Drugs Ther Perspect (2018) 34:89–98
https://doi.org/10.1007/s40267-018-0482-6

ADIS DRUG Q&A

Afatinib in advanced NSCLC: a profile of its use

Emma D. Deeks[1] · **Gillian M. Keating**[1]

Published online: 1 February 2018

Abstract Afatinib [Giotrif® (EU); Gilotrif® (USA)] is an orally administered, irreversible inhibitor of the ErbB family of tyrosine kinases that provides an important first-line treatment option for advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations (i.e. EGFR$^{actMUT+}$), and an additional treatment option for squamous NSCLC that has progressed following first-line platinum-based chemotherapy. Relative to gefitinib in the first-line treatment of EGFR$^{actMUT+}$ advanced lung adenocarcinoma, afatinib prolonged progression-free survival (PFS) and time to treatment failure (TTF), but not overall survival (OS). Afatinib also prolonged PFS, but not OS, versus cisplatin-based chemotherapy in this setting; however, afatinib improved OS versus chemotherapy in the subgroup of patients with deletions in exon 19. As a second-line treatment for advanced squamous NSCLC, afatinib prolonged PFS and OS compared with erlotinib, regardless of EGFR mutation status. Afatinib had a predictable and manageable tolerability profile.

Adis evaluation of afatinib in advanced NSCLC
Oral, irreversible inhibitor of ErbB tyrosine kinases
As first-line therapy for EGFR$^{actMUT+}$ advanced lung adenocarcinoma, prolongs PFS and TTF (but not OS) vs gefitinib and prolongs PFS (but not OS) vs chemotherapy
Prolongs OS vs chemotherapy when used first-line for advanced lung adenocarcinoma with deletions in exon 19
As second-line therapy for advanced squamous NSCLC, prolongs PFS and OS vs erlotinib
Predictable, manageable tolerability profile

What is the rationale for using afatinib in NSCLC?

Non-small cell lung cancer (NSCLC) accounts for ≈ 85% of all lung cancers, and is subdivided into squamous NSCLC (≈ 20–30% of all cases) and nonsquamous NSCLC [including adenocarcinoma (the commonest NSCLC subtype), large-cell carcinoma and other cell types] [1]. The ErbB family of tyrosine kinases includes epidermal growth factor receptor (EGFR), human epidermal growth factor receptor (HER) 2, ErbB3 and ErbB4 [2]. Dysregulation of these tyrosine kinases and their downstream signalling pathways (e.g. the PI3 K/AKT pathway) is implicated in cancer cell proliferation, angiogenesis and metastasis [2]. Activating EGFR mutations (i.e. EGFR^{actMUT}) are found in ≈ 10% of Caucasian patients and up to 50% of Asian patients with nonsquamous NSCLC, with the most common being Leu858Arg in exon 21 and deletions in exon 19 (Del19) [3].

Using EGFR tyrosine kinase inhibitors (TKIs), such as afatinib (Giotrif®; Gilotrif®), erlotinib or gefitinib, for the first-line treatment of advanced EGFR$^{actMUT+}$ NSCLC is now well established [3]. However, treatment options have historically been more limited for advanced squamous

The original version of this article was revised due to a retrospective Open Access request.

✉ Emma D. Deeks
dtp@adis.com

[1] Springer, Private Bag 65901, Mairangi Bay, 0754 Auckland, New Zealand

NSCLC, particularly in the second-line setting after progression on first-line platinum-based doublet chemotherapy [1]. Although squamous NSCLC is EGFR$^{actMUT+}$ in only 1–3% of patients, 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].

How does afatinib work?

Afatinib is a potent, selective, irreversible inhibitor of the ErbB family of tyrosine kinases [5–7]. Afatinib covalently binds to all homodimers and heterodimers formed by EGFR, HER2, ErbB3 and ErbB4, thereby inhibiting tyrosine kinase autophosphorylation and downregulating ErbB signalling [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) [5, 8], as well as inhibiting the autophosphorylation and/or proliferation of cell lines expressing wild-type EGFR, mutant EGFR (Del19 or Leu858Arg), wild-type HER2 or altered HER2 (mutations or amplifications) [5, 8–11]. Afatinib also retained (albeit reduced) activity against the Leu858Arg/Thr790Met double mutant [5, 8, 10, 11]. 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 [12].

Afatinib inhibited tumour growth or induced tumour regression in murine tumour models with EGFR mutations, including Del19, Leu858Arg and Leu858Arg/Thr790Met [5, 13]. Afatinib also demonstrated activity in mouse xenograft models of either squamous NSCLC expressing wild-type EGFR [14] or lung cancer expressing altered HER2 (mutations/amplifications) [11]. The activity of afatinib in patients with squamous NSCLC and wild-type EGFR [15] may reflect the broad blockade of ErbB receptors besides EGFR and inhibition of aberrant signalling cascades downstream of the ErbB receptors [1, 15].

For whom is afatinib indicated?

Afatinib is approved in numerous countries, including the EU [6] and USA [7], for the treatment of locally advanced [6] or metastatic [6, 7] squamous NSCLC that has progressed on [6] or after [6, 7] platinum-based chemotherapy. Afatinib is also approved in the USA for the first-line treatment of patients with metastatic NSCLC whose tumours have non-resistant EGFR mutations [7], and in the EU [6] and many other countries for the treatment of EGFR TKI-naïve patients with EGFR$^{actMUT+}$ locally advanced or metastatic NSCLC. A summary of the EU and US prescribing information for afatinib is shown in Table 1. Consult local prescribing information for further details.

What is the clinical efficacy of first-line afatinib in EGFR$^{actMUT+}$ advanced NSCLC?

Three randomized, open-label, multinational, phase 2b [16] or phase 3 [17, 18] trials have compared the efficacy of oral afatinib with that of gefitinib (LUX-Lung 7) [16], pemetrexed + cisplatin (LUX-Lung 3) [17] or gemcitabine + cisplatin (LUX-Lung 6) [18] in the first-line treatment of patients with EGFR$^{actMUT+}$ advanced lung adenocarcinoma. Eligible patients had stage IIIB or IV disease that was EGFR$^{actMUT+}$, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, measurable disease and adequate organ function. Data for afatinib in this setting are also now available from real-world studies [19–21] and a noncomparative phase 3b trial reflective of real-world practice [22].

Compared with gefitinib

First-line treatment with afatinib prolonged progression-free (PFS) and time to treatment failure (TTF) to a significantly greater extent than gefitinib in both the primary [16] and updated [23] analysis of these coprimary endpoints in LUX-Lung 7 (Table 2). By contrast, median OS (co-primary endpoint) did not significantly differ between the treatment groups at the time of the primary [23] or updated [24] OS analysis (Table 2), although LUX-Lung 7 was not powered to show a between-group difference (BGD) in this outcome. The objective response rate (ORR; assessed by independent review) was significantly ($p < 0.01$) higher with afatinib than with gefitinib [16, 23], including in the updated analysis (72.5 vs 56.0%) [23].

Subgroup analyses were generally consistent with these findings. PFS [16, 25] and TTF [16] favoured afatinib over gefitinib across various prespecified patient subgroups (including EGFR mutation type, ethnic origin, sex, presence or absence of brain metastases, ECOG PS, age < 65 or ≥ 65 years) [16] and exploratory subgroups (age < 75 or ≥ 75 years) [25]. OS generally did not significantly differ between the treatments across the prespecified subgroups, although it was significantly more favourable with afatinib than gefitinib in patients aged < 65 years ($p = 0.0228$ for age interaction) [23]. Of note, afatinib and gefitinib recipients with the Leu858Arg mutation had a

Table 1 Prescribing summary of afatinib (Giotrif [6]; Gilotrif [7]) in non-small cell lung cancer in the EU [6] and USA [7]

What are the approved indications of afatinib?	
EU	Treatment of EGFR TKI-naïve adults with locally advanced or metastatic NSCLC with activating EGFR mutation(s)
	Treatment of locally advanced or metastatic squamous NSCLC progressing on or after platinum-based chemotherapy
USA	First-line treatment of patients with metastatic NSCLC whose tumours have non-resistant EGFR mutations, as detected by a US FDA-approved test
	Treatment of metastatic squamous NSCLC progressing after platinum-based chemotherapy
How is afatinib available?	
Film-coated tablets containing 20, 30, or 40 mg (EU; USA) or 50 mg (EU) of afatinib	
What is the administration regimen of afatinib?	
40 mg once daily, taken ≥ 1 h before (EU; USA) or ≥ 2 h (USA) or ≥ 3 h (EU) after food	
Consider an ↑ to 50 mg once daily in patients who tolerate the first cycle of 40 mg/day (EU)	
Continue treatment until disease progression or unacceptable tolerability	
How should afatinib be used in special populations?	
Patients with hepatic impairment	Mild or moderate: no adjustment of starting dosage required
	Severe: not recommended (EU); closely monitor and adjust dosage if not tolerated (USA)
Patients with renal impairment	Mild or moderate: no adjustment of starting dosage required
	Severe: no adjustment of starting dosage required, but monitor and adjust dosage if not tolerated (EU); ↓ starting dosage to 30 mg once daily (USA)
	On dialysis or eGFR < 15 mL/min/1.73 m^2: not recommended (EU); no recommendations available (USA)
Patients who are female or have low body weight	Monitor closely, as afatinib exposure may ↑ (EU)
Pregnant women	Advise of the potential for foetal harm
Breast-feeding women	Advise against breast-feeding during (EU; USA) and for 2 weeks after (USA) afatinib therapy
How should afatinib be used if adverse reactions[a] occur?	
If a grade 2 (prolonged[b]/intolerable) or grade ≥ 3 adverse reaction occurs, interrupt afatinib until the adverse reaction has improved to grade 1 or 0, then resume afatinib at a dosage that is 10 mg/day lower	
Interrupt or discontinue afatinib in the event of ulcerative keratitis (EU; USA), an ejection fraction less than the upper limit of normal (EU), or severe (EU) or life-threatening (USA) bullous, blistering or exfoliative skin conditions	
Discontinue afatinib in the event of severe drug-induced hepatic impairment (EU; USA), symptomatic left ventricular dysfunction (USA), confirmed interstitial lung disease (EU; USA), or if afatinib 20 mg/day causes intolerable (EU; USA) or severe (USA) adverse reactions	
What are the potential clinically relevant interactions between afatinib and other drugs?	
P-gp inhibitors	As coadministration may ↑afatinib exposure, administer strong P-gp inhibitors as far from the afatinib dose as possible (i.e. 6 and 12 h for twice- and once-daily P-gp inhibitors, respectively) [EU]; ↓ afatinib dosage during P-gp inhibitor use if not tolerated and resume original dosage after P-gp inhibitor cessation (USA)
P-gp inducers	As coadministration may ↓ afatinib exposure, ↑ afatinib dosage as tolerated during long-term P-gp inducer use and resume original afatinib dosage 2–3 days after P-gp inducer cessation (USA)

EGFR epidermal growth factor receptor, *eGFR* estimated glomerular filtration rate, *NSCLC* non-small cell lung cancer, *P-gp* P-glycoprotein, *TKI* tyrosine kinase inhibitor, ↑ increase, ↓ decrease

[a]If diarrhoea occurs, provide patients with an antidiarrhoeal agent, to be continued until there have been no loose bowel movements for 12 h

[b]Diarrhoea that lasts > 2 days or cutaneous reactions (e.g. rash) that last > 7 days

median PFS of 10.9 and 10.8 months [16] and a median OS of 25.0 and 21.2 months [23], and the corresponding values in recipients with Del19 were 12.7 and 11.0 months (PFS) [16] and 30.7 and 26.4 months (OS) [23].

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 [26]. 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 [26].

Health-related quality of life (HR-QOL) did not significantly differ between afatinib and gefitinib, as measured by changes from baseline to the end of follow-up (median

Table 2 Efficacy of oral afatinib in the first-line treatment of advanced lung adenocarcinoma with activating EGFR mutations

Trial and outcomes	Results: afatinib vs comparator [hazard ratio (95% CI)]
LUX-Lung 7 [16, 24]	
Comparators (no. of pts)	Afatinib (160) vs gefitinib 250 mg once daily (159)
Median progression-free survival[a]	Primary analysis: 11.0* vs 10.9 months [0.73 (0.57–0.95)]
	Updated analysis[b]: 11.0* vs 10.9 months [0.74 (0.57–0.95)]
Median overall survival[a]	Primary analysis: 27.9 vs 24.5 months [0.86 (0.66–1.12)]
	Updated analysis: 27.9 vs 24.5 months [0.85 (0.66–1.09)]
Median time to treatment failure[a]	Primary analysis: 13.7** vs 11.5 months [0.73 (0.58–0.92)]
	Updated analysis: 13.7* vs 11.5 months [0.75 (95% CI 0.60–0.94)]
LUX-Lung 3 [17, 28])	
Comparators (overall no. of pts)	Afatinib (230) vs premetrexed + cisplatin (115)
Median progression-free survival[a]	11.1*** vs 6.9 months [0.58 (0.43–0.78)]
Median overall survival	All pts: 28.2 vs 28.2 months [0.88 (0.66–1.17)]
	Pts with exon 19 deletions ($n = 112$ vs 57): 33.3** vs 21.1 months [0.54 (0.36–0.79)]
	Pts with Leu858Arg mutation ($n = 91$ vs 47): 27.6 vs 40.3 months [1.30 (0.80–2.11)]
LUX-Lung 6 [18, 28]	
Comparators (overall no. of pts)	Afatinib (242) vs gemcitabine + cisplastin (122)
Median progression-free survival[a]	11.0**** vs 5.6 months [0.28 (0.20–0.39)]
Median overall survival	All pts: 23.1 vs 23.5 months [0.93 (0.72–1.22)]
	Pts with exon 19 deletions ($n = 124$ vs 62): 31.4* vs 18.4 months [0.64 (0.44–0.94)]
	Pts with Leu858Arg mutation ($n = 92$ vs 46): 19.6 vs 24.3 months [1.22 (0.81–1.83)]

The initial dosage ofafatinib was 40 mg once daily, and could be increased to 50 mg once daily after the first 28 days of treatment [16] or first 21-day cycle [17, 18] in pts without rash, diarrhoea, mucositis or other treatment-related grade > 1 AEs. If treatment-related grade ≥ 3 AEs or selected prolonged grade 2 AEs occurred, dosage could be decreased to 20 mg/day (after treatment interruption and recovery to grade ≤ 1). Chemotherapy (i.e. premetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 once every 21 days, or gemcitabine 1 g/m^2 on days 1 and 8 + cisplatin 75 mg/m^2 on day 1 of a 21-day cycle) were administered intravenously for a maximum of 6 cycles

AE adverse event, *pts* patients

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

[a]Primary endpoint

[b]Conducted at the time of the primary overall survival analysis

56 weeks) in EuroQoL-5D health status self-assessment questionnaire and EuroQol EQ visual analogue scale scores [16].

In a post hoc analysis of the patients (19 of 160; i.e. 12%) who remained on afatinib for ≥ 3 years (i.e. long-term responders), the ORR was 89% and there were too few deaths during the follow-up (median 42.1 months) for median OS to be calculated. Baseline characteristics of these patients were generally consistent with those of the overall trial population, although numerically more of the long-term responders had Del19 [27].

Compared with chemotherapy

First-line treatment with afatinib prolonged PFS to a significantly greater extent than pemetrexed + cisplatin [17] or gemcitabine + cisplatin [18] in the LUX-Lung 3 [17] and 6 [18] trials (primary endpoint; Table 2). The ORR was also significantly ($p \leq 0.001$) higher with afatinib than with pemetrexed + cisplatin (56 vs 23%) [17] or gemcitabine + cisplatin (67 vs 23%) [18], with the median duration of response of 11.1 versus 5.5 months with afatinib and pemetrexed + cisplatin in LUX-Lung 3 [17], and 9.7 versus 4.3 with afatinib and gemcitabine + cisplatin in LUX-Lung 6 [18]. The median duration of OS did not significantly differ between afatinib and either comparator regimen (Table 2) [28].

In subgroup analyses of these trials, PFS generally favoured afatinib over chemotherapy across various patient subgroups, including ethnic origin [17], sex [17, 18], age (< 65 or ≥ 65 years) [17, 18] and ECOG PS [17, 18]. Similarly, patients with common EGFR mutations (i.e. Del19 or Leu858Arg) had significantly ($p \leq 0.001$) longer median PFS with afatinib than with chemotherapy in both LUX-Lung 3 (13.6 vs 6.9 months) [17] and LUX-Lung 6 (11.0 vs 5.6 months) [18] in prespecified analyses.

Further prespecified analyses of each trial found that median OS significantly favoured afatinib versus

chemotherapy in patients with Del19, whereas no significant BGD was evident in patients with Leu858Arg (Table 2), with these findings corroborated by an exploratory pooled analysis of the studies [28]. Several subgroup analyses were consistent with these findings, including a prespecified analysis of Japanese patients from LUX-Lung 3 [29], an analysis of non-Asian patients from LUX-Lung 3 [28] and an exploratory pooled analysis of Asian patients from LUX-Lung 3 and 6 [30]. Afatinib also provided significant ($p < 0.01$) OS benefit over chemotherapy in patients aged ≥ 65 years with Del19 in LUX-Lung 3, but not LUX-Lung 6 [31].

According to a prespecified analysis of patients with asymptomatic brain metastases and common EGFR mutations (35 patients from LUX-Lung 3 and 46 patients from LUX-Lung 6), results were generally consistent with the overall trial findings, although the difference in median PFS between afatinib and pemetrexed + cisplatin (11.1 vs 5.4 months) or gemcitabine + cisplatin (8.2 vs 4.7 months) did not reach statistical significance, most likely due to the small sample sizes [32]. However, in a post hoc pooled analysis, median PFS was significantly longer with afatinib than with chemotherapy in this patient population (8.2 vs 5.4 months; $p = 0.0297$). No significant difference in OS was seen between afatinib and chemotherapy in the individual or pooled analyses [32].

The efficacy of afatinib has also been assessed in patients with uncommon EGFR mutations ($n = 75$) in a pooled post hoc analysis [33] of LUX-Lung 2 (a non-comparative phase 2 trial) [34], LUX-Lung 3 [17] and LUX-Lung 6 [18]. Afatinib appeared more active in patients with point mutations and/or deletions in exons 18–21 (commonly Gly719Xaa alone, Leu861Gln alone and Gly719Xaa + either Ser768Ile or Leu861Gln) than in patients with de novo Thr790Met mutations in exon 20 (alone or with other mutations) or exon 20 insertions. The respective mutation groups had median PFS durations of 10.7, 2.9 and 2.7 months and median OS durations of 19.4, 14.9 and 9.2 months [33].

Median PFS did not significantly differ between patients whose afatinib dosage was reduced to 30 mg once daily because of treatment-related adverse events (TRAEs) during the first 6 months of therapy 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 [35]. In LUX-Lung 3 and 6, dosage reductions occurred in 53 and 28% of afatinib recipients, with > 80% of reductions occurring in the first 6 months of treatment [35].

In terms of 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 afatinib than chemotherapy recipients had improvements in dyspnoea in LUX-Lung 3 [36], and in dyspnoea, cough and pain in LUX-Lung 6 [18]. In a longitudinal analysis of LUX-Lung 3, significantly ($p < 0.01$) better scores for global health status/quality of life and physical, role and cognitive functioning were seen with afatinib versus chemotherapy [36]. 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 [37].

Among long-term afatinib responders in LUX-Lung 3 ($n = 24$ of 229; i.e. 10%) and 6 ($n = 23$ of 239; i.e. 10%), the ORR was 71 and 78% and the median OS could not be calculated as too few deaths occurred during the follow-up period (median 64.6 and 57.0 months) [27]. Baseline characteristics of these patients were generally consistent with those of the overall trial populations, although numerically more long responders were women and had Del19 [27].

In the real-world setting

Various studies (of retrospective design, where specified [19, 20]) have confirmed the efficacy of afatinib in the first-line treatment of advanced EGFR$^{actMUT+}$ NSCLC in clinical practice [19–21]. Of these, comprehensive data are available from a Taiwanese cohort study in which 67.2% of the 140 afatinib recipients achieved a partial response, 26.4% stable disease and 6.4% progressive disease [19]. The median PFS was 11.8 months overall, but was significantly ($p < 0.05$) shorter in patients with brain metastases or > 10% pretreatment weight loss than in patients without these characteristics. Outcomes were not significantly affected by the dosage of afatinib in the first 6 months of treatment (81 patients received 40 mg and 59 received < 40 mg) or by the type of EGFR mutation [i.e. classical (Del19 and/or Leu858Arg), classical + complex (e.g. Leu858Arg + Thr790Met), or rare (e.g. G719A) ± complex mutation] [19].

Among the other studies, a South Korean analysis ($n = 165$) found that median PFS (19.1 months overall) differed significantly ($p = 0.01$) by EGFR mutation type (19.1 months for Del19, 15.8 months for Leu858Arg, 4.7 months for Thr790Met and 'not reached' for uncommon mutations); nost patients with non-irradiated brain metastases (75.9% of 29) responded significantly to treatment [21]. Moreover, in a Taiwanese study (in which 95.7% of the 467 patients were EGFR TKI naïve), TTF did not significantly differ across afatinib, gefitinib and erlotinib overall (12.2, 9.8 and 11.4 months, respectively), although it significantly favoured afatinib versus gefitinib specifically ($p = 0.035$) [20]. TTF with afatinib, gefitinib and erlotinib was 12.2, 9.4 and 12.0 months, respectively,

in patients with Del19, 11.7, 10.4 and 10.9 months in patients with Leu858Arg and 19.7, 7.5 and 7.0 months in patients with uncommon EGFR mutations, with no significant differences across the regimens in any of the mutation subgroups [20].

First-line use of afatinib is further supported by an interim analysis of a noncomparative phase 3b Asian trial conducted in a broad population of patients with EGFR TKI-naïve advanced $EGFR^{actMUT+}$ NSCLC (60% of whom had received no prior chemotherapy). The median PFS was 12.1 months and the median time to symptomatic disease progression was 15.3 months in the 479 patients treated with afatinib 40 mg/day [22]. Values for the respective outcomes were 12.6 and 15.8 months in patients with common EGFR mutations and 9.1 and 10.0 months in patients with only uncommon EGFR mutations [22].

What is the clinical efficacy of second-line afatinib in 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 [15]. Eligible patients had stage IIIB or IV disease, disease progression following first-line platinum-based doublet chemotherapy (≥ 4 cycles), life expectancy of ≈ 4 months if left untreated, an ECOG PS of 0 or 1, measurable disease and adequate organ function.

In this trial, afatinib prolonged PFS (primary endpoint) and OS to a significantly greater extent than erlotinib, with Kaplan-Meier estimates of the 6-, 12- and 18-month OS rate all significantly favouring the afatinib group (Table 3) [15]. The ORR did not significantly differ between afatinib and erlotinib (6 vs 3%), with a median duration of response of 7.3 and 3.7 months in the corresponding treatment groups. However, the disease control rate was significantly higher with afatinib than with erlotinib (51 vs 40%; $p = 0.002$) [15].

In prespecified analyses, afatinib was more favourable than erlotinib in terms of both PFS and OS across various patient subgroups (including ethnic origin, sex, best response to first-line chemotherapy, age < 65 or ≥ 65 -years, histology, ECOG PS) [15]. Retrospective analysis of archival tissue from 238 patients found only 6% of afatinib or erlotinib recipients had EGFR mutations and 6% had EGFR amplification, suggesting that outcomes were unlikely driven by molecular aberrations of EGFR [15].

HR-QOL (assessed using QLQ-C30 and QLQ-LC13) improved in significantly more afatinib than erlotinib recipients (36 vs 28% of patients; $p = 0.041$) [15]. Significantly ($p = 0.029$) more patients receiving afatinib than erlotinib had improved cough, with no significant BGDs in the proportions of patients with improved dyspnoea or pain. 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 BGD in the median times to deterioration of pain (2.5 vs 2.4 months) or cough (4.5 vs 3.7 months) [15].

Long-term responders to afatinib ($n = 15$) had baseline characteristics consistent with those of the overall trial population and had a median PFS and OS of 16.2 and 23.1 months [38].

Table 3 Efficacy of oral afatinib in the second-line treatment of advanced squamous non-small cell lung cancer in LUX-Lung 8 [15]

Outcomes	Results: afatinib vs erlotinib [hazard ratio (95% CI)]
No. of pts	398 vs 397
Median progression-free survival	
Primary analysis (primary endpoint)	2.4* vs 1.9 months [0.82 (0.68–1.00)]
Updated analysis (conducted at the time of primary overall survival analysis)	2.6* vs 1.9 months [0.81 (0.69–0.96)]
Median overall survival (primary overall survival analysis)	7.9** vs 6.8 months [0.81 (0.69–0.95)]
Kaplan–Meier overall survival rate estimates	
6 months	63.6** vs 54.6% of pts
12 months	36.4* vs 28.2% of pts
18 months	22.0* vs 14.4% of pts
Objective response rate	6 vs 3% of pts
Disease control rate	51** vs 40% of pts

Initial dosage of afatinib (40 mg once daily) could be increased to 50 mg once daily after the first 28 days of treatment in the absence of rash, diarrhoea, mucositis or other grade > 1 treatment-related AEs. If treatment-related grade ≥ 3 AEs or selected prolonged grade 2 AEs occurred, dosage could be decreased to 20 mg once daily (after treatment interruption and recovery to grade ≤ 1). The dosage of erlotinib was 150 mg once daily, with dosage reductions permitted for AEs

AE adverse event, *pts* patients

*$p < 0.05$, ** $p < 0.01$ vs erlotinib

What is the tolerability profile of afatinib?

Oral afatinib has a predictable, manageable tolerability profile in patients with advanced NSCLC. Where specified, TRAEs (all grades) were reported in 93–99% of afatinib recipients versus 96% of gefitinib recipients in LUX-Lung 7 [16], 81% of erlotinib recipients in LUX-Lung 8 [15] and 99% of gemcitabine + cisplatin recipients in LUX-Lung 6 [18]. Across LUX-Lung 3, 6, 7 and 8, the most commonly reported TRAEs (all grades) in afatinib recipients were diarrhoea (70–95% of patients), rash/acne (67–89%) and stomatitis/mucositis (29–72%) [15–18]. Among afatinib recipients, dose reductions because of AEs occurred in 27–42% of patients [15, 16] and discontinuation because of TRAEs (most commonly diarrhoea [16, 17] and paronychia [17]) in 6–8% of patients [16–18].

In comparisons between EGFR TKIs, grade 3 or 4 TRAEs were reported in 31% of afatinib recipients and 18% of gefitinib recipients in LUX-Lung 7 [16], and in 27% of afatinib recipients and 17% of erlotinib recipients in LUX-Lung 8 [15]. The most frequent (incidence > 5%) TRAEs 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 ALT or AST levels (0 vs 9%) [16], and with second-line afatinib or erlotinib in LUX-Lung 8 were diarrhoea (10 vs 3%) and rash/acne (6 vs 10%) [15].

In comparisons with chemotherapy, grade ≥ 3 TRAEs were reported in 49% of afatinib and 48% of pemetrexed + cisplatin recipients in LUX-Lung 3 [17] and in 36% of afatinib and 60% of gemcitabine + cisplatin recipients in LUX-Lung 6 [18]. The most frequent (incidence > 5%) TREAs with first-line afatinib or pemetrexed + 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%) [17]. In LUX-Lung 6, the most frequent (incidence ≥ 5%) TREAs with first-line afatinib or gemcitabine + 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%) [18].

Serious TRAEs occurred in 11% of afatinib and 4% of gefitinib recipients in LUX-Lung 7 [16], 12% of afatinib and 6% of erlotinib recipients in LUX-Lung 8 [15], and 6% of afatinib and 8% of gemcitabine + cisplatin recipients in LUX-Lung 6 [18]. Across these trials, the serious TRAEs included diarrhoea, dehydration, acute renal failure, rash/acne and interstitial lung disease (ILD) with the EGFR TKIs and thrombocytopenia with the chemotherapy. Of note, in the afatinib clinical trial programme, there have been cases of diarrhoea resulting in dehydration with or without renal impairment, including (albeit rarely) fatal cases [6, 7].

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 [7], keratitis was reported in 0.7% [7], ILD or ILD-like AEs (e.g. lung infiltration, pneumonitis, acute respiratory distress syndrome) in 1.6% [6, 7] and liver function test abnormalities in 9.7%, of which 0.2% were fatal [7].

What is the current clinical position of afatinib?

The second-generation EGFR TKI afatinib has a well characterized tolerability profile and was shown in LUX-Lung 3, 6, 7 and 8 to be effective as both a first-line treatment for EGFR$^{actMUT+}$ advanced non-squamous NSCLC and a second-line treatment for advanced squamous NSCLC (regardless of EGFR mutation status) that has progressed following platinum-based chemotherapy.

When compared with gefitinib as a first-line treatment for advanced EGFR$^{actMUT+}$ lung adenocarcinoma in LUX-Lung 7, afatinib was more effective in prolonging PFS and TTF (perhaps reflecting the broader inhibitory profile of afatinib and its potential to delay possible resistance mechanisms vs first-generation EGFR TKIs [16]), although provided no additional OS benefit. Similarly, compared with chemotherapy in this setting in LUX-Lung 3 and 6, afatinib prolonged PFS but not OS. However, an improvement in OS was seen with afatinib versus chemotherapy in the patients with Del19, but not in those with Leu858Arg, suggesting these two EGFR mutants may have distinct biological properties that result in differing responses to EGFR TKIs [39]. As a consequence of these findings, afatinib is among the agents recommended for the first-line treatment of advanced EGFR$^{actMUT+}$ non-squamous NSCLC in US [3] and EU [40] guidelines, with other options including the first-generation EGFR TKIs gefitinib [3, 40] and erlotinib [3, 40] and, more recently, the third-generation EGFR TKI osimertinib [3].

Osimertinib is active against EGFR TKI-activating mutations, as well as the exon 20 mutation Thr790Met, the acquisition of which is a common reason for resistance developing against afatinib and first-generation EGFR TKIs [40–44]. Consequently, osimertinib is approved in the EU [45] and USA [46] for the treatment of locally advanced [45] or metastatic [46] EGFR$^{Thr790Met+}$ NSCLC [45, 46] that has progressed on or after EGFR TKI therapy [46]. Use of osimertinib in this setting was approved

[45, 46], and recommended in current guidelines [3, 40], on the basis of the AURA trials. It was the encouraging findings of these studies that led to osimertinib being assessed as a first-line treatment for EGFR$^{actMUT+}$ NSCLC. In a phase 3 trial (FLAURA) in patients with previously untreated advanced EGFR$^{actMUT+}$ NSCLC, osimertinib significantly prolonged PFS versus first-generation EGFR TKI therapy and the OS data (although immature) were also promising [47]. The US guideline [3] recommendation for first-line osimertinib use is based on the findings of this study, although exclusion of afatinib from its comparator arm was a key limitation of FLAURA and afatinib and osimertinib have not been compared in head-to-head trials.

It, therefore, remains to be determined what the most effective EGFR TKI treatment approach may be for advanced EGFR$^{actMUT+}$ NSCLC [48]. Use of a first/second-generation EGFR TKI followed by osimertinib is supported by 3-year OS rates of up to 90% in LUX-Lung 7 participants who received a third-generation EGFR TKI after failing first-line afatinib or gefitinib (post hoc analysis) [23]. This treatment approach is also supported by a pooled analysis of LUX-Lung 3, 6 and 7, in which prolonged OS was seen with osimertinib use after afatinib discontinuation (median OS not yet reached at time of analysis) [49].

The alternative approach (i.e. the first-line use of a third-generation EGFR TKI, such as osimertinib) is supported by the results of FLAURA [47, 50]. There are hopes that early use of such agents may prevent/delay resistance developing [50], with separation of the PFS Kaplan–Meier curves for osimertinib and first-generation EGFR TKIs at 6 weeks in FLAURA possibly corroborating this theory [47]. However, unlike afatinib and first-generation EGFR TKIs, mechanisms of acquired resistance to first-line osimertinib are not yet fully established [47, 50], and in vitro data suggest that acquired resistance to a third-generation EGFR TKI may confer resistance to EGFR TKIs of all generations [51]. Whether such cross resistance may occur in the clinical setting is unclear, although could potentially limit treatment options after first-line osimertinib failure [50] [which currently include osimertinib continuation, local therapy or (if there are multiple symptomatic lesions) cytotoxic therapy [3]]. Using osimertinib subsequent to first/second-generation EGFR TKIs instead, may therefore delay the need for cytotoxic chemotherapy regimens in some patients.

Data from trials such as APPLE, which is designed to assess the best approach/sequence for gefitinib and osimertinib use [52], are, therefore, awaited with interest. Notably, in the EU, approval of afatinib in EGFR TKI-naïve patients with EGFR$^{actMUT+}$ advanced NSCLC is not restricted to first-line use on the basis of LUX-Lung 2, a trial in which EGFR TKI-naïve patients (who were treatment naïve or had received one prior chemotherapy regimen for advanced disease) had ORRs of 66 and 57% with first- and second-line afatinib [34].

For the second- or subsequent-line treatment of advanced squamous NSCLC, options recommended in US [3] and/or EU [40] guidelines include the immune checkpoint inhibitors nivolumab [3, 40], pembrolizumab [3, 40] and atezolizumab [3], the anti-vascular endothelial growth factor receptor 2 antibody ramucirumab (with [3, 40] or without [3], docetaxel) and the EGFR TKIs afatinib and erlotinib [40]. Afatinib was approved for use in this setting on the basis of LUX-Lung 8, in which afatinib prolonged PFS and OS relative to erlotinib in patients with advanced squamous NSCLC that had progressed after first-line platinum-based chemotherapy. Although US guidelines do not currently recommend any EGFR TKIs as subsequent therapy in squamous NSCLC [3], 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]. Methods of assessing which patients may benefit the most from receiving afatinib in this setting are currently being investigated [53, 54].

Acknowledgements The manuscript was updated from *Targeted Oncology* 2016;11(6):825–35 [55], and was reviewed by: *M. Hochmair*, Respiratory Oncology Unit, Department of Respiratory and Critical Care Medicine, Otto-Wagner-Spital, Vienna, Austria; *A. Morabito,* Thoracic Medical Oncology, Istituto Nazionale Tumori, "Fondazione G. Pascale"-IRCCS, Naples, Italy. During the peer review process, Boehringer Ingelheim Pharmaceuticals, Inc. provided a scientific accuracy review of their data at the request of the journal editor. Changes resulting from comments received were made on the basis of scientific and editorial merit.

Compliance with ethical standards

Funding The preparation of this review was not supported by any external funding.

Conflict of interest E. D. Deeks and G. M. Keating are employees of Adis/Springer, are responsible for the article content and declare no conflicts of interest.
Additional information about this Adis Drug Review can be found at http://www.medengine.com/Redeem/C10DF0600A95D8F5.

References

1. Hall PE, Spicer J, Popat S. Rationale for targeting the ErbB family of receptors in patients with advanced squamous cell carcinoma of the lung. Future Oncol. 2015;11(15):2175–91.

2. Modjtahedi H, Cho BC, Michel MC, et al. A comprehensive review of the preclinical efficacy profile of the ErbB family blocker afatinib in cancer. Naunyn Schmiedebergs Arch Pharmacol. 2014;387(6):505–21.
3. National Comprehensive Cancer Network®. Clinical practice guidelines in oncology (NCCN Guidelines®): non-small cell lung cancer (version 1.2018). Fort Washington: National Comprehensive Cancer Network®, Inc.; 2017.
4. Cancer Genome Atlas Research Network. Comprehensive genomic characterization of squamous cell lung cancers. Nature. 2012;489(7417):519–25.
5. Li D, Ambrogio L, Shimamura T, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. Oncogene. 2008;27(34):4702–11.
6. Giotrif (afatinib) film-coated tablets: EU summary of product characteristics. London: European Medicines Agency; 2017.
7. Gilotrif (afatinib) tablets, for oral use: US prescribing information. Ridgefield: Boehringer Ingelheim Pharmaceuticals, Inc.; 2018.
8. 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(2):342–50.
9. Chen G, Kronenberger P, Teugels E, et al. Targeting the epidermal growth factor receptor in non-small cell lung cancer cells: the effect of combining RNA interference with tyrosine kinase inhibitors or cetuximab. BMC Med. 2012;10:28.
10. Takezawa K, Okamoto I, Tanizaki J, et al. Enhanced anticancer effect of the combination of BIBW2992 and thymidylate synthase-targeted agents in non-small cell lung cancer with the T790M mutation of epidermal growth factor receptor. Mol Cancer Ther. 2010;9(6):1647–56.
11. Suzawa K, Toyooka S, Sakaguchi M, et al. Antitumor effect of afatinib, as a human epidermal growth factor receptor 2-targeted therapy, in lung cancers harboring *HER2* oncogene alterations. Cancer Sci. 2016;107(1):45–52.
12. Furuyama K, Harada T, Iwama E, et al. Sensitivity and kinase activity of epidermal growth factor receptor (EGFR) exon 19 and others to EGFR-tyrosine kinase inhibitors. Cancer Sci. 2013;104(5):584–9.
13. Ninomiya T, Takigawa N, Ichihara E, et al. Afatinib prolongs survival compared with gefitinib in an epidermal growth factor receptor-driven lung cancer model. Mol Cancer Ther. 2013;12(5):589–97.
14. Giotrif (afatinib): extension of indication variation assessment report. London: European Medicines Agency; 2016.
15. Soria J-C, Felip E, Cobo M, et al. 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. Lancet Oncol. 2015;16(8):897–907.
16. Park K, Tan E-H, O'Byrne K, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol. 2016;17(5):577–89.
17. Sequist LV, Yang JC-H, 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(27):3327–34.
18. Wu Y-L, Zhou C, Hu C-P, 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(2):213–22.
19. Liang SK, Hsieh MS, Lee MR, et al. Real-world experience of afatinib as a first-line therapy for advanced *EGFR* mutation-positive lung adenocarcinoma. Oncotarget. 2017;8(52):90430–43.
20. Tu C, Chen C, Hsia T, et al. Taiwan real world efficacy of 1st line EGFR TKIs treatment in EGFR mutation positive advanced non small cell lung cancer [abstract no. P1.03-053]. In: IASLC 18th World Conference on Lung Cancer.
21. Kim Y, Sun J, Park K, et al. First-line afatinib for non-small cell lung cancer in real world practice [abstract no. P3.01-023]. In: IASLC 18th World Conference on Lung Cancer. 2017.
22. Wu Y, Tu H, Feng J, et al. A Phase IIIb open-label, single-arm study of afatinib in EGFR TKI-naive patients with EGFRm + NSCLC: an interim analysis [abstract no. P3.01-036]. J Thorac Oncol. 2017;12(11 Suppl 2):S2214.
23. Paz-Ares L, Tan EH, O'Byrne K, et al. Afatinib versus gefitinib in patients with *EGFR* mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial. Ann Oncol. 2017;28(2):270–7.
24. Corral J, Park K, Yang JC, et al. Afatinib (A) vs gefitinib (G) in patients with EGFR mutation-positive (*EGFR*m+) NSCLC: updated OS data from the phase IIb trial LUX-Lung 7 (LL7) [abstract no. 93PD + poster]. Ann Oncol. 2017;28(Suppl 2):ii28–ii51.
25. Park K, Tan EH, Zhang L, et al. Afatinib versus gefitinib as first-line treatment for EGFR mutation-positive NSCLC patients aged ≥ 75 years: subgroup analysis of LUX-Lung 7 [abstract no. P3.02b-044]. J Thorac Oncol. 2017;12(1 Suppl):S1214.
26. Hirsh V, Yang JC-H, Tan E-H, et al. First-line afatinib (A) vs gefitinib (G) for patients (pts) with EGFR mutation positive (EGFRm+) NSCLC (LUX-Lung 7): patient-reported outcomes (PROs) and impact of dose modifications on efficacy and adverse events (AEs) [abstract no. 9046]. J Clin Oncol. 2016;34(15_suppl):9046.
27. Schuler M, Paz-Ares L, Sequist LV, et al. First-line afatinib in patients with *EGFR* mutation-positive (*EGFR*m+) non-small-cell lung cancer (NSCLC): analysis of long-term responders (LTRs) in the LUX-Lung 3, 6 and 7 trials [abstract no. P594]. Oncol Res Treatment. 2017;40(Suppl 3):172.
28. Yang JC-H, Wu Y-L, 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(2):141–51.
29. Kato T, Yoshioka H, Okamoto I, et al. Afatinib versus cisplatin plus pemetrexed in Japanese patients with advanced non-small cell lung cancer harboring activating *EGFR* mutations: subgroup analysis of LUX-Lung 3. Cancer Sci. 2015;106(9):1202–11.
30. Wu Y-L, Sequist LV, Hu C-P, et al. Overall survival (OS) in Asian patients with advanced non-small cell lung cancer (NSCLC) harboring common (Del19/L858R) epidermal growth factor receptor (EGFR) mutations: combined analysis of two large open-label phase III studies (LUX-Lung 3 [LL3] and LUX-Lung 6 [LL6]) comparing afatinib with chemotherapy [abstract plus slide presentation]. In: 6th Asia Pacific Lung Cancer Conference. 2014.
31. Fein L, Wu YL, Sequist LV, et al. Afatinib versus chemotherapy for EGFR mutation-positive NSCLC patients aged ≥65 years: subgroup analysis of LUX-Lung 3/6 [abstract no. P1.33]. J Thorac Oncol. 2016;11(10 Suppl):S202–S203.
32. Schuler M, Wu Y-L, Hirsh V, et al. First-line afatinib versus chemotherapy in patients with non-small cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases. J Thorac Oncol. 2016;11(3):380–90.
33. Yang JC-H, Sequist LV, Geater SL, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. Lancet Oncol. 2015;16(7):830–8.

34. Yang JC-H, Shih J-Y, Su W-C, et al. Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial. Lancet Oncol. 2012;13(5):539–48.
35. Yang JC-H, Sequist LV, Zhou C, et al. Effect of dose adjustment on the safety and efficacy of afatinib for *EGFR* mutation-positive lung adenocarcinoma: post hoc analyses of the randomized LUX-Lung 3 and 6 trials. Ann Oncol. 2016;27(11):2103–10.
36. Yang JC-H, Hirsh V, Schuler M, et al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with *EGFR* mutations. J Clin Oncol. 2013;31(27):3342–50.
37. Geater SL, Xu C-R, Zhou C, et al. Symptom and quality of life improvement in LUX-Lung 6: an open-label phase III study of afatinib versus cisplatin/gemcitabine in Asian patients with EGFR mutation-positive advanced non-small-cell lung cancer. J Thorac Oncol. 2015;10(6):883–9.
38. Goss G, Cobo M, Lu S, et al. Second-line afatinib for advanced squamous cell carcinoma of the lung: analysis of afatinib long-term responders in the phase III LUX-Lung 8 trial [abstract no. OA23.03]. J Thorac Oncol. 2017;12(1 Suppl):S334–S335.
39. Giordano P, Manzo A, Montanino A, et al. Afatinib: an overview of its clinical development in non-small-cell lung cancer and other tumors. Crit Rev Oncol Hematol. 2016;97:143–51.
40. Novello S, Barlesi F, Califano R, et al. Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(Suppl 5):v1–v27.
41. Levy BP, Rao P, Becker DJ, et al. Attacking a moving target: understanding resistance and managing progression in EGFR-positive lung cancer patients treated with tyrosine kinase inhibitors. Oncology. 2016;30(7):601–12.
42. Wu S-G, Liu Y-N, Tsai M-F, et al. The mechanism of acquired resistance to irreversible EGFR tyrosine kinase inhibitor-afatinib in lung adenocarcinoma patients. Oncotarget. 2016;7(11):12404–13.
43. Tanaka K, Nosaki K, Otsubo K, et al. Acquisition of the T790M resistance mutation during afatinib treatment in EGFR tyrosine kinase inhibitor-naïve patients with non-small cell lung cancer harboring *EGFR* mutations. Oncotarget. 2017;8(40):68123–30.
44. Hochmair MJ, Schwab S, Burghuber O, et al. Prevalence of *EGFR* T790M mutation in NSCLC patients after afatinib failure, and subsequent response to osimertinib [abstract no. P2.03-025 + poster]. In: IASLC18th World Conference on Lung Cancer. 2017.
45. Tagrisso (osimertinib): EU summary of product characteristics. London: European Medicines Agency; 2017.
46. Tagrisso™ (osimertinib) tablets for oral use: US prescribing information. Wilmington: AstraZeneca Pharmaceuticals LP; 2017.
47. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated *EGFR*-mutated advanced non-small-cell lung cancer. N Engl J Med. 2018;378(2):113–25.
48. Juan O, Popat S. Treatment choice in epidermal growth factor receptor mutation-positive non-small cell lung carcinoma: latest evidence and clinical implications. Ther Adv Med Oncol. 2017;9(3):201–16.
49. Sequist L, Wu YL, Schuler M, et al. Subsequent therapies post-afatinib among patients with *EGFR* mutation-positive NSCLC in LUX-Lung 3, 6 and 7 [poster no. 1349]. In: European Society for Medical Oncology Congress. 2017.
50. Sun JM, Park K. Can we define the optimal sequence of epidermal growth factor receptor tyrosine kinase inhibitors for the treatment of epidermal growth factor receptor-mutant nonsmall cell lung cancer? Curr Opin Oncol. 2017;29(2):89–96.
51. Park JH, Choi YJ, Kim SY, et al. Activation of the IGF1R pathway potentially mediates acquired resistance to mutant-selective 3rd-generation EGF receptor tyrosine kinase inhibitors in advanced non-small cell lung cancer. Oncotarget. 2016;7(16):22005–15.
52. Remon J, Menis J, Hasan B, et al. The APPLE trial: feasibility and activity of AZD9291 (osimertinib) treatment on positive plasma *T790 M* in *EGFR*-mutant NSCLC patients. EORTC 1613. Clin Lung Cancer. 2017;18(5):583–8.
53. Gadgeel S, Goss G, Soria JC, et al. Evaluation of the VeriStrat® serum protein test in patients with advanced squamous cell carcinoma of the lung treated with second-line afatinib or erlotinib in the phase III LUX-Lung 8 study. Lung Cancer. 2017;109:101–8.
54. Goss G, Felip E, Cobo M, et al. Impact of ErbB mutations on clinical outcomes in afatinib- or erlotinib-treated patients with SCC of the lung [abstract no. P3.01-043]. In: IASLC 18th World Conference on Lung Cancer. 2017.
55. Keating GM. Afatinib: a review in advanced non-small cell lung cancer. Targ Oncol. 2016;11(6):825–35.