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Irreversible tyrosine kinase inhibition of epidermal growth factor receptor with afatinib in *EGFR* activating mutation–positive advanced non-small-cell lung cancer

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ABSTRACT

Despite recent advances in the systemic therapy of non-small-cell lung cancer (NSCLC), the prognosis for stage IV disease remains poor. The discovery of targetable mutations has led to new treatment options. The most common mutations, the *EGFR* activating mutations, are present in about 50% of Asian patients and up to 15% of white patients. First-generation reversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have led to improved survival in patients positive for *EGFR* activating mutations, but resistance eventually leads to disease progression. The irreversible EGFR TKI afatinib was developed to counter such resistance. The clinical efficacy of afatinib has been shown in first-line studies comparing it with both cytotoxic chemotherapy and first-generation EGFR TKIs. Afatinib has also shown continued benefit beyond progression while a patient is taking an EGFR inhibitor. Furthermore, its toxicity profile is both predictable and manageable. The results of the principal clinical trials assessing afatinib are reviewed here.

Key Words Non-small-cell lung cancer, NSCLC, epidermal growth factor receptor, EGFR, tyrosine kinase inhibitors, TKIs, afatinib

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INTRODUCTION

In oncology, few treatment landscapes have changed as dramatically over the last several decades as that for non-small-cell lung cancer (NSCLC). The changes were certainly welcomed, considering the difficult reality of treating NSCLC.

Of all lung cancer cases, approximately 80% are NSCLC, and the disease often presents at an advanced stage. At least 50% of patients have stage IV disease at diagnosis. Even patients diagnosed in the early stages and treated with curative-intent surgical resection are likely to experience recurrence. Unfortunately, 60%–75% of stage I–II patients eventually develop metastatic disease[1,2]. For those reasons, new treatment options for patients with stage IV disease were needed. Although the standard first-line option of platinum-based chemotherapy did lead to improvements in survival, the tolerability of chemotherapy with respect to disease-related symptoms and quality of life (QOL) remained poor[3]. The focus of lung cancer treatment shifted significantly with the identification of specific targetable driver mutations[4].

Knowledge about the driver mutations in NSCLC, particularly in lung cancer of adenocarcinoma histology, is continually evolving. In addition to the classical targets of *EGFR* activating mutations and *ALK* rearrangements, *ROS1, BRAF, MET* skip, and *RET* mutations now also have viable treatment options[4–10].

The epidermal growth factor receptor (EGFR), a tyrosine kinase receptor protein, and its ligand, epidermal growth factor, were initially described in 1957 by Cohen and Levi-Montalcini[11]. Over time, as the link between EGFR overexpression and cancer became more evident, the interest in studying EGFR grew[12,13]. The epidermal growth factor receptor is a member of the ErbB or HER (human epidermal growth factor receptor) protein kinase family, whose four closely structurally related members are EGFR (also known as ErbB1 or HER1), ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4)[13,14].

In normal cells, the ErbB protein kinases[13] are involved in the regulation of cellular proliferation, among other

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functions. A variety of cancers, including NSCLC, have been demonstrated to be associated with abnormal signalling through ErbB pathways[13,14]. Those associations can be observed in NSCLC patients with somatic *EGFR* mutations that lead to aberrant constitutive signalling by EGFR and its associated cell signalling pathways, which in turn leads to uncontrolled proliferation of the abnormal cells. Cancers overexpressing EGFR can also become completely dependent on EGFR signalling, a phenomenon known as "oncogene addiction." In that event, inhibition of EGFR interrupts proliferation and induces apoptosis[15].

Oncogenic mutations of *EGFR* in NSCLC are present almost exclusively in cancers of adenocarcinoma histology[16]. They are also significantly more frequent in Asian patients (50% compared with 10%–15% in white patients)[16] and in women and never-smokers[17,18]. Several *EGFR* activating mutations are known, and their effect on both prognosis and potential response to therapy can vary considerably. The most common *EGFR* activating mutations include exon 19 deletions (Del19) and a Leu858Arg point mutation (L858R)[19].

Targeting the EGFR tyrosine kinase with oral tyrosine kinase inhibitors (TKIs) against EGFR has demonstrated significant clinical benefit in NSCLC patients with *EGFR* activating mutations. The first-generation EGFR TKIs gefitinib and erlotinib bind reversibly to the kinase domain of the receptor, leading to its inhibition[20]. In several randomized phase III trials, gefitinib and erlotinib, compared with chemotherapy consisting of platinum doublets, both led to increased progression-free survival (PFS) and response rates in *EGFR*-positive NSCLC[21–27]. The IPASS study demonstrated a significant median PFS advantage of 9.5 months in favour of gefitinib compared with 6.3 months for a standard chemotherapy regimen of carboplatin–paclitaxel [hazard ratio (HR): 0.48; $p < 0.001$][24]. Erlotinib was studied in two first-line phase III trials. The OPTIMAL study, which was completed in China, compared erlotinib with carboplatin–gemcitabine. A PFS benefit was shown in the erlotinib arm (median: 13.1 months vs. 4.6 months in the chemotherapy arm; HR: 0.16; $p < 0.001$)[27,28]. Similar results for erlotinib were shown in a European population, in whom the EURTAC trial demonstrated a median PFS of 9.7 months for erlotinib compared with 5.2 months for platinum-doublet chemotherapy (HR: 0.37; $p < 0.0001$)[25]. It should be noted, however, that despite clear improvements in PFS and response, overall survival (OS) was not shown to be improved with targeted agents[21,23,28–30]. That lack of improvement is believed to be a result, in large part, of the nearly inevitable development of acquired resistance to first-generation EGFR TKIs[31].

To prevent the acquired resistance mechanisms that hinder the long-term efficacy of gefitinib and erlotinib, second-generation EGFR TKIs with increased potency against their EGFR targets were developed. Second-generation EGFR TKIs form covalent bonds with receptors and therefore lead to irreversible inhibition of the pathway[32]. Although the second-generation EGFR TKI dacomitinib failed to demonstrate significant clinical benefit in phase III trials[33–36], another second-generation EGFR TKI, afatinib, is now well established as an effective treatment option in *EGFR*-positive NSCLC.

MECHANISM OF ACTION OF AFATINIB

Afatinib has affinity for three of the four ErbB family members: EGFR, HER2, and HER4. It functions by forming covalent bonds with tyrosine kinase receptors, thus leading to irreversible inhibition[32]. The inhibition of signal transduction then occurs because of reduced autophosphorylation and transphosphorylation within the tyrosine kinase dimers of the ErbB receptors. The fourth receptor in the family, HER3, does not have intrinsic activity. Its activity in the EGFR pathway comes from interaction with other ErbB family members, mainly HER2. The interactions between HER3 and its family members lead to the formation of active heterodimers[37]. In effect, afatinib inhibits the downstream signalling activity of the entire ErbB protein kinase family[32].

Afatinib Compared with Platinum-Doublet Chemotherapy as a First-Line Option in *EGFR*-Positive NSCLC

Two large open-label randomized phase III trials that were performed during overlapping time periods compared first-line afatinib with platinum-doublet chemotherapy in pathologically confirmed advanced lung adenocarcinoma harboring *EGFR* activating mutations (Table I)[38]. The LUX-Lung 3 trial took place between August 2009 and February 2011, randomizing 345 patients from 25 countries in Asia, Europe, North America, South America, and Oceania[42]. A second LUX-Lung trial, LUX-Lung 6, took place between April 2010 and November 2011, randomizing 364 Asian patients from centres in China, Thailand, and South Korea. Both trials compared oral afatinib at a dose of 40 mg daily with platinum-doublet chemotherapy[44]. The comparator arm in LUX-Lung 3 was intravenous cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 given every 3 weeks for a maximum of 6 cycles. Maintenance pemetrexed was not permitted. Patients in the trial were stratified by *EGFR* mutation (Del19, L858R, or any other mutation) and by race (Asian and non-Asian). Because cisplatin–pemetrexed was not approved in several Asian countries at that time for first-line treatment, the LUX-Lung 6 trial was designed as a companion trial to LUX-Lung 3. It used intravenous cisplatin 75 mg/m^2 on day 1 and gemcitabine 1000 mg/m^2 on days 1 and 8 every 3 weeks for a maximum of 6 cycles[44]. As in LUX-Lung 3, patients were stratified by *EGFR* mutation.

The primary endpoint of both trials was PFS by independent review (Table I). In LUX-Lung 3, a HR of 0.58 demonstrated a statistically significant benefit for afatinib compared with cisplatin–pemetrexed ($p < 0.001$). Median PFS was 11.1 months for the afatinib group and 6.9 months for the cisplatin–pemetrexed group[42]. Afatinib also led to increased objective response rates (ORRs) by independent review, with a partial response being obtained in 56.1% of patients receiving afatinib compared with 22.6% of patients receiving chemotherapy ($p < 0.001$). Similarly, the median duration of response was also longer with afatinib: 11.1 months compared with 5.5 months with chemotherapy. No significant difference in OS was observed between the two groups, with a median OS of 28.2 months being reported in both groups (HR: 0.88; $p = 0.39$). At progression, a high degree of crossover occurred. Overall, 65% of chemotherapy

TABLE I Randomized trials assessing the activity of afatinib[a]

Reference (study name)	Location	Trial arms	Pts[b] (*n*)	RR (%)	Median PFS[b] (months)	PFS difference			Median OS (months)	OS difference					
						HR	95% CI	*p* Value		Overall			Del19 mutation		
										HR	95% CI	*p* Value	HR	95% CI	*p* Value
Jackman *et al.*, 2010[40],	Global	Afatinib	585[c]	7	2.83	0.38		<0.0001	10.8	1.08		0.74	NA		NS
Hirsh *et al.*, 2013[41] (LUX-Lung 1)		Best supportive care		<1	0.95[d]				12.0						
Sequist *et al.*, 2013[42],	Global	Afatinib	345	56	13.6	0.47	0.34 to 0.65	0.001	31.6	0.78	0.58 to 1.06	NS	0.54	0.36 to 0.79	0.0015
Yang *et al.*, 2015[43] (LUX-Lung 3)		Cisplatin–pemetrexed		23	6.9[e]				28.2[b]						
Wu *et al.*, 2014[44],	China,	Afatinib	364	67	11.0	0.28	0.20 to 0.39	<0.0001	23.6	0.83	0.62 to 1.09	NS	0.64	0.44 to 0.94	0.023
Yang *et al.*, 2015[43] (LUX-Lung 6)	South Korea	Cisplatin–gemcitabine		23	5.6[e]				23.5[b]						
Park *et al.*, 2016[45],	Global	Afatinib	319	70	11.0	0.73	0.57 to 0.95	0.0073	27.9	0.86	0.66 to 1.12	0.2580	0.83	0.58 to 1.17	0.2841
Paz-Ares *et al.*, 2016[46] (LUX-Lung 7)		Gefitinib		56	10.9[e]				24.5						

[a] Adapted from Hirsh, 2015 [39].
[b] In patients with common activating mutations (Del19 or L858R, or both).
[c] Patients with *EGFR* mutations were a subgroup of all enrolees.
[d] Based on investigator assessment.
[e] Based on independent central review.
Pts = patients; RR = response rate; PFS = progression-free survival; HR = hazard ratio; CI = confidence interval; OS = overall survival; NA = not available; NS = nonsignificant.

patients crossed over to an EGFR TKI, and 62% of patients on afatinib received chemotherapy at progression[42].

The results for the principal endpoints were similar in LUX-Lung 6 (Table I)[44]. The PFS by independent review was also improved in the afatinib arm compared with the cisplatin–gemcitabine arm (median: 11.0 months vs. 5.6 months; HR: 0.28; $p < 0.0001$). Patients receiving afatinib also experienced an improved ORR, with 66.9% responding compared with 23.0% of patients receiving chemotherapy ($p < 0.0001$). Duration of response was longer in the afatinib group [median: 9.7 months; 95% confidence interval (CI): 8.3 to 12.4 months] compared with the cisplatin–gemcitabine group (median: 4.3 months; 95% CI: 2.8 to 5.8 months). Again, no OS difference was found (HR: 0.93; $p = 0.61$) at a median of 23.1 months (95% CI: 20.4 to 27.3 months) for afatinib and 23.5 months (95% CI: 18.0 to 25.6 months) for chemotherapy[44].

A preplanned pooled analysis combined the results from LUX-Lung 3 and 6 to assess the effect of afatinib on OS[43]. The analyses were planned to obtain mature OS data in the intention-to-treat population after 209 deaths in LUX-Lung 3 and 237 deaths in LUX-Lung 6. Despite the mature data, no OS difference was observed in the combined analysis. The median OS was 25.8 months (95% CI: 23.1 to 29.3 months) in the afatinib group and 24.5 months (95% CI: 21.1 to 28.1 months) in the combined chemotherapy group (HR: 0.91; $p = 0.37$)[43].

In addition to mature OS data, the pooled analysis included planned analyses of survival data stratified by known *EGFR* mutations. When examining the OS data for patients with an *EGFR* Del19 mutation, a statistically significant advantage was observed in favour of afatinib (Table I)[43]. In the combined analysis, Del19-positive patients reached a median OS of 31.7 months (95% CI: 28.1 months to 35.1 months) when receiving afatinib and 20.7 months (95% CI: 16.3 months to 25.6 months) when receiving chemotherapy (HR: 0.59; $p = 0.0001$). That result differed from the results for patients with the other common *EGFR* activating mutation, L858R. In the combined analysis for L858R-positive patients, no benefit in OS was observed. Median OS was 22.1 months (95% CI: 19.6 months to 25.4 months) with afatinib and 26.9 months (95% CI: 23.3 months to 31.7 months) with chemotherapy (HR: 1.25; $p = 0.16$). In a subgroup analysis, an OS benefit appeared to be present in all patient subgroups positive for *EGFR* Del19 and was sustained in both Asian and non-Asian populations. The statistically significant OS benefit for afatinib in patients with an *EGFR* Del19 activating mutation proved to be the first time that an OS advantage compared with chemotherapy was demonstrated for an EGFR TKI[43].

In both the LUX-Lung 3 and 6 trials, QOL was evaluated using patient-reported outcomes (PROs) from comprehensive questionnaires, including the European Organization for Research and Treatment of Cancer 30-question Quality of Life Questionnaire (Table II). Lung cancer–related symptoms were also specifically addressed with the use of the 13-question Lung Cancer module for the Quality of Life Questionnaire[42,44,47]. That approach differs from the randomized phase III trials of the first-generation EGFR TKIs, which used only the Functional Assessment of Cancer Therapy indices (FACIT.org, Elmhurst, IL, U.S.A.) for gefitinib[24,29]. In the case of erlotinib, insufficient PRO data were collected for analysis[25]. In contrast, the LUX-Lung 3 trial achieved 85% patient compliance with PRO questionnaires[47,48].

In both of the foregoing LUX-Lung trials, the baseline symptom burden was low in the afatinib and platinum-doublet arms[42]. The QOL analyses demonstrated that the lung cancer–specific symptoms of cough and dyspnea were significantly improved with afatinib. A longer time to deterioration with afatinib was also demonstrated in both trials[42,47]. The symptom of pain was not improved in LUX-Lung 3; however, pain did significantly decrease, with a longer time to deterioration, in the afatinib group in LUX-Lung 6. Overall, significantly more patients experienced an improvement in global health-status QOL. In particular, the specific scales of physical functioning, role functioning, and cognitive functioning demonstrated a significant advantage for afatinib compared with chemotherapy in both LUX-Lung trials[42,44,47].

The toxicity profile of afatinib was similar in both the LUX-Lung 3 and 6 trials[42,47]. Adverse events (AEs) were predictable and led to few discontinuations. In LUX-Lung 3, 49% of patients in the afatinib arm and 48% in the cisplatin–pemetrexed arm presented treatment-related AEs of grade 3 or greater[42]. The toxicity profile appeared to favour afatinib significantly more in LUX-Lung 6 than in LUX-Lung 3. Grade 3 or greater AEs were reported in 36% of patients receiving afatinib compared with 60% of those receiving cisplatin–gemcitabine[44]. It is hypothesized that the more favourable AE profile in LUX-Lung 6 could be partly related to improved toxicity management by treating teams experienced with the AEs of EGFR TKIs[39]. Overall, the principal AEs encountered with afatinib were predictable and manageable. The 3 most common AEs connected to afatinib in both trials were diarrhea (grade 3 or greater toxicity: 15% in LUX-Lung 3 and 5% in LUX-Lung 6), rash or acne (grade 3 or greater toxicity: 16% in LUX-Lung 3 and 15% in LUX-Lung 6), and stomatitis or mucositis (grade 3 or greater toxicity: 9% in LUX-Lung 3 and 5% in LUX-Lung 6)[42,44,47].

In patients with advanced NSCLC with activating *EGFR* mutations, LUX-Lung 3 and 6 demonstrated improved ORR, PFS, and PROs with afatinib. For patients with Del19 mutations, an OS benefit for afatinib was shown in comparison with cisplatin-doublet chemotherapy in the first line[43,49]. Although afatinib was the first EGFR TKI to show an OS benefit, a head-to-head comparison would be required to determine whether afatinib or a first-generation EGFR TKI would yield the greatest clinical benefit in untreated patients.

Reversible Compared with Irreversible EGFR Inhibition in Untreated Patients with EGFR Activating Mutations

The exploratory phase IIB LUX-Lung 7 trial randomized patients at multiple centres in 13 countries[45]. The trial included untreated patients with unresectable (stages IIIB and IV) lung adenocarcinoma with either a Del19 or L858R *EGFR* activating mutation and good performance status (Eastern Cooperative Oncology Group 0 or 1). Patients were stratified based on mutation type and on the presence or absence of brain metastasis. This open-label trial randomly

TABLE II Patient-reported quality-of-life (QOL) outcome assessments in first-line *EGFR* mutation–positive clinical trials[a]

Reference (study name)	Study arms	Assessments	Time of completion	Outcomes
Mok *et al.*, 2009[24] (IPASS)	Gefitinib Carboplatin–paclitaxel	FACT-L, FACT-TOI	At randomization, week 1, every 3 weeks until day 127, once every 6 weeks from day 128 until disease progression, and when the study drug was discontinued	Significantly more patients in the gefitinib group than in the carboplatin–paclitaxel group experienced a clinically relevant improvement in QOL by scores on the FACT-TOI; rates of reduction in symptoms were similar
Park *et al.*, 2016[45], Paz-Ares *et al.*, 2016[46] (LUX-Lung 7)	Afatinib Gefitinib	EQ-5D, EQ-VAS	At baseline and every 8 weeks until progression	Afatinib maintained QOL; no statistical difference between the two agents was evident
Rosell *et al.*, 2012[25] (EURTAC)	Erlotinib Cisplatin–docetaxel or –gemcitabine	Completion of the Lung Cancer Symptom Scale	At baseline, every 3 weeks, end-of-treatment visit, and every 3 months during follow-up	Because of low compliance, data collected were insufficient for any analysis to be completed
Sequist *et al.*, 2013[42], Yang *et al.*, 2015[47] (LUX-Lung 3)	Afatinib Cisplatin–pemetrexed	EORTC QLQ-C30, EORTC QLQ-LC13	At baseline and every 3 weeks until disease progression	Compared with chemotherapy, afatinib was associated with improvements in lung cancer–related symptoms and QOL, and delay in deterioration of symptoms
Wu *et al.*, 2014[44] (LUX-Lung 6)	Afatinib Gemcitabine–cisplatin	EORTC QLQ-C30, EORTC QLQ-LC13	At baseline and every 3 weeks until disease progression	Compared with chemotherapy, afatinib was associated with improvements in lung cancer–related symptoms of cough, dyspnea, and pain, and in global health status or QOL

[a] Adapted from Hirsh, 2015[39].

FACT-L = Functional Assessment of Cancer Therapy–Lung, FACT-TOI = Functional Assessment of Cancer Therapy–Trial Outcome Index; EQ-5D = EuroQol (EuroQoL Group, Rotterdam, Netherlands) 5-dimension questionnaire; EQ-VAS = EuroQol visual analog scale; EORTC = European Organization for Research and Treatment of Cancer; QLQ-C30 = 30-item Quality of Life Questionnaire; QLQ-LC13 = Quality of Life Questionnaire–Lung Cancer module.

assigned patients to oral gefitinib 250 mg daily or to oral afatinib 40 mg daily.

Between December 2011 and August 2013, 319 patients were randomized to the trial. Other than a slightly higher proportion of women in the gefitinib arm (67% vs. 57%), both arms were well-balanced. Three clinical variables were designated as primary endpoints: PFS by independent central review, time to treatment failure, and OS (Table I). However, of those 3 primary endpoints, PFS was described as the most clinically meaningful. The median duration of follow-up for PFS was 27.3 months. The trial demonstrated that, compared with gefitinib, afatinib led to a statistically significant PFS advantage, with a HR of 0.73 (95% CI: 0.57 to 0.95) by blinded independent assessment[45]. The median PFS was 11.0 months with afatinib (95% CI: 10.6 months to 12.9 months) and 10.9 months with gefitinib (95% CI: 9.1 months to 11.5 months). An exploratory analysis of Kaplan–Meier estimates for PFS was also undertaken. The analysis estimated PFS at 12 months to be 47.4% with afatinib (95% CI: 39.2% to 55.2%) and 41.3% with gefitinib (95% CI: 33.0% to 49.5%). At 24 months, the estimate favoured afatinib by a larger margin: the PFS was 17.6% with afatinib (95% CI: 11.7% to 24.6%) and 7.6% with gefitinib (95% CI: 3.5% to 13.8%)[45].

The second primary endpoint of time to treatment failure also favoured afatinib over gefitinib, this time with a HR of 0.73 ($p = 0.0073$). The median time to treatment failure was 13.7 months with afatinib (95% CI: 11.9 months to 15.0 months) and 11.5 months with gefitinib (95% CI: 10.1 months to 13.1 months). Treatment beyond progression was allowed when the investigator deemed that the patient benefited clinically from treatment. Treatment beyond radiologic progression occurred slightly more frequently with afatinib (35% of patients) than with gefitinib (30% of patients). The PFS benefit appeared to be present for all the subgroups evaluated, including those stratified by mutation type[45].

At the time of publication, the OS data remained immature. The median OS was 27.9 months in the afatinib arm (95% CI: 25.1 months to 32.2 months) and 25.0 months in the gefitinib arm (95% CI: 20.6 months to 29.3 months), but the HR of 0.87 was not statistically different ($p = 0.33$). A total of 93 OS events occurred in the afatinib group compared with 101 events in the gefitinib group[45].

The secondary endpoint of ORR by independent review also favoured afatinib. At least a partial response was attained in 70% of patients receiving afatinib compared with 56% of those receiving gefitinib ($p = 0.0083$)[45]. A single complete response was observed in each group. The median duration of response was 10.1 months with afatinib (interquartile range: 5.6–16.8 months) and 8.4 months with gefitinib (interquartile range: 6.2–13.1 months).

The safety data showed that 42% of patients receiving afatinib required at least 1 dose reduction because of AEs (Table II)[45]. In the case of gefitinib, the 250 mg daily dose is fixed, and no dose reduction scheme exists. Actual treatment discontinuations were therefore no different in

the two groups, with only 6.3% of patients in each group discontinuing treatment. Reduction to the dose of afatinib did not appear to have a detrimental effect on efficacy.

In the first head-to-head randomized trial comparing reversible with irreversible EGFR inhibition, afatinib demonstrated a statistically significant PFS benefit. The PFS advantage appeared to occur after a longer time on treatment, which might be indicative of more-durable inhibition[45].

Irreversible EGFR Inhibition Beyond Progression with an EGFR TKI

The phase III LUX-Lung 5 trial randomized 202 patients from 23 countries in a 2:1 ratio to concurrent oral afatinib 40 mg daily and intravenous paclitaxel 80 mg/m^2 weekly or to an investigator's choice of single-agent chemotherapy[50]. The included patients had stage IIIB or IV NSCLC that had progressed after 1 or more lines of chemotherapy, including a platinum doublet and pemetrexed, and had also progressed on a first-generation EGFR TKI after at least 12 weeks of treatment. Patients also had to have maintained at least stable disease for a minimum of 12 weeks on single-agent afatinib. The primary study endpoint was PFS.

Of 1154 patients treated with single-agent afatinib after progression, 625 failed to attain the minimum requirement of 12 weeks of clinical benefit and were therefore excluded. The primary endpoint of PFS was significantly prolonged in the afatinib–paclitaxel group, reaching a median of 5.6 months compared with 2.8 months for patients receiving the investigator's choice of chemotherapy (HR: 0.60; $p = 0.003$)[50]. The PFS advantage was observed in all pre-specified subgroups. Median PFS was 3.8 months with paclitaxel ($n = 21$), 2.9 months with pemetrexed ($n = 16$), and 2.1 months with other chemotherapies ($n = 23$).

The key secondary endpoints of clinical benefit rate and ORR favoured afatinib–paclitaxel. The combination was associated with a clinical benefit rate of 74.5% compared with 45.6% for single-agent chemotherapy (odds ratio: 3.41; $p < 0.0001$) and an ORR of 32.1% compared with 13.2% for chemotherapy (odds ratio: 3.41; $p = 0.005$). However, no difference in OS was observed, the median OS being 12.2 months in both groups ($p = 0.994$)[50].

Despite the use of a combination therapy, time to deterioration of global health status and QOL were not negatively affected[50]. Adverse events were more frequent in the combination arm, with serious treatment-related AEs occurring in 11.4% of patients receiving afatinib and in 3.3% of those receiving single-agent chemotherapy. However, it should be noted that patients had longer exposure to afatinib–paclitaxel (median: 133 days vs. 51 days). The AEs most frequently associated with combination therapy were diarrhea (53.8%), alopecia (32.6%), and asthenia (27.3%).

The LUX-Lung 5 study was the first randomized prospective trial to demonstrate that patients with oncogene-addicted NSCLC who experience an initial clinical benefit with an EGFR TKI can, beyond progression, continue to benefit from an irreversible EGFR TKI such as afatinib. That finding supported the hypothesis that, in patients with *EGFR* activating mutations, dependence on ErbB family receptor signalling continues despite progression[50].

Afatinib in the Relapsed or Refractory Setting in Patients with NSCLC

The phase IIB/III LUX-Lung 1 trial attempted to show a benefit for afatinib monotherapy in patients refractory to both first-generation EGFR TKIs and platinum-doublet chemotherapy[40]. The trial was an international multicentric double-blind randomized trial. It included patients with stage IIIB/IV NSCLC of adenocarcinoma histology who were progressing after 1 or 2 lines of chemotherapy and who, in addition, had progressive disease after 12 weeks or more of treatment with erlotinib or gefitinib. Patients were required to have an Eastern Cooperative Oncology Group performance status of 2 or better, and patients with brain metastasis were excluded from the trial. *EGFR* mutation status was not required for inclusion, and a preceding 12-week period on EGFR TKI was deemed to be sufficient to enrich the trial population with patients having *EGFR* activating mutations and acquired resistance[51].

All patients received best supportive care and were randomized to receive either oral afatinib 50 mg daily or placebo. Of 585 patients randomly allocated, 390 were assigned to the afatinib group, and 195 were assigned to placebo. The chosen primary endpoint, OS, was not statistically different when afatinib was compared with placebo. The median OS was 10.8 months with afatinib (95% CI: 10.0 months to 12.0 months) and 12.0 months with placebo (95% CI: 10.2 months to 14 months) for a HR of 1.08 ($p = 0.74$, Table I)[40].

By independent review, the confirmed ORR was 7% with afatinib, with all responses being partial; only a single partial response was observed in the placebo group ($p = 0.0071$). Confirmed disease control at 8 weeks was also greater for the afatinib group, with 58% of patients having at least stable disease; in the placebo arm, 18% of patients experienced stable disease or better ($p < 0.0001$).

Although the primary endpoint was negative, afatinib appeared to confer a benefit for the secondary endpoint of PFS by both independent and investigator assessment. By independent review, the median PFS was 2.83 months in the afatinib arm and 0.95 months in the placebo arm (HR: 0.38; $p < 0.0001$)[40]. The benefit was present in all assessed subgroups except in patients with known negative *EGFR* status. In a subgroup analysis, the benefit appeared to be more pronounced for patients with known *EGFR* activating mutations and for those who had experienced a complete response, partial response, or stable disease for a minimum of 6 months on an EGFR TKI before progressing ($n = 214$). In those patients, the median PFS was 4.5 months in the afatinib group and 1.0 months in the placebo group (HR: 0.37; 95% CI: 0.26 to 0.52).

In addition to PFS benefit, afatinib was associated with improvements in lung cancer–related symptoms. The QOL and PROs results were published separately and demonstrated statistically significant improvements in disease-related cough ($p < 0.0001$), dyspnea ($p = 0.006$), and pain ($p < 0.0111$)[41]. With better symptom control, patient-reported physical functioning and overall QOL on the European Organization for Research and Treatment of Cancer 30-question Quality of Life Questionnaire for global health status was better in treated patients ($p < 0.05$). In this population, afatinib was well-tolerated. The most

common grade 3 AEs were diarrhea (17% of patients) and acneiform rash (14%).

The primary endpoint of LUX-Lung 1 was negative, and results should therefore be interpreted with caution. However, results of the PFS, ORR, and PROS analyses favoured the treatment group, especially the patients with evidence of a prior sustained response to EGFR TKIs who subsequently developed resistance. Afatinib could therefore potentially be beneficial in patients with *EGFR* activating mutations who progress after a first-line EGFR TKI, particularly in resistance not mediated by a T790M mutation.

AE Management with Afatinib

Although the AEs that occur with afatinib have been shown to be manageable in the prospective trials already described, proactive treatment of symptoms early after onset is required to prevent worsening of toxicity. To that end, patient education is of utmost importance[39].

Early recognition and management of diarrhea is particularly needed to prevent dose reduction or discontinuation. An antidiarrheal agent such as loperamide should be made available to the patient and should be started at onset of diarrhea. Furthermore, adequate hydration is recommended (3–4 L daily)[48]. If grade 2 toxicity persists beyond 48 hours or if toxicity reaches grade 3, patients should be assessed for dehydration and electrolyte imbalance, and afatinib should be held until symptoms resolve to grade 1 toxicity or less. Afatinib can then be restarted at a dose reduced by 10 mg to a minimum of 20 mg.

In the skin, EGFR is expressed in the basal layer of the epidermis and has a role in the stimulation of epithelial growth[52]. An acneiform skin rash is therefore a common AE of afatinib therapy[53]. Grade 1 toxicity can be managed with moderate- or low-strength topical steroids and a topical antibiotic such as clindamycin–erythromycin 1%–2% twice daily. However, oral antibiotics such as doxycycline 100 mg, minocycline 100 mg, or oxytetracycline 500 mg (all twice daily for 6 weeks) should be added for grade 2 toxicity. Grade 3 toxicity requires treatment interruption and dose reduction by 10 mg until symptoms improve to grade 1.

Treatment interruptions and dose reductions were not associated with decline in clinical benefit. In a subgroup analysis of the pooled analysis of LUX-Lung 3 and 6, a nonsignificant trend for improved PFS was observed in patients with grade 2 or greater diarrhea or rash. Median PFS was 11.76 months for patients experiencing grade 2 or greater diarrhea compared with 9.69 months for patients not reporting diarrhea (HR: 0.81; $p = 0.27$). Median PFS was 13.60 months when grade 2 or greater rash was present and 9.69 months when rash was absent (HR: 0.86; $p = 0.300$)[42].

SUMMARY

Afatinib differs from the first-generation EGFR TKIs in its ability to form irreversible covalent bonds with tyrosine kinase receptors, thus leading to the inhibition of downstream signalling by the entire ErbB protein kinase family[32].

The clinical activity of afatinib in patients with advanced NSCLC harbouring an *EGFR* activating mutation has been demonstrated in several large randomized clinical trials. In LUX-Lung 3 and LUX-Lung 6, a benefit for PFS, ORR, duration of response, and QOL was demonstrated for afatinib compared with platinum-doublet chemotherapy[42,44]. Furthermore, in a preplanned pooled analysis of the two trials, a statistically significant OS benefit was shown for patients having *EGFR* Del19–positive NSCLC. That finding proved to be the first time that, compared with chemotherapy, an EGFR TKI showed an OS benefit[43].

In the recent LUX-Lung 7 trial, reversible and irreversible EGFR TKIs were compared in the first-line setting[45]. In that prospective randomized trial, a benefit in favour of afatinib was observed, and that benefit appeared to occur after a longer time on treatment, which might be indicative of more durable inhibition.

Overall, the toxicity profile of afatinib is predictable and manageable with symptom control and dose reductions as needed. Importantly, dose reductions are not associated with worse clinical outcomes[42].

Further research will be required to determine whether third-generation EGFR TKIs such as osimertinib will lead to additional clinical improvement in the first-line management of *EGFR*-positive NSCLC[54]. Furthermore, several trials are assessing a possible benefit of afatinib in combination with other agents[55].

CONFLICT OF INTEREST DISCLOSURES

We have read an understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: SMBA has received speaker fees from Amgen and Bristol–Myers Squibb. VH has received fees as an advisory board member for Boehringer Ingelheim, AstraZeneca, Roche, Merck, Pfizer, Amgen, and Bristol–Myers Squibb.

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