analysis of EGFR tyrosine kinase inhibitors compared with chemotherapy as second-line treatment in pretreated advanced non-small cell lung cancer. *PLoS One* 2014; **9:** e102777.

32 Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000; **18:** 2095–103.

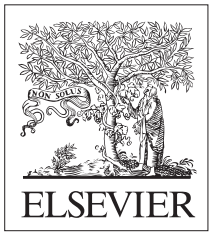
33 Garassino MC, Martelli O, Broggini M, et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. *Lancet Oncol* 2013; **14:** 981–88.

34 Yi ES, Harclerode D, Gondo M, et al. High c-erbB-3 protein expression is associated with shorter survival in advanced non-small cell lung carcinomas. *Mod Pathol* 1997; **10:** 142–48.

35 Nelson V, Ziehr J, Agulnik M, Johnson M. Afatinib: emerging next-generation tyrosine kinase inhibitor for NSCLC. *Onco Targets Ther* 2013; **6:** 135–43.

36 Garon EB, Balmanoukian A, Hamid O, et al. Preliminary clinical safety and activity of MK-3475 monotherapy for the treatment of previously treated patients with non-small cell lung cancer (NSCLC). *J Thorac Oncol* 2013; **8** (suppl 2)**:** abstr MO18.02.

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



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