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ADIS DRUG EVALUATION

Afatinib: A Review in Advanced Non-Small Cell Lung Cancer

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Abstract Afatinib (Giotrif®, Gilotrif®) is an orally administered, irreversible inhibitor of the ErbB family of tyrosine kinases. In the first-line treatment of patients with advanced lung adenocarcinoma with activating epidermal growth factor receptor (EGFR) mutations, afatinib significantly prolonged progression-free survival (PFS) and time to treatment failure (TTF), but not overall survival (OS), compared with gefitinib (LUX-Lung 7 trial). In the overall population of patients receiving first-line treatment for advanced lung adenocarcinoma with activating EGFR mutations, afatinib significantly prolonged PFS, but not OS, compared with pemetrexed plus cisplatin (LUX-Lung 3 trial) or gemcitabine plus cisplatin (LUX-Lung 6 trial). However, in both LUX-Lung 3 and LUX-Lung 6, OS was significantly prolonged in the subgroup of patients with deletions in exon 19 receiving afatinib versus chemotherapy. In the second-line treatment of advanced squamous non-small cell lung cancer (NSCLC), afatinib significantly prolonged PFS and OS, compared with erlotinib, regardless of EGFR mutation status (LUX-Lung 8 trial). Afatinib had a predictable and manageable tolerability profile in patients with advanced NSCLC. In conclusion, afatinib is an important option for the first-line treatment of patients with advanced NSCLC and activating EGFR mutations, and provides an additional option for the treatment of patients with squamous NSCLC that has progressed following first-line platinum-based chemotherapy.

Afatinib: clinical considerations in advanced NSCLC
Orally administered, irreversible inhibitor of the ErbB family of tyrosine kinases
Compared with gefitinib, afatinib significantly prolonged PFS and TTF, but not OS, in the first-line treatment of advanced lung adenocarcinoma with activating EGFR mutations
Compared with chemotherapy, afatinib significantly prolonged PFS, but not OS, in the overall population of patients receiving first-line treatment for advanced lung adenocarcinoma with activating EGFR mutations
Compared with chemotherapy, afatinib significantly prolonged OS in the subgroup of patients with deletions in exon 19
Compared with erlotinib, afatinib significantly prolonged PFS and OS in the second-line treatment of advanced squamous NSCLC, regardless of EGFR mutation status
Predictable, manageable tolerability profile

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1 Introduction

Non-small cell lung cancer (NSCLC) accounts for ≈85 % of all lung cancers, and is subdivided into squamous NSCLC (which accounts for ≈20–30 % of NSCLC cases) and nonsquamous NSCLC [including adenocarcinoma (the commonest subtype of NSCLC), large-cell carcinoma and other cell types] [1]. NSCLC is frequently diagnosed at a late stage and has a high mortality rate [2].

The ErbB family of tyrosine kinases includes epidermal growth factor receptor (EGFR), human epidermal growth factor receptor (HER) 2, ErbB3 and ErbB4 [3]. Dysregulation of these tyrosine kinases and their downstream signalling pathways (e.g. the PI3K/AKT pathway) is implicated in cancer cell proliferation, angiogenesis and metastasis [3].

Activating EGFR mutations [most commonly the Leu858Arg point mutation in exon 21 and deletions in exon 19 (Del19)] are found in ≈10 % of Caucasian patients and up to 50 % of Asian patients with nonsquamous NSCLC [2]. The use of EGFR tyrosine kinase inhibitors (TKIs) [i.e. afatinib (Giotrif®, Gilotrif®), erlotinib, gefitinib] for the first-line treatment of patients with advanced NSCLC and activating EGFR mutations is now well established [2].

Treatment options are limited in advanced squamous NSCLC, particularly in the second-line setting in patients who have progressed following first-line platinum-based doublet chemotherapy [1]. Although activating EGFR mutations occur in only 1–3 % of patients with squamous NSCLC, the ErbB receptor family may still represent a rational therapeutic target [1]. For example, EGFR and ErbB3 are commonly overexpressed in squamous cell carcinoma (SCC), and there may also be an increase in EGFR gene copy number (polysomy or amplification), mutations or amplification in ErbB2, and mutations in ErbB3 and ErbB4 [1]. The PI3K/AKT pathway also appears to be an important oncogenic driver in SCC [1, 4]. Afatinib was recently approved in the US and the EU for the treatment of advanced squamous NSCLC, regardless of EGFR mutation status [5, 6].

This narrative review provides an overview of the clinical efficacy and tolerability of afatinib in patients with advanced NSCLC and activating EGFR mutations and in patients with advanced squamous NSCLC, as well as summarizing its pharmacological properties.

2 Pharmacodynamic Properties of Afatinib

The anilino-quinazoline afatinib is a potent, selective, irreversible inhibitor of the ErbB family of tyrosine kinases [6, 7]. Afatinib covalently binds to all homodimers and heterodimers formed by EGFR, HER2, ErbB3 and ErbB4, thereby inhibiting tyrosine kinase autophosphorylation and downregulating ErbB signalling [5, 6, 8].

In vitro, afatinib potently inhibited the tyrosine kinase activity of wild-type EGFR, HER2 and ErbB4 and mutant forms of EGFR (including Leu858Arg) [7, 8], as well as inhibiting the autophosphorylation and/or proliferation of cell lines expressing wild-type EGFR and EGFR with Del19 or Leu858Arg mutations [7–10]. Afatinib also retained (albeit reduced) activity against the Leu858Arg/Thr790Met double mutant [7, 8, 10]. Cell lines expressing less common EGFR mutations (including Gly719Xaa point mutations in exon 18 and the Leu861Gln point mutation in exon 21) also showed sensitivity to afatinib [11].

Afatinib inhibited tumour growth or induced tumour regression in murine tumour models with EGFR mutations, including Del19, Leu858Arg and the Leu858Arg/Thr790Met double mutant [7, 12]. Afatinib also demonstrated activity in mouse xenograft models of squamous NSCLC expressing wild-type EGFR [13]. The activity of afatinib in patients with squamous NSCLC and wild-type EGFR [14] (see Section 4.2) may reflect the broad blockade of ErbB receptors besides EGFR and inhibition of aberrant signalling cascades downstream of the ErbB receptors [1, 14].

3 Pharmacokinetic Properties of Afatinib

Afatinib tablets had a geometric mean bioavailability of 92 % relative to afatinib oral solution [5]. The maximum plasma concentration (C_{max}) was reached ≈2–5 h after oral administration of afatinib tablets [5, 6, 15]. C_{max} and area under the plasma concentration-time curve values increased slightly more than dose proportionally with the administration of afatinib 20–50 mg [5, 6, 15]. With repeated administration, steady-state plasma afatinib concentrations were reached within 8 days [5, 6]. Afatinib exposure was reduced when it was administered with a high-fat meal; afatinib should not be taken with food (Section 6) [5, 6]. Afatinib was ≈95 % plasma protein bound in vitro [5, 6].

Afatinib undergoes minimal enzymatic metabolism, with the major circulating metabolites being adducts of afatinib covalently bound to plasma proteins [5, 6, 16]. Afatinib is predominantly excreted in faeces (85 %), with 4 % of the dose excreted in urine; the parent drug accounted for ≈88 % of the recovered dose [5, 6, 16]. At steady state, the mean elimination half-life of afatinib was ≈37 h [5, 6, 15].

Pharmacokinetic data indicate that adjustments to the starting dosage of afatinib are not needed in patients with mild or moderate renal impairment [5, 6]. US prescribing information recommends that the afatinib dosage be reduced to 30 mg once daily in patients with severe renal impairment [estimated glomerular filtration rate (eGFR) of 15–29 mL/min/1.73 m^2], although dosage recommendations cannot be made for patients with an eGFR of <15 mL/min/1.73 m^2 or patients undergoing dialysis, as afatinib has not been studied in these populations [5]. The EU summary of product characteristics (SmPC) states that treatment with afatinib is not recommended in patients with severe renal impairment (creatinine clearance <30 mL/min), reflecting limited data in this population [6].

Afatinib exposure is not altered to a clinically significant extent in patients with mild or moderate hepatic impairment, and the starting dosage of afatinib does not need to be adjusted in these patients [5, 6]. US prescribing information recommends that patients with severe hepatic impairment be closely

monitored and the afatinib dosage adjusted if it is not well tolerated [5]. The EU SmPC states that treatment with afatinib is not recommended in patients with severe hepatic impairment, reflecting a lack of data in this population [6].

Afatinib was a substrate of the transporters P-gp and BCRP in vitro, meaning that strong P-gp inhibitors and inducers have the potential to increase and decrease afatinib exposure, respectively [5, 6]. The US prescribing information states that if not tolerated, the afatinib dosage should be decreased by 10 mg/day in patients requiring therapy with a P-gp inhibitor (e.g. ritonavir, ciclosporin, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, amiodarone); the previous afatinib dosage can be resumed (as tolerated) after the P-gp inhibitor has been discontinued [5]. The EU SmPC states that if treatment with P-gp inhibitors is required, their dosing should be staggered (e.g. P-gp inhibitors administered once or twice daily should be taken 12 and 6 h apart from afatinib) [6]. According to the US prescribing information, the afatinib dosage should be increased by 10 mg/day (as tolerated) in patients requiring long-term therapy with a P-gp inducer [e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, hypericum (St. John's wort)]; the previous afatinib dosage can be resumed 2–3 days after discontinuing the P-gp inducer [5].

4 Therapeutic Efficacy of Afatinib

4.1 First-Line Treatment of EGFR Mutation-Positive Advanced NSCLC

Randomized, open-label, multinational, phase 2b (LUX-Lung 7 [17]) or phase 3 (LUX-Lung 3 [18], LUX-Lung 6 [19]) trials compared the efficacy of oral afatinib with that of gefitinib (LUX-Lung 7), pemetrexed plus cisplatin (LUX-Lung 3) or gemcitabine plus cisplatin (LUX-Lung 6) in the first-line treatment of patients with advanced lung adenocarcinoma and activating EGFR mutations. Inclusion criteria included stage IIIB or IV lung adenocarcinoma, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, measurable disease (RECIST version 1.1) and adequate organ function [17–19], with activating EGFR mutations [18, 19] or common activating EGFR mutations (Del19 or Leu858Arg) [17].

In LUX-Lung 7, 57 % of patients were Asian and 32 % of patients were White [17]. At baseline, Del19, a Leu858Arg mutation alone and a Leu858Arg mutation plus Del19 were present in 58, 41 and 0.3 % of patients, respectively [17].

LUX-Lung 3 enrolled patients from Asia, Europe, North and South America and Australia (with east Asian patients comprising 72 % of the population) [18] and LUX-Lung 6 enrolled patients from China, South Korea and Thailand [19]. In terms of activating EGFR mutations, ≈50 % of patients in each trial had Del19, ≈40 % had the Leu858Arg mutation and ≈10 % had other mutations [18, 19].

Treatment continued until disease progression, intolerable adverse events, or any other reason necessitating withdrawal in LUX-Lung 3, 6 and 7 [17–19], although in LUX-Lung 7, treatment was permitted beyond radiological progression in the case of continued clinical benefit as judged by the investigator [17]; regimen details are shown in Table 1. Co-primary endpoints in LUX-Lung 7 were progression-free survival (PFS; assessed by independent review), overall survival (OS) and time to treatment failure (TTF) [17], and the primary endpoint in LUX-Lung 3 and LUX-Lung 6 was PFS (assessed by independent review) [18, 19]. Efficacy was assessed in the intent-to-treat (ITT) population [17–19]. Some analyses are available as abstracts [20–22] and/or a slide presentation [22].

4.1.1 Comparison with Gefitinib

Results of the primary PFS analysis in LUX-Lung 7 demonstrated that first-line treatment with afatinib prolonged PFS and TTF to a significantly greater extent than gefitinib in patients with advanced lung adenocarcinoma and activating EGFR mutations (Table 1) [17]. Kaplan-Meier estimates of the PFS rate with afatinib and gefitinib were 47 versus 41 % at 12 months, 27 versus 15 % at 18 months and 18 versus 8 % at 24 months. Median OS did not significantly differ between afatinib and gefitinib recipients at the time of the primary PFS analysis (27.9 vs. 25.0 months) [17], or in the final OS analysis (Table 1) [20]. Landmark analyses demonstrated that the OS rate with afatinib and gefitinib was 61 versus 51 % at 24 months and 48 versus 40 % at 30 months [20]. It should be noted that LUX-Lung 7 was not powered to show a between-group difference in OS [the sample size was based on controlling the width of the hazard ratio (HR) CI for PFS], and that numerically more patients who discontinued gefitinib versus afatinib received subsequent therapy with EGFR TKIs (52 vs. 43 %) [17].

The objective response rate (ORR; assessed by independent review) was significantly higher with afatinib than with gefitinib (70 vs. 56 %; $p = 0.0083$), with a median duration of response of 10.1 and 8.4 months in the corresponding treatment groups [17].

No significant differences were seen between afatinib and gefitinib in terms of changes from baseline to the end of follow-up (median 56 weeks) in mean EuroQoL-5D health status self-assessment questionnaire (EQ-5D) scores (from 0.72 to 0.77 with afatinib and from 0.73 to 0.80 with gefitinib) or mean EuroQol EQ visual analogue scale (EQ-VAS) scores (from 69.7 to 74.5 with afatinib and from 71.2 to 76.0 with gefitinib) [17].

In terms of both PFS and TTF, prespecified analyses favoured afatinib over gefitinib across various patient subgroups (including EGFR mutation type, ethnic origin, sex, presence or absence of brain metastases, age <65 or ≥65 years,

Table 1 Efficacy of oral afatinib in the first-line treatment of EGFR mutation-positive advanced lung adenocarcinoma

Study	Treatment	No. of pts	Median PFS[a] (months)	HR (95 % CI)	Median OS (months)	HR (95 % CI)	Median TTF (months)	HR (95 % CI)
Comparison with GEF								
LUX-Lung 7 [17, 20]	AFA[b]	160	11.0*[c]	0.73 (0.57–0.95)	27.9[c,d]	0.86 (0.66–1.12)	13.7**[c]	0.73 (0.58–0.92)
	GEF[e]	159	10.9[c]		24.5[c,d]		11.5[c]	
Comparisons with chemotherapy								
Overall population								
LUX-Lung 3 [18, 23]	AFA[b]	230	11.1***[c]	0.58 (0.43–0.78)	28.2	0.88 (0.66–1.17)		
	PEM + CIS[f]	115	6.9[c]		28.2			
LUX-Lung 6 [19, 23]	AFA[b]	242	11.0****[c]	0.28 (0.20–0.39)	23.1	0.93 (0.72–1.22)		
	GEM + CIS[g]	122	5.6[c]		23.5			
Pts with exon 19 deletions								
LUX-Lung 3 [23]	AFA	112			33.3**	0.54 (0.36–0.79)		
	PEM + CIS	57			21.1			
LUX-Lung 6 [23]	AFA	124			31.4*	0.64 (0.44–0.94)		
	GEM + CIS	62			18.4			
Pts with the Leu858Arg mutation								
LUX-Lung 3 [23]	AFA	91			27.6	1.30 (0.80–2.11)		
	PEM + CIS	47			40.3			
LUX-Lung 6 [23]	AFA	92			19.6	1.22 (0.81–1.83)		
	GEM + CIS	46			24.3			

AE adverse event, *AFA* afatinib, *CIS* cisplatin, *GEF* gefitinib, *GEM* gemcitabine, *HR* hazard ratio, *IV* intravenous, *od* once daily, *OS* overall survival, *PEM* pemetrexed, *PFS* progression-free survival, *pts* patients, *TTF* time to treatment failure

*$p < 0.05$, **$p < 0.01$, ***$p = 0.001$, ****$p < 0.0001$ vs. comparator

[a] Assessed by independent review

[b] The initial AFA dosage was 40 mg od. The AFA dosage could be increased to 50 mg od after the first 28 days of treatment [17] or after the first 21-day cycle [18, 19] if pts did not experience rash, diarrhoea, mucositis or other treatment-related AEs of greater than grade 1 severity. In the event of treatment-related AEs of at least grade 3 severity or selected prolonged grade 2 AEs, the AFA dosage could be decreased to 20 mg/day (after treatment interruption and recovery to grade 1 or less)

[c] Primary endpoint

[d] Final OS analysis; data available as an abstract [20]

[e] GEF 250 mg od

[f] IV PEM 500 mg/m^2 and IV CIS 75 mg/m^2 once every 21 days for a maximum six cycles

[g] GEM 1000 mg/m^2 on days 1 and 8 and IV CIS 75 mg/m^2 on day 1 every 21 days for a maximum six cycles

ECOG performance status) [17]. The median PFS duration was 10.9 months with afatinib and 10.8 months with gefitinib in the subgroup of patients with the Leu858Arg mutation and 12.7 and 11.0 months in the corresponding treatment groups in the subgroup of patients with Del19 [17].

Afatinib dose reduction did not appear to affect PFS, with no significant difference between patients receiving afatinib <40 mg once daily and those receiving afatinib ≥40 mg once daily in median PFS (12.8 vs. 11.0 months) [21]. The afatinib dosage was reduced to 30 mg once daily in 39 % of patients, with 13 % experiencing a further dose reduction to 20 mg once daily [21].

4.1.2 Comparisons with Chemotherapy

First-line treatment with afatinib prolonged PFS to a significantly greater extent than pemetrexed plus cisplatin [18] or gemcitabine plus cisplatin [19] in patients with advanced lung adenocarcinoma and activating EGFR mutations, according to the results of LUX-Lung 3 [18] and LUX-Lung 6 [19] (Table 1). In the overall patient population, the median duration of OS did not significantly differ between afatinib and the comparator arm of either trial (Table 1) [23].

The ORR (assessed by independent review) was significantly ($p \leq 0.001$) higher with afatinib than with pemetrexed plus cisplatin (56 vs. 23 %) [18] or gemcitabine plus cisplatin (67 vs. 23 %) [19]. Median durations of response were 11.1 months with afatinib and 5.5 months with pemetrexed plus cisplatin in LUX-Lung 3 [18] and 9.7 months with afatinib and 4.3 months with gemcitabine plus cisplatin in LUX-Lung 6 [19].

In terms of health-related quality of life (HR-QOL) [assessed using the European Organisation for the Research and Treatment of Cancer core cancer questionnaire (QLQ-C30) and its module specific to lung cancer (QLQ-LC13)], significantly ($p \leq 0.01$) more patients receiving afatinib than chemotherapy had improvements in dyspnoea in LUX-Lung 3 (64 vs. 50 %) [24], and in

dyspnoea (71 vs. 48 %), cough (76 vs. 55 %) and pain (64 vs. 47 %) in LUX-Lung 6 [19]. In LUX-Lung 3, longitudinal analysis demonstrated significantly ($p < 0.01$) better scores for global health status/quality of life and physical, role and cognitive functioning with afatinib versus chemotherapy [24]. In LUX-Lung 6, significantly ($p < 0.05$) more afatinib than chemotherapy recipients had improvements in global health status/quality of life and in physical, role and social functioning [25].

In both LUX-Lung 3 [18] and LUX-Lung 6 [19], analyses generally favoured afatinib over chemotherapy across various patient subgroups (including ethnic origin [18], sex [18, 19], age <65 or ≥65 years [18, 19], ECOG performance status [18, 19]) in terms of PFS outcomes.

In patients with common EGFR mutations (i.e. Del19 or Leu858Arg), median PFS was significantly ($p \leq 0.001$) longer with afatinib than with chemotherapy in both LUX-Lung 3 (13.6 vs. 6.9 months) [18] and LUX-Lung 6 (11.0 vs. 5.6 months) [19], according to prespecified analyses. Median OS significantly favoured afatinib versus chemotherapy in patients with Del19 in both LUX-Lung 3 and LUX-Lung 6, with no significant between-group difference in patients with the Leu858Arg mutation in either trial (Table 1) [23]. OS was also significantly ($p = 0.0001$) prolonged with afatinib versus chemotherapy in patients with Del19, but not in those with the Leu858Arg mutation, in an exploratory pooled analysis of LUX-Lung 3 and LUX-Lung 6 [23].

Several subgroup analyses also found that OS was prolonged with afatinib versus chemotherapy in patients with Del19, but not in patients with the Leu858Arg mutation, including in a prespecified analysis of Japanese patients from LUX-Lung 3 [26], in an analysis of non-Asian patients from LUX-Lung 3 [23] and in an exploratory pooled analysis of Asian patients from LUX-Lung 3 and LUX-Lung 6 [22]. For example, in Japanese patients ($n = 83$) enrolled in LUX-Lung 3, median PFS was significantly ($p < 0.01$) longer with afatinib than with pemetrexed plus cisplatin in the overall population (13.8 vs. 6.9 months), in patients with common EGFR mutations (13.8 vs. 6.9 months) and in patients with Del19 (16.4 vs. 3.1 months), but not in patients with the Leu858Arg mutation (13.7 vs. 8.3 months) [26]. Median OS was significantly longer with afatinib than with pemetrexed plus cisplatin in patients with Del19 (46.9 vs. 31.5 months), but not in patients with the Leu858Arg mutation (41.7 vs. 40.3 months) [26].

Results of a prespecified subgroup analysis in patients with asymptomatic brain metastases and common EGFR mutations (35 patients from LUX-Lung 3 and 46 patients from LUX-Lung 6) were generally consistent with findings in the overall population, although the difference in median PFS between patients receiving afatinib and those receiving pemetrexed plus cisplatin (11.1 vs. 5.4 months) or gemcitabine plus cisplatin (8.2 vs. 4.7 months) did not reach statistical significance, most likely reflecting the small sample sizes [27]. A post hoc pooled analysis found that median PFS was significantly longer with afatinib than with chemotherapy (8.2 vs. 5.4 months; $p = 0.0297$) (HR 0.50; 95 % CI 0.27–0.95). No significant difference in OS was seen between afatinib and chemotherapy in either the individual or pooled analyses [27].

A post hoc analysis pooling data from LUX-Lung 2 [28] (see Section 7 for further details), LUX-Lung 3 [18] and LUX-Lung 6 [19] examined the efficacy of afatinib in patients with uncommon EGFR mutations ($n = 75$) [29]. Uncommon mutations included point mutations and/or deletions in exons 18–21 (most frequent of these were Gly719Xaa alone, Leu861Gln alone and Gly719Xaa plus either Ser768Ile or Leu861Gln; group 1), de novo Thr790Met mutations in exon 20 (alone or in combination with other mutations; group 2) and exon 20 insertions (group 3). Afatinib appeared more active in group 1 than in groups 2 or 3, with median PFS durations of 10.7, 2.9 and 2.7 months, respectively, and median OS durations of 19.4, 14.9 and 9.2 months, respectively [29].

Median PFS did not significantly differ between patients whose afatinib dosage was reduced to 30 mg once daily because of treatment-related adverse events during the first 6 months of treatment and those whose afatinib dosage remained at 40 mg once daily in LUX-Lung 3 (11.3 vs. 11.0 months) and LUX-Lung 6 (12.3 vs. 11.0 months), according to post hoc analyses [30]. In LUX-Lung 3 and LUX-Lung 6, dosage reductions occurred in 53 and 28 % of afatinib recipients, respectively, with >80 % of reductions occurring in the first 6 months of treatment [30].

4.2 Second-Line Treatment of Metastatic Squamous NSCLC

A randomized, open-label, multinational, phase 3 trial (LUX-Lung 8) compared the efficacy of second-line treatment with afatinib with that of erlotinib in patients with advanced squamous NSCLC [14]. Inclusion criteria included stage IIIB or IV squamous NSCLC, disease progression following first-line treatment with platinum-based doublet chemotherapy (at least four cycles), life expectancy of ≈4 months if left untreated, an ECOG performance status of 0 or 1, measurable disease (RECIST version 1.1) and adequate organ function. The study included non-east Asian (78 %) and east Asian (22 %) patients. At baseline, 96 % of patients had squamous histology and 4 % had mixed (predominantly

Table 2 Efficacy of oral afatinib in the second-line treatment of advanced squamous non-small cell lung cancer: results of the LUX-Lung 8 trial [14]

	AFA[a] ($n = 398$)	ERL[b] ($n = 397$)	HR (95 % CI)
Median PFS (months) [independent review]			
Primary PFS analysis[c]	2.4*	1.9	0.82 (0.68–1.00)
Updated PFS analysis[d]	2.6*	1.9	0.81 (0.69–0.96)
Median OS[e] (months)	7.9**	6.8	0.81 (0.69–0.95)
Kaplan-Meier OS rate estimates (% of pts)			
6 months	63.6**	54.6	
12 months	36.4*	28.2	
18 months	22.0*	14.4	
ORR (% of pts) [independent review]	6	3	
DCR (% of pts) [independent review]	51**	40	

AE adverse event, *AFA* afatinib, *DCR* disease control rate, *ERL* erlotinib, *HR* hazard ratio, *od* once daily, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *pts* patients

* $p < 0.05$, ** $p < 0.01$ vs. ERL

[a] The initial AFA dosage was 40 mg od. The AFA dosage could be increased to 50 mg od after the first 28 days of treatment if pts did not experience rash, diarrhoea, mucositis or other treatment-related AEs of greater than grade 1 severity. In the event of treatment-related AEs of at least grade 3 severity or selected prolonged grade 2 AEs, the AFA dosage could be decreased to 20 mg od (after treatment interruption and recovery to grade 1 or less)

[b] ERL 150 mg od, with dosage reductions permitted for AEs

[c] Primary endpoint

[d] Conducted at the time of the primary OS analysis

[e] Primary OS analysis

squamous) histology; EGFR testing was not mandated. Patients initially received oral afatinib 40 mg once daily or erlotinib 150 mg once daily until disease progression, intolerable adverse events, or any other reason necessitating withdrawal (see Table 2 for permitted dosage adjustments). The primary endpoint was PFS (assessed by independent review). Efficacy was assessed in the ITT population [14].

Second-line treatment with afatinib prolonged PFS to a significantly greater extent than erlotinib in patients with advanced squamous NSCLC (Table 2), according to the results of both the primary PFS analysis and an updated PFS analysis (conducted at the time of the primary OS analysis) [14].

OS was significantly prolonged with afatinib versus erlotinib, according to the results of the primary OS analysis (Table 2) [14]. Kaplan-Meier estimates of the 6-, 12- and 18-month OS rates all significantly favoured patients receiving afatinib versus erlotinib (Table 2) [14].

The ORR did not significantly differ between patients receiving afatinib and those receiving erlotinib (6 vs. 3 %), with a median duration of response of 7.3 and 3.7 months in the corresponding treatment groups [14]. However, the disease control rate was significantly higher with afatinib than with erlotinib (51 vs. 40 %; $p = 0.002$) [14].

HR-QOL (assessed using QLQ-C30 and QLQ-LC13) improved in significantly more afatinib than erlotinib recipients (36 vs. 28 % of patients; $p = 0.041$) [14]. Significantly more patients receiving afatinib than erlotinib had improved cough (43 vs. 35 %; $p = 0.029$), with no significant between-group differences in the proportions of patients with improved dyspnoea (51 vs. 44 %) or pain (40 vs. 39 %). The median time to deterioration of dyspnoea was significantly longer with afatinib than with erlotinib (2.6 vs. 1.9 months; $p = 0.0078$), with no significant between-group difference in the median times to deterioration of pain (2.5 vs. 2.4 months) or cough (4.5 vs. 3.7 months) [14].

Prespecified analyses found that in terms of both PFS and OS, afatinib was favoured over erlotinib across various patient subgroups (including ethnic origin, sex, best response to first-line chemotherapy, age <65 or ≥65 years, histology, ECOG performance status) [14]. Retrospective analysis of archival tissue from 238 patients found that only 6 % of afatinib or erlotinib recipients had EGFR mutations and 6 % had EGFR amplification, suggesting that outcomes were unlikely to be driven by molecular aberrations of EGFR [14].

5 Tolerability and Safety of Afatinib

Oral afatinib had a predictable, manageable tolerability profile in patients with advanced NSCLC. Where specified, treatment-related adverse events (all grades) were reported in 93–99 % of afatinib recipients, compared with 96 % of gefitinib recipients in LUX-Lung 7 [17],

81 % of erlotinib recipients in LUX-Lung 8 [14] and 99 % of gemcitabine plus cisplatin recipients in LUX-Lung 6 [19]. Across LUX-Lung 3, 6, 7 and 8, the most commonly reported treatment-related adverse events (all grades) in afatinib recipients were diarrhoea (70–95 % of patients), rash/acne (67–89 %) and stomatitis/mucositis (29–72 %) [14, 17–19].

In comparisons between EGFR TKIs, treatment-related adverse events of grade 3 or 4 severity were reported in 31 % of afatinib recipients and 18 % of gefitinib recipients in LUX-Lung 7 [17], and in 27 % of afatinib recipients and 17 % of erlotinib recipients LUX-Lung 8 [14]. The most frequent (incidence of >5 %) treatment-related grade 3 or 4 adverse events reported with first-line afatinib or gefitinib in LUX-Lung 7 were diarrhoea (13 vs. 1 %), rash/acne (9 vs. 3 %), fatigue (6 vs. 0 %) and increased alanine aminotransferase or aspartate aminotransferase levels (0 vs. 9 %) [17]. In LUX-Lung 8, the most frequent (incidence of >5 %) treatment-related grade 3 or 4 adverse events reported with second-line afatinib or erlotinib were diarrhoea (10 vs. 3 %) and rash/acne (6 vs. 10 %) [14].

In comparisons with chemotherapy, treatment-related adverse events of at least grade 3 severity were reported in 49 % of afatinib recipients and 48 % of pemetrexed plus cisplatin recipients in LUX-Lung 3 [18] and in 36 % of afatinib recipients and in 60 % of gemcitabine plus cisplatin recipients in LUX-Lung 6 [19]. The most frequent (incidence of >5 %) treatment-related adverse events of at least grade 3 severity reported with first-line afatinib or pemetrexed plus cisplatin in LUX-Lung 3 were rash/acne (16 vs. 0 %), diarrhoea (14 vs. 0 %), paronychia (11 vs. 0 %), stomatitis/mucositis (9 vs. 1 %), fatigue (1 vs. 13 %), neutropenia (0.4 vs. 18 %), leukopenia (0.4 vs. 8 %) and anaemia (0.4 vs. 6 %) [18]. In LUX-Lung 6, the most frequent (incidence of ≥5 %) treatment-related adverse events of at least grade 3 severity reported with first-line afatinib or gemcitabine plus cisplatin were rash/acne (15 vs. 0 %), diarrhoea (5 vs. 0 %), stomatitis/mucositis (5 vs. 0 %), hypokalaemia (1 vs. 8 %), vomiting (0.8 vs. 19 %), neutropenia (0.4 vs. 27 %), leukopenia (0.4 vs. 15 %), thrombocytopenia (0.4 vs. 10 %), anaemia (0.4 vs. 9 %), decreased neutrophil count (0 vs. 10 %), nausea (0 vs. 8 %) and decreased white blood cell count (0 vs. 6 %) [19].

Serious treatment-related adverse events were reported in 11 % of afatinib recipients [including diarrhoea (6 %)] and 4 % of gefitinib recipients [including interstitial lung disease (ILD; 3 %), diarrhoea (1 %)] in LUX-Lung 7 [17] and in 12 % of afatinib recipients [including diarrhoea (4 %), dehydration (2 %), acute renal failure (1 %)] and 6 % of erlotinib recipients [including diarrhoea (2 %)] in LUX-Lung 8 [14]. Serious treatment-related adverse events were reported in 6 % of afatinib recipients [including diarrhoea (1 %), rash/acne (1 %)] and 8 % of gemcitabine plus cisplatin recipients [including thrombocytopenia (2 %)] in LUX-Lung 6 [19].

Dose reductions because of adverse events occurred in 27–42 % of patients receiving afatinib [14, 17], with discontinuation because of treatment-related adverse events occurring in 6–8 % of afatinib recipients [17–19] [most commonly because of diarrhoea (1–3 % [17, 18]) and paronychia (1 % [18])].

Across the afatinib clinical trial programme, there have been cases of diarrhoea resulting in dehydration with or without renal impairment, including, rarely, fatal cases [5, 6]. At the onset of diarrhoea, patients should be provided with an antidiarrhoeal agent, which should be continued until loose bowel movements have ceased for 12 h; see Section 6 for recommended dosage modifications [5, 6].

Adverse reactions of special interest include bullous and exfoliative skin disorders, ILD, keratitis and hepatotoxicity [5, 6]. Among 4257 patients who received afatinib across 44 clinical trials, grade 3 cutaneous reactions characterized by bullous, blistering and exfoliating lesions were reported in 0.2 % of patients [5]. Afatinib should be discontinued in patients who develop life-threatening bullous, blistering or exfoliating lesions; see Section 6 for recommended dosage modifications in patients with less severe cutaneous reactions [5].

ILD or ILD-like adverse reactions (e.g. lung infiltration, pneumonitis, acute respiratory distress syndrome) were reported in 1.6 % of 4257 afatinib recipients [5, 6]. Afatinib should be withheld during evaluation of patients with suspected ILD and discontinued in patients with confirmed ILD [5, 6].

Keratitis was reported in 0.7 % of 4257 afatinib recipients [5]. Afatinib should be withheld during evaluation of patients with suspected keratitis and treatment should be interrupted or discontinued if a diagnosis of ulcerative keratitis is confirmed [5].

Liver function test abnormalities were reported in 9.7 % of 4257 afatinib recipients, of which 0.2 % were fatal [5]. The US prescribing information states that patients receiving afatinib should undergo periodic monitoring of liver function tests during treatment, and that afatinib should be withheld in patients who develop worsening liver function [5]. The EU SmPC recommends periodic liver function testing in patients with pre-existing liver disease and states that interruption of afatinib may become necessary in patients who develop worsening liver function [6]. Afatinib should be discontinued in patients who develop severe hepatic impairment [5, 6].

6 Dosage and Administration of Afatinib

Afatinib is approved for the treatment of locally advanced [6] or metastatic [5, 6] squamous NSCLC that has progressed on or after platinum-based chemotherapy in the EU [6] and after platinum-based chemotherapy in the US [5]. Afatinib is also approved in the US for the first-line treatment of patients with metastatic NSCLC whose tumours have EGFR Del19 or exon 21 (Leu858Arg) substitution mutations as detected by a US FDA-approved test [5], and in the EU for the treatment of EGFR TKI-naïve patients with locally advanced or metastatic NSCLC with activating EGFR mutations [6].

The recommended dosage of oral afatinib is 40 mg once daily, continued until disease progression or until treatment is no longer tolerated by the patient [5, 6]. Afatinib should not be taken with food; rather, it is recommended that afatinib be taken ≥1 h before [5, 6] or ≥2 h [5] or ≥3 h [6] after a meal.

US prescribing information states that afatinib should be withheld for any adverse reaction of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade 3 or higher, for diarrhoea of grade 2 or higher persisting for ≥2 days while taking antidiarrhoeal medication, for grade 2 cutaneous reactions that are prolonged (>7 days) or intolerable, and for renal impairment of grade 2 or higher [5]. Treatment with afatinib can be resumed (at a 10 mg/day reduced dosage) when the adverse reaction fully resolves, returns to baseline or improves to grade 1 [5]. The EU SmPC states that afatinib treatment should be interrupted for NCI CTCAE grade 2 adverse reactions that are prolonged (i.e. diarrhoea persisting for >2 days, rash persisting for >7 days) or intolerable, and for adverse reactions of at least grade 3 severity [6]. Afatinib should be interrupted until the adverse reaction resolves to grade 0 or 1, and can then be resumed at a lower dosage (dosage reduced by 10 mg decrements) [6].

Females of reproductive potential should be advised to use effective contraception during afatinib treatment and for ≥2 weeks after the last dose [5].

Local prescribing information should be consulted for more information related to special warnings and precautions for afatinib, and for recommended dosage modifications because of adverse reactions or drug interactions.

7 Place of Afatinib in the Management of Advanced Non-Small Cell Lung Cancer

US National Comprehensive Cancer Network (NCCN) guidelines currently recommend first-line treatment with afatinib, erlotinib or gefitinib in patients with metastatic NSCLC and activating EGFR mutations [2]. There has been uncertainty as to whether there is a difference in efficacy between the first-generation EGFR TKIs gefitinib and erlotinib, which reversibly bind to EGFR and inhibit EGFR signalling, and afatinib, which is a second-generation irreversible ErbB inhibitor that blocks signalling from all dimers formed by EGFR, HER2, ErbB3 and ErbB4 (Section 2). The exploratory LUX-Lung 7 trial demonstrated that in terms of PFS and TTF, afatinib was more effective than gefitinib in the first-line treatment of patients with advanced lung adenocarcinoma and activating EGFR mutations (Section 4.1.1). However, OS did not significantly differ between patients receiving afatinib and those receiving gefitinib.

Compared with chemotherapy, afatinib significantly prolonged PFS and was better tolerated in the first-line treatment of patients with advanced lung adenocarcinoma and activating EGFR mutations, according to the results of LUX-Lung 3 and LUX-Lung 6 (Sects. 4.1.2 and 5). OS was significantly improved with afatinib versus chemotherapy in the subgroup of patients with Del19, but not in those with the Leu858Arg mutation. These results suggest that Del19 and Leu858Arg may represent two subtypes of EGFR mutant NSCLC with distinct biological properties that result in different responses to EGFR TKIs [31].

In the EU, the approval of afatinib in EGFR TKI-naïve patients with advanced NSCLC and activating EGFR mutations is not restricted to first-line use (Section 6). This reflects the results of LUX-Lung 2, a noncomparative, multinational, phase 2 trial in which EGFR TKI-naïve patients with advanced lung adenocarcinoma and activating EGFR mutations who were treatment naïve or had received one prior chemotherapy regimen for advanced disease were administered first-line ($n = 61$) or second-line ($n = 68$) treatment with afatinib [28]. The ORR (primary endpoint; independent review) was 61 %, with a median duration of response of 12.9 months. The ORR was 66 % in patients with Del19 or Leu858Arg mutations, 39 % in patients with other mutations, 66 % in patients receiving first-line treatment and 57 % in patients receiving second-line treatment. Median PFS and OS were 10.1 and 24.8 months, respectively [28].

In LUX-Lung 8, PFS and OS were significantly prolonged with second-line afatinib versus erlotinib in patients with advanced squamous NSCLC (Section 4.2). Based on the results of LUX-Lung 8, afatinib was recently approved for the second-line treatment of patients with advanced squamous NSCLC, regardless of EGFR mutation status (Section 6). Historically, docetaxel was the standard second-line treatment recommended for use in

patients with advanced squamous NSCLC that had progressed following first-line platinum-based chemotherapy [32]. Other agents recently approved for use as subsequent therapy in advanced squamous NSCLC, and recommended by NCCN guidelines [2], include the immune checkpoint inhibitors nivolumab and pembrolizumab and the anti-vascular endothelial growth factor receptor 2 antibody ramucirumab in combination with docetaxel. Erlotinib (which was previously included in NCCN guidelines as an option for subsequent therapy in advanced squamous NSCLC [2]), was selected as the comparator agent in LUX-Lung 8, rather than docetaxel [14]. OS and PFS did not appear to significantly differ between docetaxel and erlotinib in patients receiving second-line treatment for advanced squamous NSCLC with wild-type EGFR status, according to subgroup analysis of the phase 3 TAILOR trial [33]. It should be noted that NCCN guidelines do not currently recommend any EGFR TKIs as subsequent therapy in squamous NSCLC [2]. However, the oral route of administration of afatinib, and other EGFR TKIs, may represent an advantage over intravenous options (e.g. chemotherapy agents, immune checkpoint inhibitors, ramucirumab) for some patients [1].

The better outcomes seen with afatinib versus gefitinib in LUX-Lung 7 (PFS and TTF) and versus erlotinib in LUX-Lung 8 (PFS and OS) may reflect the broader inhibitory profile of afatinib and its potential to delay possible resistance mechanisms, compared with first-generation EGFR TKIs [17]. The majority of patients receiving EGFR TKIs will eventually develop resistance and disease progression [34]. Acquired resistance to afatinib and other EGFR TKIs is most commonly associated with the exon 20 mutation Thr790Met [34, 35]. Afatinib showed activity against EGFR with Thr790Met in preclinical studies (Section 2), although it did not appear to be highly active in patients with de novo Thr790Met mutations in a pooled analysis of the LUX-Lung 2, 3 and 6 trials [29] (Section 4.1.2). Osimertinib, an oral third-generation EGFR TKI, was recently approved in the US for the treatment of patients with metastatic EGFR Thr790Met mutation-positive NSCLC who have progressed on or after EGFR TKI therapy [36] and in the EU for the treatment of patients with advanced, EGFR Thr790Met mutation-positive NSCLC [37].

The tolerability profile of afatinib is well characterized. Diarrhoea and dermatological adverse events were reported most frequently in patients with advanced NSCLC who received afatinib (Section 5). However, few patients discontinued afatinib because of treatment-related adverse events, indicating that treatment-related adverse events were usually successfully managed using dosage reductions and supportive measures [14].

In conclusion, afatinib is an important option for the first-line treatment of patients with advanced NSCLC and activating EGFR mutations, and provides an additional option for the treatment of patients with squamous NSCLC that has progressed following first-line platinum-based chemotherapy.

Data Selection Afatinib: 220 records identified	
Duplicates removed	26
Excluded at initial screening (e.g. press releases; news reports; not relevant drug/indication)	28
Excluded during initial selection (e.g preclinical study; review; case report; not randomized trial)	52
Excluded by author (e.g. not randomized trials; review; duplicate data; small patient number; phase 1/2 trials)	78
Cited efficacy/tolerability articles	17
Cited articles not efficacy/tolerability	19
Search Strategy: EMBASE, MEDLINE and PubMed from 2014 to present. Previous Adis Drug Evaluation published in 2014 was hand-registries/databases and websites were also searched for relevant data. Key words were afatinib, BIBW-2992, Gilotrif, non -small cell lung, advanced, metastatic, exon 19 deletion, del19, exon 21, L858R mutation, EGFR mutation, first -line, 1st-line, squamous. Records were limited to those in English language. Searches last updated 24 October 2016.	

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Compliance with Ethical Standards

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