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Research Paper

Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung: Final analysis of the randomised phase 3 LUX-Lung 8 trial

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ABSTRACT

Background: LUX-Lung 8 was a randomised, controlled, phase 3 study comparing afatinib and erlotinib as second-line treatment of patients with advanced squamous cell carcinoma (SCC) of the lung. We report the final overall survival (OS) and safety analyses of LUX-Lung 8 and investigate the characteristics of patients who achieved long-term benefit (≥12 months' treatment).

Methods: LUX-Lung 8 (NCT01523587) enroled patients between March 2012 and January 2014 in 183 cancer centres located in 23 countries worldwide and this final analysis had a data cut-off of March 2018. Eligible patients had stage IIIB or IV lung SCC and had progressed after at least four cycles of platinum-based chemotherapy. Patients were randomly assigned (1:1) to receive afatinib (40 mg per day) or erlotinib (150 mg per day) until disease progression. Endpoints included OS and safety; a post-hoc analysis of patients with long-term benefit (≥12 months on treatment) was also conducted.

Findings: 795 eligible patients were randomly assigned (398 to afatinib, 397 to erlotinib). OS was significantly prolonged with afatinib compared with erlotinib (median 7·8 months vs 6·8 months; hazard ratio 0·84; 95% CI 0·73–0·97; p = 0·0193). These findings were consistent with those of the primary analysis and were consistent across subgroups. Adverse events (AEs) were manageable with dose interruption and reduction, with similar AEs being experienced between both groups. Twenty-one (5·3%) patients receiving afatinib and 13 (3·3%) patients receiving erlotinib achieved long-term benefit; median OS was 34·6 months and 20·1 months, respectively. Amongst 132 afatinib-treated patients who underwent tumour genetic analysis, *ERBB* family mutations were more common in patients with long-term benefit than in the overall population (50% vs 21%).

Interpretation: Afatinib is a treatment option for patients with SCC of the lung progressing on chemotherapy who are ineligible for immunotherapy, particularly those with *ERBB* family genetic aberrations. Afatinib has a predictable and manageable tolerability profile, and long-term treatment may be well tolerated.

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Research in context

Evidence before this study

We reviewed PubMed and congress abstracts/presentations at the American Society of Clinical Oncology, European Society of Medical Oncology and World Congress of Lung Cancer congresses, up to January 2020, to identify the agents for the treatment of lung SCC that have emerged since LUX-Lung 8 was conducted and completed,. The treatment landscape has markedly expanded with many new, effective agents now recommended for the first- and second-line treatment of lung SCC, including several immuno-oncology agents. As such, the role of afatinib in the treatment of progressive lung SCC is now less clear than when LUX-Lung 8 was originally published. Therefore, while conducting the final survival analysis of LUX-Lung 8, we additionally investigated potential biomarkers that were suggestive of long-term benefit from afatinib.

Added value of this study

The analyses reported here suggest that patients with certain *ERBB* family genetic aberrations may be particular candidates for afatinib-containing treatment; although patient numbers were low, patients with long-term disease control were found to have these mutations more often than those with a shorter OS.

Implications of all the available evidence

While the role of afatinib in the treatment of progressive lung SCC is now less clear than when LUX-Lung 8 was originally published, data from this study suggest that patients with *ERBB* mutations are most likely to benefit from afatinib. Afatinib may therefore be a useful second- or third-line option for patients with SCC of the lung progressing on or following chemotherapy who are ineligible for immunotherapy or who have received chemo-immunotherapy, particularly those with *ERBB* family genetic aberrations.

1. Introduction

Squamous cell carcinoma (SCC) of the lung is the second most common histological subtype of non-small cell lung cancer (NSCLC) after adenocarcinoma, accounting for ~30% of cases [1]. Over the last 5 years, the available first-line treatment options for patients with advanced SCC of the lung have markedly expanded [2,3]. While first-line treatment for SCC has traditionally been platinum-doublet chemotherapy, the checkpoint inhibitor agents, pembrolizumab and atezolizumab, have recently demonstrated significant clinical activity in this setting, either as monotherapy (depending on PD-L1 expression) [4,5] or combined with chemotherapy [6,7]. Further options include the checkpoint inhibitor, nivolumab, combined with the anti-CTLA-4 monoclonal antibody, ipilimumab, [8] and nivolumab plus ipilimumab and chemotherapy [9]. Second-line treatment options have also expanded [2,3,10] but is dependant on the first-line treatment delivered and patient profile. Potential options include nivolumab [11], atezolizumab [12], pembrolizumab [13]; single-agent docetaxel [14,15]; the vascular endothelial growth factor receptor (VEGFR)−2 targeted monoclonal antibody ramucirumab in combination with docetaxel [16]; and the irreversible *ERBB* family blocker afatinib [17]. However, a major challenge remains in identifying the optimal second-line treatment for patients with SCC of the lung, especially with immunotherapy moving into first line in combination with chemotherapy.

Overexpression of the epidermal growth factor receptor (EGFR/ERBB1) is more commonly detected in SCC than in non-SCC NSCLC (~80% vs 44%) [18,19], although *EGFR* mutations are less prevalent in SCC (≤5% vs 20−50%) [20]. Overexpression may explain why some patients with SCC of the lung are sensitive to EGFR-targeted treatments, such as erlotinib [21], even though *EGFR* mutations occur infrequently in these patients [20]. In addition to EGFR, genetic alterations and deregulated expression of other members of the ERBB protein family, including HER2 (ERBB2), HER3 (ERBB3) [22], and HER4 (ERBB4) [22] have been identified in patients with lung SCC.

Afatinib is an irreversible tyrosine kinase inhibitor (TKI) that selectively blocks signalling from all homo- and heterodimers formed by EGFR, HER2, HER3, and HER4 [23,24]. Based on its broader mechanism of action [23] and encouraging activity in patients with cancers of squamous histology [25], it was hypothesised that afatinib would have improved efficacy compared with erlotinib in patients with advanced SCC of the lung. This was investigated in the randomised, phase 3 LUX-Lung 8 study (NCT01523587) [17]. Erlotinib was the only EGFR TKI approved in this setting at the time of study planning [26], but is no longer indicated for SCC in the United States or Europe [26,27].

In the primary analysis of the LUX-Lung 8 study, afatinib significantly prolonged the primary endpoint of progression-free survival (PFS) compared with erlotinib (median 2·4 months vs 1·9 months; hazard ratio [HR] 0·82, 95% confidence interval [CI] 0·68−1·00; p = 0·0427) [17]. In addition, overall survival (OS) was significantly prolonged with afatinib compared with erlotinib (median 7·9 months vs 6·8 months; HR 0·81, 95% CI 0·69−0·95; p = 0·0077). Both drugs had manageable safety profiles, with higher levels of treatment-related grade 3 diarrhoea and stomatitis reported with afatinib, and of treatment-related grade 3 rash/acne with erlotinib. In addition to significant improvements in PFS and OS, patients receiving afatinib reported significant improvements in overall quality of life and the disease-related symptom, cough, compared with erlotinib [28].

A previously reported secondary analysis of LUX-Lung 8 described 245 patients who underwent tumour genetic analysis (TGA) using next-generation sequencing (132 in the afatinib arm and 113 in the erlotinib arm) [29]. *ERBB* family mutations were detected in 53/245 patients (21·6%) in the TGA cohort. Of note, PFS and OS were longer amongst afatinib-treated patients with *ERBB* mutations than those without [29]. However, EGFR expression level did not appear to correlate with outcomes in these patients. *ERBB* mutations were detected in five of 10 evaluable patients (50%) with long-term benefit from afatinib (receiveing ≥12 months of treatment) whereas amongst the three patients who achieved long-term benefit on erlotinib and underwent TGA, one had an *EGFR* mutation and two were *ERBB* wild type.

The LUX-Lung 8 data set was also used to investigate the ability of the VeriStrat® serum protein test, which classifies patients as either VeriStrat-Good (VS-G) or VeriStrat-Poor (VS-P), to predict outcomes in patients with SCC of the lung [30]. The analysis found that VS-G classification was strongly associated with favourable survival outcomes in patients treated with afatinib or erlotinib compared with VS-P classification, and, in VS-G patients, afatinib was associated with longer OS than erlotinib.

Based on the findings of the LUX-Lung 8 study, afatinib was approved for the treatment of patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy [31,32]. Here, we present the final analysis of OS and safety data from the LUX-Lung 8 study. In addition, to further explore factors that may be predictive of the efficacy of afatinib in this setting, we conducted a post-hoc analysis of clinical outcomes, safety, and biomarker status in patients who derived long-term benefit, defined as receiving treatment for ≥12 months.

2. Methods

2.1. Study design and patients

Full details of the study design have been reported previously [17]. Briefly, LUX-Lung 8 was a randomised, controlled, phase 3 study conducted worldwide. Eligible patients were aged ≥18 years and had a diagnosis of stage IIIB or IV NSCLC of squamous (including mixed) histology. Patients were to have received at least four cycles of platinum-based doublet chemotherapy as first-line treatment and have experienced disease progression. Other inclusion criteria included an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1·1, and adequate organ function [17].

Exclusion criteria included previous treatment with EGFR TKIs or antibodies, active brain metastases, radiotherapy within 4 weeks before randomisation, and the presence of any other malignancy.

The study protocol was designed in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Guideline for Good Clinical Practice, and applicable region-specific regulatory requirements. It was approved by independent ethics committees at each centre. All patients provided written informed consent. Eligible patients were randomly assigned (1:1) to afatinib or erlotinib. Randomisation was stratified by ethnic origin (eastern Asian vs non-eastern Asian). Neither clinicians nor patients were blinded as to treatment assignment.

2.2. Procedures

Patients in the afatinib arm received oral afatinib 40 mg once daily. The dose could be escalated to 50 mg once daily in the absence of treatment-related adverse events (AEs) of more than grade 1. Afatinib was paused for no more than 14 days if patients had any grade ≥3 treatment-related AE, grade 2 diarrhoea lasting ≥2 days, or nausea/vomiting for 7 or more consecutive days despite best supportive care. After treatment interruption and recovery to grade 1 or baseline grade, the afatinib dose was reduced by 10 mg decrements to a minimum dose of 20 mg. Treatment was permanently discontinued in patients who did not recover to grade ≤1 or baseline grade. Patients in the erlotinib arm received the approved daily oral dose of 150 mg. In the event of AEs, dose reduction of erlotinib was permitted according to approved label instructions.

Tumour assessments were performed using computed tomography or magnetic resonance imaging of no more than five target lesions at baseline and at weeks 8, 12, 16, and every 8 weeks thereafter until confirmed progression or withdrawal. Scans were reviewed by a blinded independent central imaging group. AEs were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 3·0.

2.3. Outcomes

OS and safety were investigated at the final data cut-off March 19, 2018. To reduce the time to trial closure, and because other key efficacy endpoints had already been met, OS and safety were the only endpoints included in the final analysis [17]. As of April 2015 (primary data cut-off), only 9 (1%) patients remained on treatment, so minimal changes were anticipated. OS was defined as the time from randomisation to death. Safety was assessed based on the evaluation of AEs and laboratory findings.

A post-hoc analysis was conducted to investigate clinical outcomes in patients with long-term benefit. These were defined as patients with ≥12 months' treatment on the study drug. PFS was assessed in these patients and was defined as the time from randomisation to progression or death, whichever occurred first. PFS was assessed by a central independent review committee according to RECIST version 1·1. TGA of baseline tumour samples was conducted using next-generation sequencing (NGS) in a cohort enriched for patients with PFS of more than 2 months, as previously described [29]. The VeriStrat® serum protein test was used, as previously described, to assign a VeriStrat® status to each evaluable sample [30].

2.4. Statistical analysis

Survival in the two arms was compared using a log-rank test stratified by ethnic origin, 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. Greenwood's standard error estimate was used to calculate Kaplan–Meier estimates and 95% CIs. Efficacy analyses were performed in the randomised (intention-to-treat) population. Safety analyses included all patients receiving at least one dose of study drug. Analysis of AEs was descriptive. Statistical analyses were performed using SAS Version 9·2.

2.5. Role of the funding source

Employees of Boehringer Ingelheim played a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication and as such are included in the author list. To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfil their role and obligations as authors under the ICMJE criteria. All authors had access to the collated data and the funder, all the authors and the corresponding author took the decision to submit for publication.

3. Results

Between March 30, 2012 and Jan 30, 2014, 977 patients were screened and 795 were enroled (398 to the afatinib group and 397 to the erlotinib group; Fig. 1) at 183 cancer centres in 23 countries worldwide [17]. The cut-off date for this final analysis was March 19, 2018; at this time all patients had discontinued treatment, the main reason being due to disease progression (Fig. 1).

Patient baseline demographics and disease characteristics have previously been reported [17]. The baseline characteristics were generally well balanced between the treatment arms (Table 1). Median age was 64 years, 84% (666 patients) were men, 22% (172 patients) were of eastern Asian origin, and 94% (751 patients) were current or ex-smokers (light or other).

At the final data cut-off, 369 and 367 patients had died in the afatinib and erlotinib arms, respectively. The median OS was 7·8 months in the afatinib arm compared with 6·8 months in the erlotinib arm (HR 0·84, 95% CI 0·73–0·97; p = 0·0193; Fig. 2A).

The effect of afatinib on OS was consistent across subgroups (Fig. 2B). Improvements in OS with afatinib compared with erlotinib were observed in Eastern Asian patients, male patients, patients with a best response of stable disease to first-line chemotherapy, patients with less than a 16-week interval between the end of first-line and the beginning of second-line treatment, patients with squamous histology (versus those with mixed squamous histology), other current and ex-smokers with a history of more than 15 pack years, patients with an ECOG PS of 1 at baseline, patients aged <65 years, and patients who did not receive maintenance therapy.

The median time on treatment was 63 days (interquartile range [IQR] 46–149·5) for the afatinib arm and 57 days (IQR 42–114) for the erlotinib arm. The overall AE profile was similar between the afatinib and erlotinib arms; 390 of 392 (99·5%) patients in the afatinib

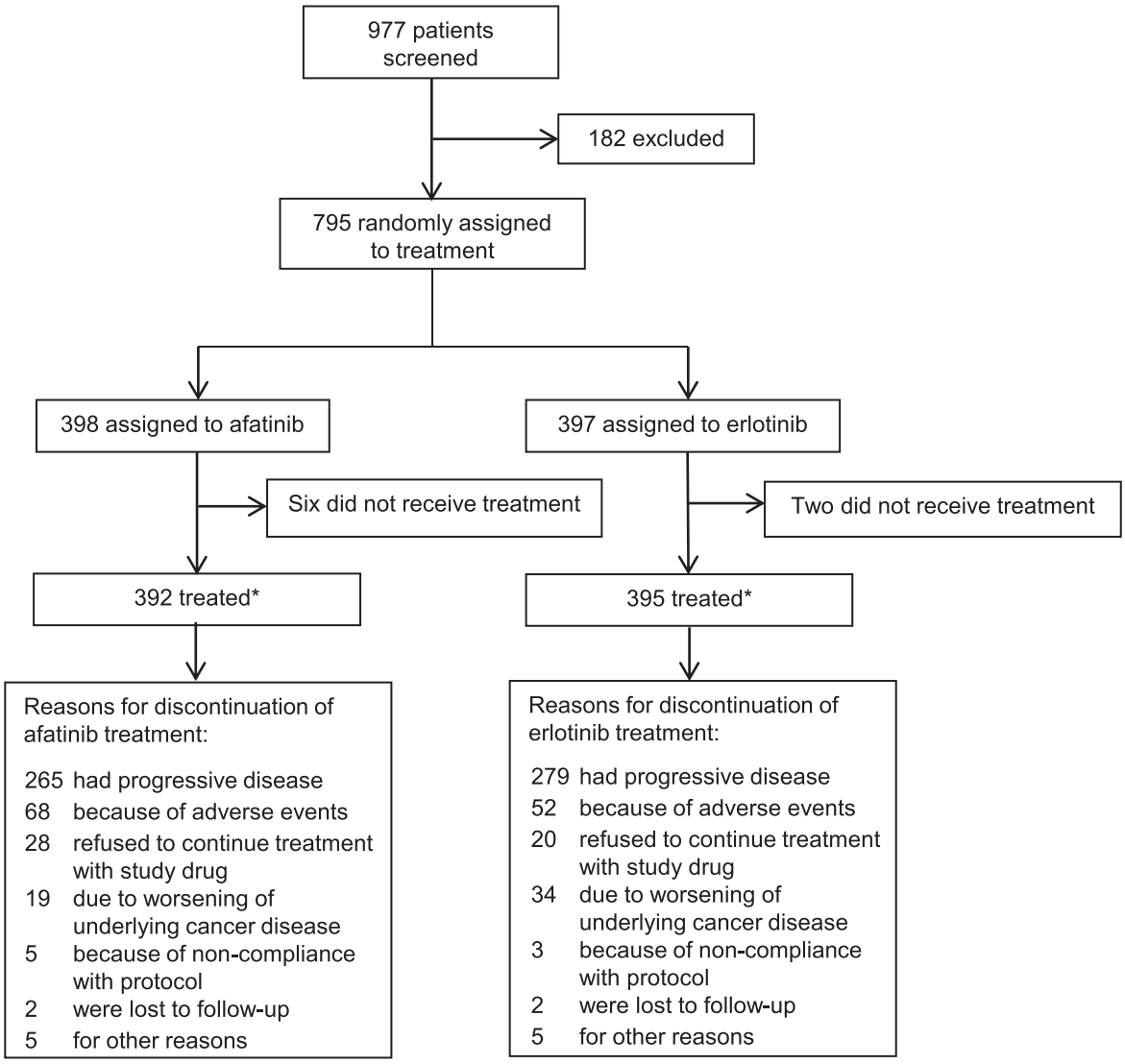

Fig. 1. Trial profile.
*Received at least one dose of study drug.

arm and 385 of 395 (97·5%) patients in the erlotinib arm reported any AE. Grade 3 or greater AEs were reported in 224 (57·1%) and 227 (57·5%) patients in the afatinib and erlotinib arms, respectively, and serious AEs were reported in 174 (44·4%) and 175 (44·3%) patients, respectively (appendix p 2). A list of all-cause AEs is presented in the appendix (p 4).

The most common any-grade treatment-related AEs with afatinib were diarrhoea, rash/acne, and stomatitis, while rash/acne, diarrhoea, pruritus and fatigue were the most common with erlotinib (Table 2). The incidences of treatment-related grade ≥3 diarrhoea and stomatitis were higher with afatinib than erlotinib, while the incidence of treatment-related grade ≥3 rash/acne was higher with erlotinib than afatinib.

The proportion of patients with AEs leading to dose reduction was higher for afatinib than for erlotinib (104 patients, 26·5% vs 56 patients, 14·2%; appendix p 5), although AEs leading to treatment discontinuation were similar between the arms (80 patients, 20·4% vs 66 patients, 16·7%). AEs leading to discontinuation in ≥1% of patients in the afatinib and erlotinib groups, respectively, were diarrhoea (4·1% vs 1·5%), rash (1·5% vs 1·0%), malignant neoplasm progression (1·8% vs <1%), pneumonia (1·5% vs <1%) and dyspnoea (1·3% vs 1·5%; appendix p 5).

Treatment-related AEs leading to death were reported for six patients in the afatinib arm (interstitial lung disease [*n* = 2], pneumonia, respiratory failure, acute renal failure, general physical health deterioration [*n* = 1 each]) and five patients in the erlotinib arm (interstitial lung disease, pneumonia, peritonitis, pneumonitis, intestinal obstruction [*n* = 1 each]).

In total, 21 (5·3%) patients in the afatinib arm and 13 (3·3%) in the erlotinib arm received treatment for ≥12 months and were defined as having received long-term benefit. Baseline characteristics were broadly balanced between the treatment groups in patients with long-term benefit, with some notable exceptions (Table 1). Patients receiving afatinib were on average younger than those receiving erlotinib (median age 64 *vs* 71 years). All 13 patients in the erlotinib group had stage IV cancer at screening, but 14% of afatinib-treated patients had stage IIIB. Erlotinib-treated patients also had a better response to chemotherapy, with 62% of patients exhibiting a complete or partial response versus 48% in the afatinib group (the remaining patients all had stable disease).

All afatinib-treated patients with long-term benefit (*N* = 21) initially received 40 mg afatinib. During treatment, six patients had their dose reduced to 30 mg and three patients further reduced to 20 mg afatinib. The dose was increased to 50 mg in

Table 1
Baseline and demographic characteristics.

Characteristic	Overall population		Patients with long-term benefit	
	Afatinib (*n* = 398)	Erlotinib (*n* = 397)	Afatinib (*n* = 21)	Erlotinib (*n* = 13)
Sex				
Male	335 (84%)	331 (83%)	16 (76%)	10 (77%)
Female	63 (16%)	66 (17%)	5 (24%)	3 (23%)
Median age, years (range)	65·0 (36–84)	64·0 (35–88)	64·0 (54–81)	71·0 (40–78)
Baseline ECOG PS				
0	126 (32%)	134 (34%)	7 (33%)	4 (31%)
1	269 (68%)	262 (66%)	14 (67%)	9 (69%)
2*	3 (<1%)	1 (<1%)	0	0
Ethnic origin				
Non-eastern Asian	312 (78%)	311 (78%)	17 (81%)	12 (92%)
Eastern Asian	86 (22%)	86 (22%)	4 (19%)	1 (8%)
Smoking status				
Never smoker	26 (7%)	18 (5%)	2 (10%)	1 (8%)
Light ex-smoker†	11 (3%)	12 (3%)	2 (10%)	0
Current and other ex-smoker	361 (91%)‡	367 (92%)‡	17 (81%)	12 (92%)
Median time since diagnosis, years(range)	0·8 (0·2–9·3)	0·7 (0·2–13·5)	N/A	N/A
Tumour histology§				
Squamous	381 (96%)	382 (96%)	20 (95%)	12 (92%)
Mixed	17 (4%)	15 (4%)	1 (5%)	1 (8%)
Previous platinum doublet				
Carboplatin-based	249 (63%)	229 (58%)	N/A	N/A
Cisplatin-based	163 (41%)	198 (50%)	N/A	N/A
Other	5 (1%)	8 (2%)	N/A	N/A
Clinical stage at screening				
IIIA	1 (<1%)	4 (1%)	0	0
IIIB	48 (12%)	48 (12%)	3 (14%)	0
IV	349 (88%)	345 (87%)	18 (86%)	13 (100%)
Best response to chemotherapy				
CR or PR	186 (47%)	185 (47%)	10 (48%)	8 (62%)
SD	161 (40%)	167 (42%)	11 (52%)	5 (38%)
PD	4 (1%)	3 (<1%)	0	0
Unknown	47 (12%)	42 (11%)	0	0

Data are *n* (%) unless otherwise specified. CR=complete response; ECOG=Eastern Cooperative Oncology Group; N/A=not available; PD=progressive disease; PR=partial response; PS=performance status; 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.

three patients; in addition, one further patient had a dose increase to 50 mg before reverting to 40 mg (Fig. 3A). The frequency of dose reductions due to diarrhoea, rash/acne, and stomatitis amongst the patients with long-term benefit on afatinib was 19·0%, 4·8%, and 4·8%, respectively.

Median OS amongst the 21 afatinib-treated patients with long-term benefit was 34·6 months (95% CI 24·1–52·2; Table 3); OS and treatment duration for each patient with long-term benefit in the afatinib arm is shown in Fig. 3B. Median duration of treatment for patients receiving afatinib was 19 months (range 12·3–51·3), and median PFS was 17·7 months (95% CI 11·1–not calculable; Table 3). Median OS for patients with long-term benefit on erlotinib was 20·1 months (95% CI 18·6–not calculable (Table 3; appendix p6). Median duration of treatment for these patients was 14·7 months (range 12·7–30·8), and median PFS was 14·7 months (95% CI 13·3–not calculable; Table 3).

Most patients with long-term benefit who had undergone VeriStrat® testing were classified as VS-G (15/17; 88%), but two patients had VS-P classification and still achieved OS of 34·6 and 18·8 months. amongst 132 afatinib-treated patients who underwent TGA, several biomarkers were more commonly observed in patients with long-term disease control than in the overall population. *ERBB* family mutations were of particular note, observed in five of 10 TGA patients (50%) with long-term benefit, and included *EGFR* (*n* = 2; R1052K and unknown)), *ERBB2* (*n* = 2; Q57R, E395K)) and *ERBB4* (*n* = 1; G668V; Fig. 3B). In contrast to long-term responders, of the remaining afatinib-treated patients who underwent TGA, 81% were *ERBB* wild-type, 7% had mutations in *EGFR*, 7% had *ERBB2* mutations, 5% had *ERBB3* mutations, and 2% were *ERBB4*-mutated.

4. Discussion

Results from this final analysis of LUX-Lung 8 were consistent with those previously reported for the primary analysis [17]. In the updated analysis, OS was significantly longer with afatinib than erlotinib (median 7·8 *vs* 6·8 months [HR 0·84, $p = 0·0193$]). As for the primary analysis, the clinical significance of the 1·0 month extension in OS could be debated. The effect was consistent across subgroups including large groups such as those of eastern-Asian origin, patients with stable disease following first-line chemotherapy, patients with ECOG PS of 1, and younger patients (<65 years).

The nature of the AEs was similar between treatment arms, reflecting the similar mechanism of action of both drugs, and, overall, AEs were manageable with dose interruptions and reductions. The AEs leading to treatment discontinuation were mainly treatment class-related AEs, such as diarrhoea (of which the incidence was higher in the afatinib group) or rash/acne; although the overall rate of treatment discontinuation due to AEs was slightly higher with afatinib than erlotinib. The incidence of AEs leading to dose reduction was at the level expected.

Twenty-one patients in the afatinib group (5·3%) and 13 in the erlotinib group (3·3%) received long-term benefit from treatment. Afatinib-treated patients achieved a prolonged median OS of 34·6 months, with a median treatment duration of 19·0 months. There did not appear to be any demographic characteristics that predisposed patients to receive long-term benefit from these treatments. However, in the afatinib group, patients with long-term benefit were more likely to have *ERBB* family mutations than patients with no long-term benefit. Similarly, in the primary analysis of the LUX-Lung

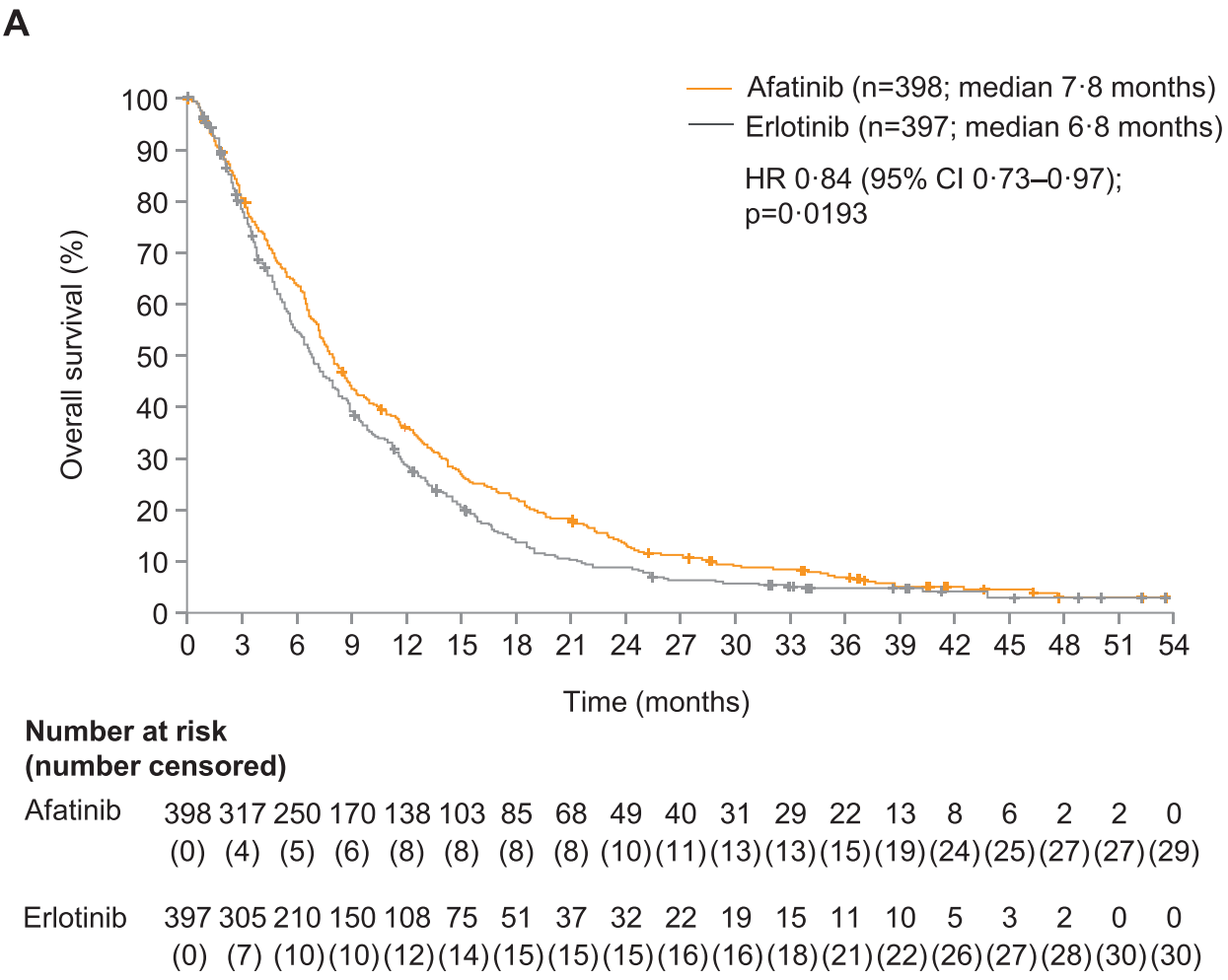

Fig. 2. Overall survival

(A) ITT population. (B) Subgroup analysis of ITT population.

CI=confidence interval; CR=complete response; CT=chemotherapy; ECOG PS=Eastern Cooperative Oncology Group performance status; HR=hazard ratio; ITT=intent to treat; PR=partial response; SD=stable disease. *Seven patients had a best response of progressive disease. †<15 pack years and stopped >1 year before diagnosis. ‡Four patients had ECOG PS of 2 at baseline (protocol violations).

8 cohort, OS was longer amongst afatinib-treated patients with *ERBB* mutation-positive tumours than those without [29]. Patient screening for these biomarkers may be a useful predictive tool, as it is possible that patients with *ERBB* mutations are more likely to respond to afatinib than those without.

The majority of long-term responders in this study had VS-G classification. The benefit of VS-G classification in terms of outcome with afatinib was previously observed in the primary analysis of the LUX-Lung 8 cohort; VS-G classification was strongly associated with favourable survival outcomes with afatinib or erlotinib, compared

Table 2
Treatment-related adverse events.

Adverse event	Afatinib (*n* = 392)				Erlotinib (*n* = 395)			
	All grades	Grade 3	Grade 4	Grade 5	All grades	Grade 3	Grade 4	Grade 5
Total	366 (93%)	99 (25%)	5 (1%)	6 (2%)	322 (82%)	64 (16%)	2 (<1%)	5 (1%)
Diarrhoea	274 (70%)	39 (10%)	2 (<1%)		134 (34%)	9 (2%)	1 (<1%)	
Rash or acne*	262 (67%)	23 (6%)			267 (68%)	41 (10%)		
Stomatitis*	110 (28%)	16 (4%)			31 (8%)			
Fatigue*	56 (14%)	5 (1%)			47 (12%)	7 (2%)		
Nausea	51 (13%)	4 (1%)			29 (7%)	3 (<1%)		
Decreased appetite	50 (13%)	3 (<1%)			41 (10%)	2 (<1%)		
Paronychia*	41 (11%)	2 (<1%)			17 (4%)	1 (0•3%)		
Dry skin	34 (9%)	2 (<1%)			41 (10%)			
Pruritus	32 (8%)	1 (<1%)			47 (12%)			
Dehydration	14 (4%)	3 (1%)	4 (1%)		3 (1%)	3 (1%)		

Data shown *n* (%) are treatment-related adverse events in >10% of patients with adverse events (all grade) or ≥1% of patients with grade 3–5 adverse events in any treatment group. *Grouped terms.

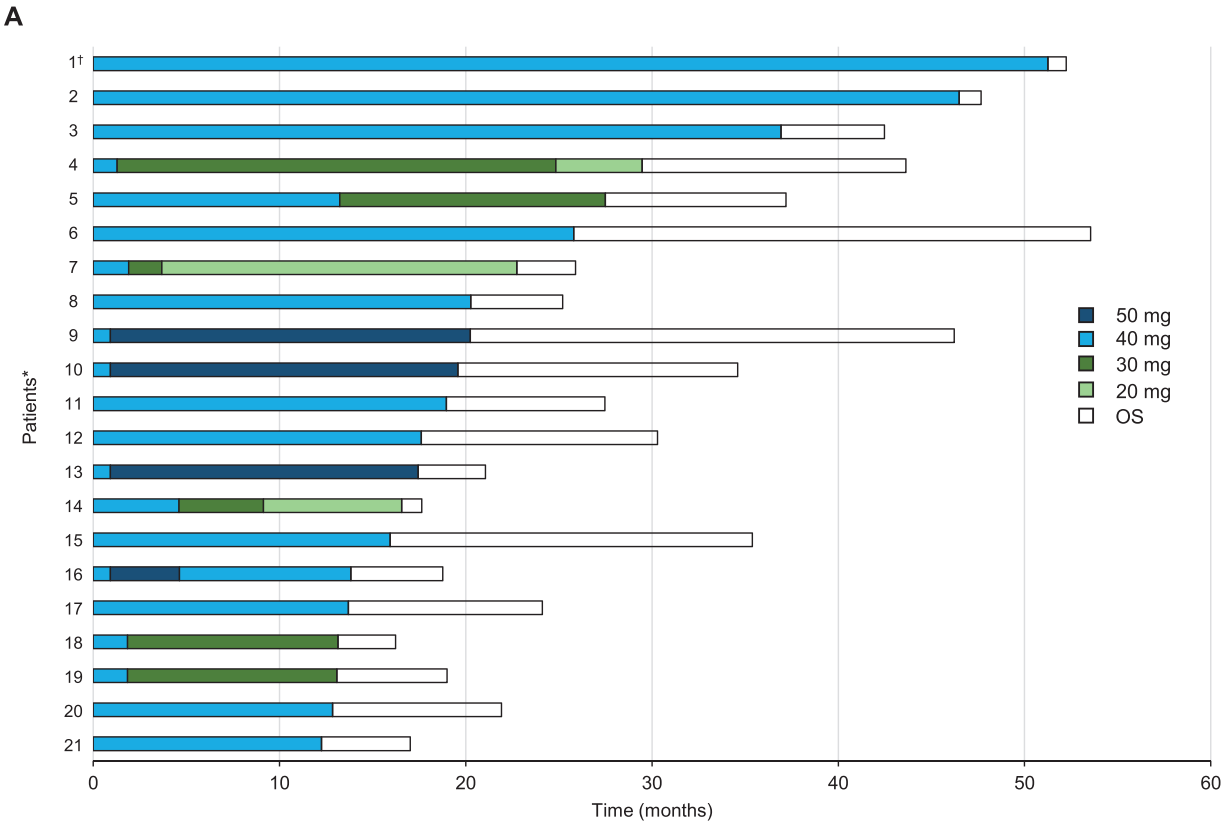

Fig. 3. *Afatinib in patients with long-term benefit*

(A) Afatinib dose over time. (B) Efficacy outcomes and biomarkers in patients with long-term benefit. Next-generation sequencing was undertaken in 10/21 patients with long-term benefit and 132/398 afatinib-treated patients overall. CR=complete response; PR=partial response; OS=overall survival; SD=stable disease; VS-G=VeriStrat-Good; VS-P=VeriStrat poor; WT=wild-type.

*Patients were ordered and numbered by treatment duration (at data cut-off), with patient 1 being on treatment longest. †Patient transferred to commercial drug on discontinuation from study drug. §Patient also had rearrangements in two genes. ¶First observed response at time of tumour measurement. **≥1 Mutation present in at least 3/10 patients with long-term benefit, or part of the *ERBB* family (*EGFR, ErbB2, ErbB3, ErbB4*). *ERBB* family mutations included: *EGFR* (*n* = 2; *R1052K* and unknown), *ERBB2* (*n* = 2; *Q57R, E395K*) and *ERBB4* (*n* = 1; *G668V*).

with VS-P classification [30]. Thus, the data support these previous findings that patients surviving for longer are more likely to be VS-G than VS-P. However, patient numbers in this post-hoc analysis were limited and the findings therefore need to be interpreted with caution. As such, further analysis will be required to establish whether VeriStrat® classification can provide prognostic information.

In summary, these data suggest that afatinib is a valid treatment option for patients with SCC of the lung who have progressed on or after chemotherapy. Patients with certain *ERBB* family genetic aberrations may be particular candidates for afatinib-containing treatment sequences; although patient numbers were low, patients with long-term disease control were found to have these mutations more often than those with a shorter OS. However, it is worth noting that as next-generation sequencing is not currently performed routinely in patients with SCC of the lung, this might compromise the potential use of afatinib as a second-line option in those patients most likely to benefit. Afatinib has a well-established, predictable safety profile, which is manageable with supportive care and tolerability-guided dose reductions, and long-term treatment may be well tolerated. Although this trial was performed when the standard of care for first-line treatment was chemotherapy, immunotherapy with a PD-L1 inhibitor with or without chemotherapy is now an established first-line treatment for eligible patients [2,3]. A recent real-world study showed that second-line afatinib was generally well tolerated and effective in patients with metastatic squamous NSCLC who had received first-line pembrolizumab plus platinum-based chemotherapy [33,34]. Further trials to determine the optimum second-line and third-line therapy in patients with SCC of the lung, particularly in those who have received prior chemo-immunotherapy, are warranted.

Table 3
Outcomes in patients with long-term benefit.

	Patients receiving afatinib (*n* = 21)	Patients receiving erlotinib (*n* = 13)
Median treatment duration, months (range)	19·0 (12·3–51·3)	14.7 (12·7–30·8)
Median OS, months (95% CI)	34·6 (24·1–52·2)	20·1 (18·6–NC)
Median PFS, months (95% CI)	17·7 (11·1–NC)	14·7 (13·3–NC)
Complete response	1 (5%)*	0 (0%)
Partial response	6 (29%)*	2 (15%)
Stable disease	13 (62%)*	11 (85%)

Data are *n* (%) unless otherwise specified. CI=confidence interval; NC=not calculable; OS=overall survival; PFS=progression-free survival. *One patient was not evaluable.

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Contributors

SL, AA contributed to study conception and design. SL, KS contributed to methodologies and software used for study data analysis. DI,

AA contributed to study data validation. SL contributed to the formal analysis of the data, MC, KS, EG, DI, AM, YJM, AA, EF. MC, KS contributed to study data visualisation. GDG, MC, SL, KS, AA contributed to study supervision. DI, AA contributed to study data validation. MC, KS, EG, DI, AM, YJM, AA, EF contributed to study. MC, KS, KHL, VG contributed to study data curation. All authors were involved in the drafting and reviewing of the manuscript and provided approval for submission.

Data sharing

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfil their role and obligations as authors under the ICMJE criteria. Furthermore, clinical study documents (e.g. study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the BI Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/transparency_policy.html

Prior to providing access, documents will be examined, and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants.

Clinical Study Reports and Related Clinical Documents can be requested via this link:

https://trials.boehringer-ingelheim.com/trial_results/clinical_submission_documents.html

All such requests will be governed by a Document Sharing Agreement.

Bona fide, qualified scientific and medical researchers may request access to de-identified, analysable participant clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Data Sharing Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request.

Researchers should use https://trials.boehringer-ingelheim.com to request access to study data.

Declaration of Competing Interest

GDG received travel expenses from AstraZeneca and advisory board honoraria from Celgene. SL received research support from AstraZeneca, Hutchison MediPharma, Bristol-Myers Squibb, Heng Rui, Roach, speaker fees from AstraZeneca, Roche, Hansoh, advisor and consultant of AstraZeneca, Boehringer Ingelheim, Hutchison MediPharma, Simcere, ZaiLab, GenomiCare and Roche. KHL received honoraria from AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer for advisory board meetings. AM received honoraria from Roche, Pfizer, AstraZeneca, Takeda, Bristol-Myers Squibb, Merck Sharp & Dohme, Boehringer Ingelheim. AA received honoraria from Bristol-Myers Squibb, Merck Sharp & Dohme, Eli Lilly, Roche, AstraZeneca. EF received personal fees for advisory boards from Abbvie, Blue Print Medicines, Guardant Health, Janssen, Medscape, Merck KGaA, Samsung, GlaxoSmithKline, Bayer; advisory board and speakers' bureau fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Takeda; speakers' bureau fees from Prime Oncology, Touchime; research funding from Grant For Oncology Innovation (GOI), Fundación Merck Salud; Grífols: independent member of the board. AC and SB are employees of Boehringer Ingelheim. MC, KS, EG, VG, DI, YJM have no conflicts to disclose.

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Supplementary materials

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