



Review

Clinical perspective of afatinib in non-small cell lung cancer

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ABSTRACT

Reversible ATP-competitive inhibitors targeting the epidermal growth factor receptor (EGFR) have been established as the most effective treatment of patients with advanced non-small cell lung cancer (NSCLC) harboring “activating” mutations in exons 19 and 21 of the *EGFR* gene. However, clinical activity is limited by acquired resistance which on average develops within 10 months of continued treatment. The mechanisms for acquired resistance include selection of the EGFR T790M mutation in approximately 50% of cases, and *MET* gene amplification, *PIK3CA* gene mutation, transdifferentiation into small-cell lung cancer and additional rare or unknown mechanisms. Afatinib is a small molecule covalently binding and inhibiting the EGFR, HER2 and HER4 receptor tyrosine kinases. In preclinical studies, afatinib not only inhibited the growth of models with common activating EGFR mutations, but was also active in lung cancer models harboring wild-type EGFR or the EGFR L858R/T790M double mutant. Clinical efficacy of afatinib has been extensively studied in the LUX-Lung study program. These trials showed promising efficacy in patients with EGFR-mutant NSCLC or enriched for clinical benefit from EGFR tyrosine kinase inhibitors gefitinib or erlotinib. Here we review the current status of clinical application of afatinib in NSCLC. We also discuss clinical aspects of resistance to afatinib and strategies for its circumvention.

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1. Introduction

Reversible epithelial growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI), such as gefitinib and erlotinib, have shown favorable efficacy in patients with advanced non-small cell lung cancer (NSCLC) harboring somatic “activating” *EGFR* mutations [1]. Compared with standard chemotherapy, EGFR-TKIs provided higher objective response rates (ORRs), prolonged progression-free survival (PFS) as well as improved quality of life (QOL) in these patients [2–4]. However, almost all responding patients ultimately acquire resistance, with median PFS times ranging between 9 and 12 months. The mechanisms of acquired EGFR-TKI resistance have been studied by molecular characterization of repeat tumor biopsies. Based on limited case numbers these include acquisition of the

EGFR T790M mutation (49%), *MET* gene amplification (5%), mutations in the *PIK3CA* gene (5%), epithelial to mesenchymal transition (5%), transformation from NSCLC to small cell lung cancer (SCLC) (14%) and other yet unknown mechanisms (30%) [5].

According to one model the EGFR T790M mutation confers resistance to gefitinib or erlotinib therapy by increasing the affinity of the mutant EGFR for its substrate, ATP [6]. Accordingly, reversible EGFR-TKI can no longer effectively compete for ATP and thus cannot abrogate the EGFR-dependent oncogenic signals. Subsequently, TKI which irreversibly inhibit their target protein via the formation of covalent bonds in the pocket of the catalytic site have been developed. Such TKI, which not only block the EGFR but additional ERBB family receptor tyrosine kinases, were modestly efficacious in inhibiting signaling via the mutant EGFR T790M receptor and tumor growth in preclinical studies [7–9]. Further studies both *in vitro* and *in vivo* validated the notion that irreversible ERBB family blockers could be potentially effective in inhibiting EGFR T790M -derived signaling pathways [10–12].

Afatinib (BIBW2992) is an irreversible inhibitor of all ERBB family receptor tyrosine kinases derived from the anilino-quinazoline chemical series that was designed to covalently bind to Cys 773 of EGFR, Cys 805 of HER2 and Cys 803 of ErbB4 [13]. Preclinical studies indicate that afatinib inhibits the kinase activity of wild type and mutant forms of EGFR, HER2 and ErbB4 [11,13]. *In vitro*, afatinib has

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a potency similar to that of gefitinib for inhibiting EGFR L858R and to lapatinib for inhibiting HER2. However, afatinib was more effective than erlotinib, gefitinib or lapatinib in inhibiting the survival of lung cancer cell lines harboring wild type EGFR (H1666) or the L858R/T790M double mutant (NCI-H1975). Furthermore, afatinib also potently inhibited the kinase activity of ErbB4 with an EC_{50} of 1 nM. Compared with afatinib, the reversible inhibitor lapatinib was 30-fold less potent on ErbB4 while erlotinib and gefitinib were above 500-fold and 300-fold less potent, respectively [13]. Consistently, afatinib also showed activity in tumor xenograft models resistant to first generation EGFR-TKIs, including tumors harboring the EGFR L858R/T790M double mutant, and in models dependent on HER2 overexpression [11].

Results from such preclinical studies provided scientific rationale for clinical testing of afatinib. Several administration schedules were studied, including a “2 weeks on – 2 weeks off” schedule [14], a “3 weeks on – 1 week off” schedule [15], and continuous dosing [16,17]. Overall, pharmacokinetic parameters indicated good oral bioavailability and moderately fast absorption of afatinib [18]. Continuous dosing of afatinib at 50 mg/d was recommended for phase II trials [16,17]. Generally, the incidence of severe drug-related adverse events were very low and encouraging efficacy was observed in phase I studies.

Based on the favourable safety and promising efficacy results, afatinib has been evaluated in a series of clinical trials (LUX-Lung program, Table 1) for advanced lung cancer patients who acquired resistance to gefitinib/erlotinib or as first line treatment for patients with EGFR mutant NSCLC [19]. Recently, the results of the LUX-Lung 1 [20], 2 [21] and 3 [22] studies were published. In addition, interim analyses of LUX-lung 5 have been presented at the American Society of Clinical Oncology 2012 Annual Meeting [23,24].

2. Afatinib in third or fourth line therapy, and in patients pretreated with EGFR-TKI

The efficacy of afatinib in a NSCLC patient population enriched for clinical benefit from first generation EGFR-TKI was studied in a phase IIb/III trial (LUX-Lung 1). This study included patients with advanced lung adenocarcinoma who had failed 1 or 2 lines of chemotherapy and progressed after ≥ 12 weeks of therapy with erlotinib or gefitinib [20]. Between May 2008 and September 2009, 697 patients were identified and 585 patients were randomized (2:1) to receive either afatinib ($n = 390$) plus best supportive care (BSC) or placebo plus BSC ($n = 195$). Afatinib significantly improved the PFS (a secondary endpoint) from 1.1 months in placebo group to 3.3 months (hazard ratio [HR] 0.38, 95% CI 0.31–0.48; $p < 0.0001$). The benefit in PFS was consistent in all subgroups except for patients with EGFR wild type NSCLC. In patients highly enriched for EGFR mutations (83% positivity, including: patients had complete response (CR)/partial response (PR) to prior EGFR-TKI and/or were treated for ≥ 48 weeks with prior EGFR-TKIs), the PFS was 4.4 months in afatinib group and 1.0 months in placebo group. Afatinib also showed a pronounced PFS benefit over placebo (median PFS 4.53 months vs 0.99 months, HR = 0.37, 95% CI 0.26–0.52) for the subgroup of patients meeting the Jackman criteria [25] of acquired resistance to EGFR-TKI ($n = 214$). In addition, the afatinib group experienced a higher number of confirmed objective responses (7% vs <1% in placebo group) and disease control for ≥ 8 weeks (58% in afatinib group vs 18% in placebo group). Moreover, a greater proportion of patients in the afatinib group experienced clinically meaningful improvements in the three prespecified NSCLC-related HRQoL items, including: cough (46% vs 25%, $p < 0.0001$), dyspnoea (51% vs 36%, $p < 0.006$), and pain (50% vs 32%, $p < 0.0001$).

However, afatinib failed to show a benefit in terms of overall survival (the primary endpoint of LUX-Lung 1). The median OS was

10.8 months in the afatinib group and 12.0 months in the placebo group (HR 1.08, 95% CI 0.86–1.35; $p = 0.74$). These exceptionally high OS rates in both treatment arms of this putative “last line” population can at best be explained by enrichment in patients with prognostically superior cancer biologies, and by the impact of post-progression treatment. Indeed, a greater proportion (albeit not statistically significant) of patients in the placebo group received further cancer treatment after disease progression than those in the afatinib group. Consistent with the potential confounding effects of subsequent cancer therapies, a *post hoc* analysis of patients not receiving any subsequent systemic cancer therapy suggested an overall survival benefit from afatinib.

LUX-Lung 5 has a different design, but also addresses patients with metastatic NSCLC, who had failed prior chemotherapy and erlotinib/gefitinib [23]. The study has two parts: Part A is a single-armed trial of afatinib monotherapy (50 mg/d). Upon progression patients with clinical benefit ≥ 12 weeks in part A enter part B, which randomizes between continuation of afatinib (40 mg/d) in combination with weekly paclitaxel (80 mg/m²) versus investigators' choice monochemotherapy. From April 2010 to May 2011, a total of 1154 patients were enrolled into part A and received afatinib monotherapy. Similar to LUX-Lung 1, the median PFS (the primary endpoint) for part A was 3.3 months, and the disease control rate was 64%. Again, when applying clinical enrichment criteria for acquired resistance, median PFS was longer (4.2 months, $n = 597$) for those with enrichment than those without (2.8 months, $n = 557$, $p < 0.0001$).

LUX-Lung 4 was a phase II study [26] conducted in Japan, which also confirmed the efficacy of afatinib as third or fourth line therapy in patients ($n = 62$) enriched for acquired resistance to erlotinib or gefitinib. Median PFS of the total population was 4.6 months, and 4.4 months in those patients meeting acquired resistance criteria (82%).

Taken together, these data indicate that afatinib has clinical efficacy in patients with advanced NSCLC progressing after chemotherapy and first generation EGFR-TKI treatment. The efficacy was more pronounced in patients clinically enriched for benefit from EGFR-TKI (*i.e.* clinical enrichment for EGFR mutant NSCLC).

3. First and second line therapy in EGFR-TKI-naïve patients

Efficacy of afatinib in first line or second line (EGFR-TKI-naïve) settings was tested in the LUX-Lung 2, 3, 6 and 7 trials. Results of LUX-Lung 2 and 3 were reported recently, while LUX-Lung 7 (NCT01466660) is still recruiting.

LUX-Lung 2 was a single arm phase II study in patients with EGFR-mutant lung adenocarcinoma [21]. A total of 129 patients were treated either in the first line setting or following progression after chemotherapy. Afatinib starting doses were 50 mg ($n = 99$) or 40 mg ($n = 30$). 79 (61%) of 129 patients obtained an objective response (2 CR, 77 PR). Similar ORRs were observed when analyzed by starting dose (18 of 30 patients [60%] at 40 mg vs 61 of 99 patients [62%] at 50 mg). No significant difference was recorded in the ORRs between patients with EGFR deletion exon 19 and those with the EGFR L858R mutation (69% vs 63%, OR 0.76, 95%CI 0.34–1.69), nor between first and second line treatment (66% vs 57%, OR 0.71, 0.35–1.44). Median PFS for all patients was 10.1 months. Median OS was 24.8 months for all patients and 23.3 months for patients receiving afatinib as second line therapy. OS has not been reached for patients receiving afatinib as first line treatment (the lower 95% CI was 22 months).

LUX-Lung 3 was a randomized, open-label, phase III study investigating afatinib (40 mg/d, $n = 230$) versus pemetrexed and cisplatin (CP) ($n = 115$) as first line treatment for patients with advanced

Table 1
LUX-Lung clinical trials program.

Title	Phase	Trial status	Key information of inclusion	Afatinib	Control arm	Patients (n)	Primary end point	Mutation status	Therapy line	Study design
LUX-Lung 1 [20]	IIb/III	Analysed	Chemotherapy and TKIs pretreated	50 mg	placebo	585	OS	Not required	Third or fourth line	Randomized, placebo controlled
LUX-Lung 2 [21]	II	Analysed	Naïve to TKIs	40 mg or 50 mg	No	129	ORR	EGFR Mutation Positive	First or second line	Single arm, open label
LUX-Lung 3 [22]	III	Analysed	advanced adenocarcinoma	40 mg	Pemetrexed + cisplatin	345	PFS	EGFR Mutation Positive	First line	Randomized(2:1), open-label
LUX-Lung 4 [17]	I/II	Ongoing	Chemotherapy and/or TKIs pretreated	50 mg		90	Part I: safety Part 2: ORR	Not required	≥Second line	open-label
LUX-Lung 5 [23]	III	Ongoing	Chemotherapy and TKIs pretreated (≥12 weeks before PD)	Part A: 50 mg Part B: 40 mg + paclitaxel	Part A: No Part B: investigator's choice chemotherapy	1154	PFS	Not required	Third or fourth line	Randomized, open-label
LUX-Lung 6(NCT01121393)	III	Ongoing	Advanced Adenocarcinoma	40 mg	Gemcitabine + Cisplatin	364	PFS	EGFR Mutation Positive	First line	Randomized, Open-label,
LUX-Lung 7 (NCT01466660)	IIb	Recruiting	Advanced Adenocarcinoma	40 mg	Gefitinib	264	PFS	EGFR Mutation Positive	First line	Randomized, Open label
LUX-Lung 8 (NCT01523587)	III	Recruiting	Advanced Squamous Cell Carcinoma; naïve to TKIs or C225	40 mg	erlotinib	800	PFS	Not required	Second	Randomized, Open label

OS: Overall survival; TKI: Tyrosine kinase inhibitor; ORR: Objective response rate; PFS: Progression free survival; PD: Progressive disease; EGFR: Epithelial growth factor receptor.

adenocarcinoma of the lung harboring *EGFR* mutations, including “rare mutations” [22]. Median PFS was 11.1 months for patients treated with afatinib compared with 6.9 months for patients treated with CP ($p = 0.0004$). In 308 patients with common *EGFR* mutations (Del19/L858R), median PFS of patients treated with afatinib was prolonged as compared to CP (13.6 vs 6.9 months, HR = 0.47, 95% CI 0.34–0.65; $p < 0.0001$). Afatinib also was superior to CP in terms of ORR (56% vs 23%; $p < 0.0001$) and delay in time to deterioration of cancer-related symptoms (cough and dyspnoea), as well as in quality-of-life analyses.

Very similar to LUX-Lung 3, LUX-Lung 6 (NCT01121393) is a randomized, open label, phase III study, comparing the efficacy of afatinib with gemcitabine plus cisplatin first line treatment for patients with lung adenocarcinoma harboring an *EGFR* mutation. The study was commenced in 2010 and results are awaited.

Both LUX-Lung 2 and 3 revealed that the median PFS reached by afatinib in the first line setting amounted 13–14 months in patients with common *EGFR* mutations, indicating high clinical efficacy. Gefitinib in general provided median PFS times in the range of 8–10 months [2,27,28] in similar patient populations. Based on this observation LUX-Lung 7 was initiated, a randomized, open-label, phase IIb trial comparing afatinib to gefitinib in the first-line treatment of patients with *EGFR*-mutant advanced NSCLC. The trial is now recruiting. Median PFS in trials using erlotinib as first line treatment ranged from 9.7–14.1 months [4,29,30]. In addition, the ORRs in studies applying erlotinib as first line treatment in *EGFR* mutation patients were between 58% and 73%, while the ORR was 61% in LUX-Lung 2 and 56% in LUX-Lung 3. Although the efficacy data were numerically similar between erlotinib and afatinib in first line treatment, the central, independent radiological review in LUX-Lung 2 and 3 strengthened the efficacy results compared with those assessed only by investigators in both EORTC and OPTIMAL trials.

4. Impact of *EGFR* mutation status on clinical benefit from afatinib

4.1. *EGFR* mutation status

In LUX-Lung 1 trial, of the 141 patients with tumor tissue available for analysis, 96 were positive for *EGFR* mutations. In these patients, afatinib conferred a longer median PFS than placebo (3.3 months vs 1.0 months, HR 0.51, 95% CI 0.31–0.85; $p = 0.009$). In contrast, there was no difference in PFS between these treatment groups in the 45 patients with *EGFR* wild type tumors. Data from a single center (West German Cancer Center) analysis of patients enrolled in LUX-Lung 5 confirmed this observation [31]. Of 25 patients with known *EGFR* mutation status, 11 patients with *EGFR* mutant tumors experienced prolonged survival as compared to 14 patients with *EGFR* wild type tumors (HR 0.29, 95% CI 0.07–0.64; $p = 0.0058$). Another phase II trial investigated afatinib as a third-line treatment in Korean patients with *EGFR* wild type lung adenocarcinoma [32]. Among 38 eligible patients, no objective response was observed. Only 9 (24%) patients achieved disease control. Median PFS was 4.1 weeks, similar to that in LUX-Lung 1. These results argue for sustained tumor dependency on *EGFR* signaling despite progression after erlotinib or gefitinib. At the same time, it is suggested that afatinib has limited activity in *EGFR* wild type NSCLC.

4.2. Afatinib in common and uncommon *EGFR* mutations

In LUX-Lung 2, there was no apparent difference in median PFS between patients with *EGFR* Del 19 and *EGFR* L858R mutations (13.7 months, both). In contrast, median PFS for patients with

uncommon *EGFR* mutations only amounted 3.7 months. Consistently, the median OS of patients with uncommon *EGFR* mutations was 16.7 months as compared to 38.7 months for *EGFR* Del 19 and 31.5 months for *EGFR* L858R, respectively. In LUX-Lung 3, uncommon mutations (including: *de novo* T790M, exon 20 insertions, G719X, L861Q, S768I) comprised 10.7% of the trial population ($n = 37$, 26 in the afatinib arm, 11 in the CP arm). Of 32 patients with target lesions, 19/23 on afatinib and 8/9 on CP experienced tumor shrinkage. Formal statistical analyses to compare afatinib with CP were not applied because of the small size of the uncommon mutation cohort, baseline imbalances and its molecular heterogeneity [33]. Hence, afatinib seems to induce objective responses in patients with NSCLC harboring uncommon *EGFR* mutations, but disease control is less durable. Previous studies have shown that different TKIs may have specific activities in patients with specific *EGFR* mutation. For example, erlotinib or gefitinib seemed to be more active in patients with *EGFR* Del 19 than in patients with *EGFR* L858R mutation [29,34,35] and showed less activity in other mutations [36]. Neratinib exhibited enhanced activity in patients with *EGFR* G719X mutations ($N = 4$, 3 PR), but was less active in patients with *EGFR* del 19 or L858R mutant NSCLC ($N = 83$, 0 PR) [37]. Considering the small sample size in this study, the difference in efficacy of neratinib in patients with tumors expressing *EGFR* del 19 or L858R mutations or other uncommon mutations should be verified in larger cohorts.

While afatinib retains significant *in vitro* and *in vivo* inhibitory activity in cancer models harboring *EGFR* T790M mutations [7], the clinical efficacy of afatinib in *EGFR* T790M mutant NSCLC is still unclear. In LUX-Lung 3 there were 13 treatment-naïve patients with either isolated or coexisting *EGFR* T790M mutations. 11 patients received afatinib resulting in 1 PR, 7 SD and 3 PD; PFS times of these patients ranged from 0.3 to 11.0 months. One patient with *EGFR* T790M mutant NSCLC treated with CP obtained a PR, a second one achieved SD, and PFS times were 6.7 and 2.6 months [33]. Based on these small case numbers no definitive conclusion can be drawn on the clinical activity of afatinib on *EGFR* T790M mutant NSCLC.

4.3. Acquired resistance to afatinib

The results from LUX-Lung 2 and 3 with a median PFS of 12–14 months obtained by first line afatinib in *EGFR*-mutant NSCLC clearly demonstrate that acquired resistance also is a major clinical issue in treatment with this irreversible pan-ERBB inhibitor. Currently, there is no extensive clinical data available which points at the mechanistic basis of afatinib resistance. Rebiopsy of a pulmonary nodule in a patient with *EGFR* del 19 mutant NSCLC progressing after first line afatinib revealed the *EGFR* T790M mutation, which had not been detected in the pretreatment tumor tissue [38].

Using an *in vitro* cell culture system, Kim et al. [38] modeled the acquired resistance to first line treatment with irreversible ERBB-family blockers using PC9 cells (*EGFR* exon 19 del E746-A750). They found that gene dosage of the *EGFR* T790M allele was the main factor that significantly abrogated the efficacy of afatinib in these models. Similarly, by generating models of resistance to dacomitinib (PF00299804, another irreversible pan-ERBB TKI) with PC9 cell line, Ercan et al. [39] demonstrated that resistance to dacomitinib, at least in part, was due to selection of a pre-existing *EGFR* T790M amplified clone both *in vitro* and in a xenograft model *in vivo*.

These findings suggest that afatinib administered at current clinically recommended doses may not be sufficient to effectively suppress NSCLC clones harboring the *EGFR* T790M mutation. More potent therapies against *EGFR* T790M mutant NSCLC are in need. Considering the multiple reasons responsible for acquired resistance to gefitinib and erlotinib, including *MET* amplification [40,41], insulin-like growth factor receptor I [42], *PIK3CA* mutation, or small cell lung cancer transformation [5], some of these may also play

Table 2

Summary of the most frequent treatment-related adverse events recorded in LUX-LUNG 1, 2, 3.

	LUX-Lung 1 [20]		LUX-Lung 2 [21]				LUX-Lung 3 [22]	
	Afatinib 50 mg (N = 390)		Afatinib 50 mg (n = 99)		Afatinib 40 mg (n = 30)		Afatinib 40 mg (n = 229)	
	All grades	≥3 grades	All grades	≥3 grades	All grades	≥3 grades	All grades	≥3 grades
Diarrhoea	339 (87%)	66 (17%)	93 (94%)	22 (22%)	29 (97%)	2 (7%)	218 (95%)	33 (14%)
Rash or acne	305 (78%)	56 (14%)	93 (94%)	28 (28%)	27 (90%)	2 (7%)	204 (89%)	37 (16.2%)
Stomatitis	237 (61%)	12 (3%)	89 (90%)	8 (8%)	15 (50%)	0	165 (72%)	19 (8%)
Nail effect	153 (39%)	20 (5%)	85 (86%)	8 (8%)	24 (80%)	2 (7%)	NR	NR
Decreased appetite	119 (31%)	14 (4%)	27 (27%)	1 (1%)	9 (30%)	1 (3%)	47 (21%)	7 (3%)
Fatigue	115 (29%)	23 (6%)	23 (23%)	2 (2%)	8 (27%)	1 (3%)	40 (18%)	3 (1%)
Dose reduction due to AEs	150(38%)		66 (67%)		11 (37%)		NR	
Drug related discontinuation	30(8%)		11(9%)				18 (8%)	
Drug related death and reason	2 patients, 1 heart failure, 1 acute renal and hepatic failure		1 patient, interstitial lung disease				4 patients, dyspnea, sepsis, ARDS, death (unknown cause)	

NR, Not reported; AE, Adverse event; ARDS, Acute respiratory distress syndrome.

an important role in the development of acquired resistance to afatinib.

4.4. Potential strategies for overcoming resistance caused by EGFR T790M

The EGFR T790M mutation enables cancer cells to maintain oncogenic EGFR signaling in the presence of current EGFR-TKI, suggesting that tumor growth and proliferation remains dependent on EGFR. Previous studies have shown promising synergistic anti-tumor effects of combined treatment of EGFR-mutant xenografts with cetuximab and an EGFR-TKI [43,44]. Based on these results, a phase I/II trial of cetuximab and erlotinib in patients with lung adenocarcinoma and acquired resistance to erlotinib was carried out. Though the results turned out to be negative, 11 out of 13 patients achieved stable disease and objective tumor shrinkages, which suggested that combined EGFR blockade may have some clinical value [45]. The combination of afatinib and cetuximab was also tested in a mouse model [46]. Interestingly, this combination induced nearly complete responses in EGFR T790M transgenic murine NSCLC models. Further study showed that combined treatment effectively depleted both phosphorylated and total EGFR. These results provided the rationale for a clinical trial testing afatinib in combination with cetuximab in NSCLC patients with acquired resistance to erlotinib or gefitinib. An interim analysis of this ongoing study reported clinical results from 26 treated patients, 22 of which received the predefined maximum dose (afatinib 40 mg daily + cetuximab 500 mg/m² biweekly). All 26 patients experienced disease control. Confirmed PR were observed in 8/22(36%) evaluable patients, including 4/13 (29%) confirmed PRs in patients with EGFR T790M-positive NSCLC. No dose-limiting toxicity was reported for cycle 1. Common adverse events were grade 1/2 rash (35/46%) and diarrhea (50/19%), respectively, and three patients (11.5%) suffered from grade 3 rash. These exciting results confirmed the findings observed in xenografts model and led to an expansion of the trial to 80 patients [47].

Another intriguing preclinical observation was that afatinib significantly down-regulated thymidylate synthase (TS) expression in gefitinib-resistant NSCLC cell lines. Furthermore, the combination of afatinib with 5-fluorouracil or pemetrexed synergistically inhibited the proliferation of NSCLC cells with the EGFR T790M mutation both *in vitro* and *in vivo* [48]. These results provided a scientific rationale for clinical testing of the combination of afatinib with pemetrexed in patients who developed acquired resistance to reversible EGFR TKIs, particularly those with an EGFR T790M mutation. The preliminary results of afatinib combined with pemetrexed in patients with advanced solid tumors showed an acceptable safety and tolerability profile. The disease control rate was 76%

(16/21) including 2 PRs. Tumor entities enrolled in this trial were not reported [49].

5. Toxicities of afatinib

Preclinical studies indicate that afatinib is a potent and irreversible inhibitor of all receptor tyrosine kinases of the ERBB family. Through covalent binding afatinib's on-target residence time is maximized and its pharmacodynamic properties are determined by the receptor half-life. It may thus be expected that afatinib has enhanced toxicities as compared to gefitinib or erlotinib. The most frequent adverse events in clinical trials of afatinib were diarrhea and rash or acne, which consistently occurred in 78% to 97% of patients treated within the LUX-Lung trials. NCI-CTC grade 3 diarrhea occurred in 17% to 22% of patients. Stomatitis and nail effects also appeared frequently (Table 2). These toxicities were overlapping with those observed in erlotinib and gefitinib trials, but appeared to occur at somewhat higher rates [2,3,29]. In particular, the incidences of stomatitis were 61% in LUX-Lung 1, 90% (50 mg) and 50% (40 mg) in LUX-Lung 2, and 72% in LUX-Lung 3, respectively. In comparison, reported incidences of stomatitis in second/third-line treatment with erlotinib amounted 19% [3], 17% in first-line gefitinib [2], and 13% in first-line erlotinib [29]. In spite of this, the incidences of severe adverse events (grade ≥3) were generally low. Most patients tolerated prolonged afatinib treatment very well. Toxicities could be managed by dose reductions to 40 mg or 30 mg, and only less than 10% of patients (8% in LUX-Lung 1, and 9% in LUX-Lung 2) required afatinib discontinuation due to drug-related adverse events. There were 2 and 1 deaths possibly related to afatinib in LUX-Lung 1 and LUX-Lung 2 study, respectively. Moreover, afatinib provided a significantly better quality of life compared with placebo in LUX-Lung 1, and with CP in LUX-Lung 5.

In the LUX-Lung 2 trial, the incidence of severe adverse events, in particular diarrhea and rash/acne, in the 40 mg group was significantly lower than in the 50 mg group, while the clinical efficacy was similar. Accordingly, a starting dose of 40 mg was recommended for LUX-Lung 3 and 6.

6. Conclusions

Several clinical trials of afatinib treatment in patients with advanced NSCLC have now been published. The emerging data support clinical activity of this irreversible pan-ERBB inhibitor in patients with EGFR-mutant NSCLC, either in the first-line setting or in patients pretreated with chemotherapy and erlotinib/gefitinib. In addition, some evidence for clinical activity in heavily pretreated NSCLC with unknown EGFR status and pulmonary squamous cell

carcinoma has been gathered. Median PFS of patients with NSCLC harboring common *EGFR* mutations receiving first-line afatinib in LUX-Lung 5 was numerically longer than the PFS reported from most trials of first-line gefitinib or erlotinib in similar populations. Only a formal head-to-head comparison of afatinib and erlotinib/ gefitinib will solve the question whether the irreversible pan-ERBB blocker provides a clinically relevant advantage over reversible *EGFR*-TKI. This is currently addressed in the ongoing LUX-Lung 7 study.

Despite its impressive activity in *EGFR*-stratified patients, afatinib's clinical usage is hampered by acquired resistance. While the mechanistic basis of afatinib resistance is still under investigation, the selection for highly expressed *EGFR* T790M clones may be one of the escape mechanisms in NSCLC. First clinical evidence obtained with combined afatinib and cetuximab treatment seems promising; however the long-term efficacy and toxicities of this approach requires additional studies.

In summary, afatinib is an interesting novel drug which certainly expands the current armamentarium for treatment of advanced NSCLC, in particular in those patients suffering from pulmonary adenocarcinoma harboring somatic *EGFR* mutations.

Conflict of Interest

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