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REVIEW

Afatinib: emerging next-generation tyrosine kinase inhibitor for NSCLC

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Abstract: The discovery of epidermal growth-factor receptor (EGFR)-activating mutations and the introduction of oral EGFR tyrosine kinase inhibitors (EGFR-TKIs) have expanded the treatment options for patients with non-small cell lung cancer. The first two reversible EGFR-TKIs, erlotinib and gefitinib, are approved for use in the first-line setting in patients with known EGFR-activating mutations and in the second- and third-line settings for all NSCLC patients. These first-generation EGFR-TKIs improve progression-free survival when compared to chemotherapy in patients with EGFR-activating mutations in the first-line setting. However, nearly all patients develop resistance to EGFR-directed agents. There is a need for further therapy options for patients with disease progression after treatment with reversible EGFR-TKIs. Afatinib is an irreversible ErbB family blocker that inhibits EGFR, HER2, and HER4. In vitro and in vivo, afatinib have shown increased inhibition of the common EGFR-activating mutations as well as the T790M resistance mutation when compared to erlotinib and gefitinib. Clinically, afatinib has been evaluated in the LUX-Lung series of trials, with improvement in progression-free survival reported in patients with EGFR-activating mutations in both first- and second-/third-line settings when compared to chemotherapy. Further investigation is needed to determine the precise role that afatinib will play in the treatment of patients with non-small cell lung cancer and EGFR-activating mutations.

Keywords: afatinib, EGFR, irreversible EGFR inhibitor, EGPR-TKIs, LUX lung, resistance mutation, targeted therapy

Introduction

Lung cancer is the leading cause of cancer death globally, with a low 5-year survival rate of 15%.[1] Non-small cell lung carcinoma (NSCLC) is the most common type, comprising 85% of lung cancers.[1] Risk factors for lung cancer are well described, and include first- and secondhand cigarette smoking,[2,3] radon gas,[4] asbestos,[5] and other airborne chemicals and particulates.[1] However, among lung cancer patients who have not been exposed to traditional risk factors, a substantial proportion are found to have oncogene-driven malignancies, including patients whose tumors are driven by epidermal growth-factor receptor (EGFR).

The vast majority of NSCLC patients are diagnosed at advanced stages, at which point locoregional therapy is not an option.[1] Until recently, cytotoxic chemotherapy administered intravenously was the only treatment option for these patients, with unsatisfactory median overall survival rates in the 12-month range.[6] With the discovery of EGFR mutations, and subsequent introduction of oral EGFR tyrosine kinase inhibitors (EGFR-TKIs), the therapeutic options have expanded for NSCLC patients.

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Epidermal growth factor receptor-activating mutations

The EGFR family of cell surface-receptor tyrosine kinases controls the intracellular signaling pathways that promote cell growth, proliferation, differentiation, and migration.[7] Members of the ErbB family include EGFR (HER1/ErbB1), HER2 (ErbB2), HER3 (ErbB3), and HER4 (ErbB4). These cell-membrane receptors are composed of an extracellular domain containing a ligand-binding pocket and an intracellular catalytic domain.[8] Binding of extracellular growth-factor ligands causes dimerization of the receptors, leading to homo- or heterodimers.[9] Formation of these dimers activates the receptors' tyrosine kinase activity, initiating intracellular signaling cascades.

Lung adenocarcinoma with activating EGFR mutations is now a well-described molecular subgroup of lung adenocarcinoma. Multiple aberrations in the signal-transduction pathways controlled by EGFR have been implicated in NSCLC. For example, mutations in genes encoding EGFR pathway proteins result in dysregulation of the proteins' tyrosine kinase activity and lead to proliferation, survival, and dissemination of malignant cells.[10,11] Elevated gene copy number and increased expression of the receptor proteins have also been described.[11]

Multiple specific EGFR-activating mutations have been identified, including short in-frame single nucleotide mutations, in-frame duplications/insertions, and single-nucleotide substitutions, all surrounding the adenosine triphosphate (ATP)-binding pocket.[12] The most common EGFR mutations in patients with lung adenocarcinoma are deletions in exon 19 (the LREA deletion) and a single amino acid substitution in exon 21 – L858R. These mutations are located within the catalytic domain and result in constitutive EGFR activation (Figure 1).[8] Exon 19 deletion and exon 21 L858R mutation account for 10%–15% of Caucasian patients and 50% of Asian patients with NSCLC. Less common mutations include L861Q in exon 21 and G719X in exon 18.[13] While EGFR-activating mutations occur at a higher prevalence in certain populations, such as females, never-smokers, and Asians, clinical characteristics alone cannot be used to predict EGFR status, and National Comprehensive Cancer Network (NCCN) guidelines recommend mutational analysis of tumor tissue to verify the presence of EGFR mutations prior to initiating EGFR-directed therapy. Roughly 20,000 patients in the United States are diagnosed with lung adenocarcinoma with activating EGFR mutations yearly.

The era of EGFR-TKIs

There is evidence that tumors with EGFR-activating mutations become completely dependent on EGFR to activate downstream intracellular signaling cascades. When inhibited

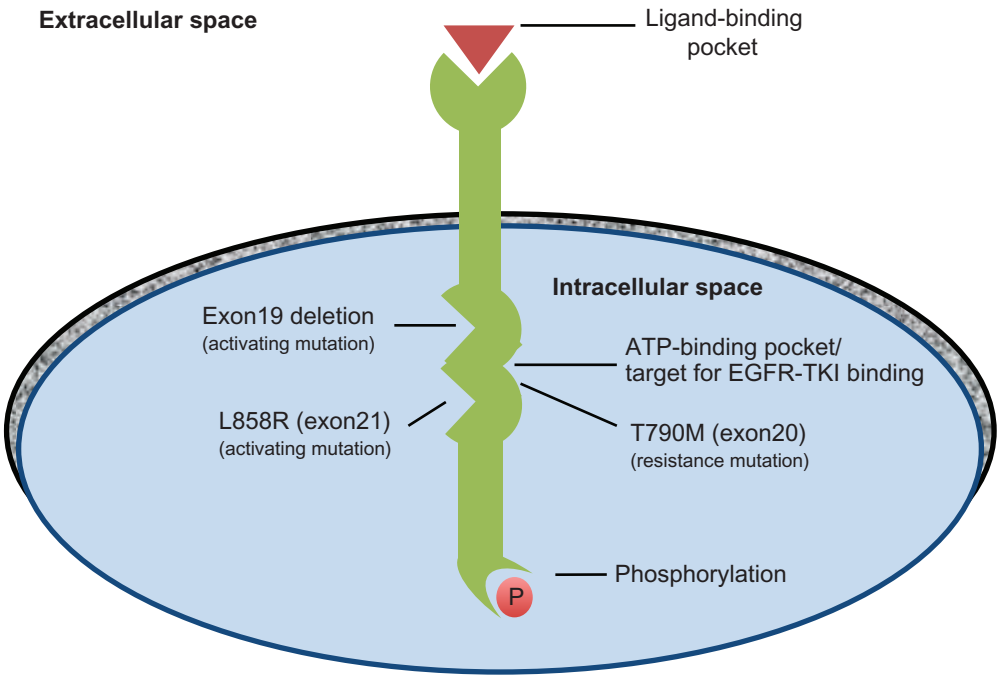

Figure 1 The EGFR receptor and locations of activating and resistance mutations.
Abbreviations: EGFR, epidermal growth-factor receptor; ATP, adenosine triphosphate; TKI, tyrosine kinase inhibitor.

by EGFR-TKIs, the tumor cells are unable to replicate and undergo apoptosis.[14] TKIs compete with ATP at the receptor intracellular catalytic domain, thus preventing ATP binding, autophosphorylation, and downstream intracellular signaling.[9,15] Erlotinib and gefitinib, the first-generation EGFR-TKIs, bind reversibly to the kinase domain and effectively inhibit both wild-type and mutated EGFR.[13]

Initial FDA approval for erlotinib in 2004 was based on the results of the BR21 trial, a phase III international, randomized, double-blind, placebo-controlled trial comparing erlotinib 150 mg daily plus best supportive care (BSC) with BSC alone in second- and third-line settings in 731 unselected patients with stage IIIB or IV NSCLC and Eastern Cooperative Oncology Group performance status of 0–3.[16] The response rate (RR) to erlotinib was 9% versus 1% for placebo ($P < 0.001$). Progression-free survival (PFS) was longer in the erlotinib group, at 2.2 months versus 1.8 months for placebo ($P < 0.001$). Note that EGFR mutation testing was not part of this trial.

As the biology of EGFR-activating mutations was better clarified, first-generation EGFR-TKIs were tested specifically in patients with EGFR-activating mutations. Tumors with activating EGFR mutations were found to have unique sensitivity to targeted therapy with EGFR-TKIs,[17,18] with RRs around 75% in the first-line setting,[19,20] a vast improvement over the 9% seen in unselected populations. Some data suggest that patients with EGFR exon 19 deletions are more susceptible to the activity of reversible EGFR-TKIs compared to those with the exon 21 L858R mutation.[18,21]

Further studies then compared first-generation EGFR-TKIs (erlotinib and gefitinib) to chemotherapy in patients with EGFR-activating mutations in advanced NSCLC. In the first-line setting, a European randomized trial, EURTAC, compared erlotinib 150 mg daily to platinum-containing chemotherapy regimens (cisplatin or carboplatin with docetaxel or gemcitabine) in 174 patients with advanced NSCLC. PFS was 9.7 months in the erlotinib group versus 5.2 months in the chemotherapy group. There was no difference in overall survival (OS). There were fewer adverse events in patients treated with erlotinib.[22] Similar results were reported in an analogous trial in Chinese patients – OPTIMAL.[23] Based on these studies, the NCCN guidelines were amended in 2011 to recommend erlotinib for first-line use in patients with documented EGFR mutations.

Gefitinib is approved in the European Union for use in advanced-stage EGFR-mutated NSCLC.[24] Its approval is based on demonstrated improved PFS when compared to chemotherapy in the first-line setting for Asian patients with EGFR mutations in three phase III randomized controlled trials (IPASS, NEJ002, and WJTPG3405).[25–27] While gefitinib is not approved in the United States, the NCCN guidelines comment that "in areas of the world where gefitinib is available, it may be used in place of erlotinib."[1]

At the present time, erlotinib and gefitinib are used in the first-line treatment of patients with advanced NSCLC and EGFR-activating mutations. Erlotinib and gefitinib can also be used in second- and third-line settings in unselected patients, regardless of EGFR mutation status.[1] While RR and PFS in the EGFR-mutated population favors the use of EGFR-TKIs as compared to chemotherapy in the first-line setting, disease progression typically occurs after a median of 10–14 months on an EGFR-TKI.[25,28] Once progression occurs, further treatment options are limited, particularly for patients with moderate to poor performance status who will be unable to tolerate toxicities from cytotoxic chemotherapy. Thus, there is a need for therapy options after progression on first-generation anti-EGFR agents.

Resistance to first-generation EGFR-TKIs

Nearly all EGFR-mutated patients eventually develop resistance to reversible EGFR-TKIs after a median of 14 months.[28] In clinical practice, it is not always feasible to obtain tissue sampling with EGFR testing at the time of progression. For these reasons, Jackman et al[29] proposed criteria to define acquired resistance that have been used in multiple clinical studies.

The Jackman criteria are as follows: patients who have a tumor known to harbor an EGFR-activating mutation (such as exon 19 deletion or exon 21 L858R mutation, amongst others), or show objective clinical benefit from treatment with EGFR-TKI as defined by objective response or durable stable disease (>6 months), and then have systemic progression of disease while on continuous treatment with EGFR-TKI should be considered to have acquired resistance. These criteria have been noted to have a positive predictive value of 66% for EGFR-sensitizing mutations.[29]

There are multiple known mechanisms of resistance to first-generation EGFR-TKIs. Most mechanisms are thought to be secondary (acquired). The most common secondary resistance mutation is the T790M missense mutation in exon 20, which accounts for 50%–60% of patients with disease progression while on a first-generation EGFR-TKI.[30–32] The T790M mutation is referred to as the gatekeeper mutation, as it occurs within the ATP-binding site in a similar location to known resistance mutations in other tyrosine kinases (Figure 1).[8,14] It is hypothesized to interfere with

first-generation EGFR-TKI binding by steric hindrance; the T790M mutation produces a bulky methionine side chain in the receptor kinase domain.[33] Besides T790M, other secondary resistance mutations include D761Y in exon 19,[34] T854A in exon 21,[35] and L747S in exon 19.[36]

An additional mechanism of resistance is amplification of MET tyrosine kinase, which can occur in up to 22% of patients and can coexist with or be independent of EGFR T790M.[37] Less common resistance mechanisms include histologic transformation to a small-cell carcinoma, occurring in up to 14% of patients resistant to EGFR-TKIs,[31,32] and morphologic changes consistent with an epithelial–mesenchymal transition, the therapeutic implications of which are unknown.[38]

There are also reports of primary resistance genotypes, including T790M missense mutation, in a small subset of patients.[39] It has been hypothesized that low levels of T790M in the presence of common activating mutations might reduce effectiveness of reversible EGFR-TKIs in first-line treatment.[39–41] Indeed, up to 20%–30% of EGFR-mutated patients do not respond to first-generation EGFR-TKIs.[18,25]

Attempts to overcome resistance

Currently, there is no standard option for advanced NSCLC patients who experience progression after treatment with a reversible EGFR-TKI, and patients who are candidates for further therapy are typically treated with cytotoxic chemotherapy or enrolled in clinical trials investigating novel agents for acquired resistance. Some have advocated continuing an EGFR-TKI, either the same medication or switching to the other first-generation option;[42–44] however, there is no consensus surrounding this practice. The rationale for continuing a first-generation TKI is that many tumors remain addicted at least in part to the EGFR signaling pathway despite acquired resistance.[42] Riely et al[42] demonstrated decreased positron emission tomography avidity and tumor size with reintroduction of an EGFR-TKI even after progression on an EGFR-TKI.

Many drugs have been studied in patients who progressed after treatment with a reversible EGFR-TKI, including XL-647,[45] dasatinib,[46] and neratinib,[47] with little success. Combinations of therapy such as cetuximab plus erlotinib[48] and gefitinib plus everolimus[42] have also been tried. The most promising drug thus far has been afatinib (BIBW2992; Boehringer-Ingelheim Pharma, Ingelheim, Germany),[49,50] an ErbB family blocker with reported in vitro and in vivo activity against EGFR mutant tumors harboring exon 19 deletions, exon 21 L858R mutations and the exon 20 T790M "resistance" mutations.

Pharmacology

Afatinib is a highly selective, irreversible inhibitor of EGFR, ErbB2/HER2, and ErbB4/HER4.[49] Like gefitinib and erlotinib, afatinib is an aniline–quinazoline derivative.[50] Afatinib covalently binds directly to the ATP-binding site in the kinase domains of both EGFR (Cys 773) and HER2 (Cys 805).[49] The irreversible, covalent binding of afatinib leads to longer suppression of receptor kinase activity than with reversible first-generation EGFR-TKIs, as the kinase activity is suppressed until the synthesis of new receptors.[9] Afatinib further improves on the activity of first-generation EGFR-TKIs by its activity against multiple receptors. The irreversible binding of afatinib to HER2 inactivates the preferred dimerization partner of EGFR, preventing the dimer formation that promotes the receptors' tyrosine kinase activity.[33,49]

Afatinib has shown preclinical activity in both first-line and second-line settings. Both in vivo and in vitro models have shown that afatinib has increased affinity for the EGFR L858R mutation compared to the first-generation EGFR-TKIs.[51] In cell-culture models, acquired resistance may develop at a slower rate when irreversible or second-generation EGFR-TKIs such as afatinib are used in the first-line setting.[52] Additionally, afatinib has higher potency than reversible EGFR-TKIs in reducing survival of NSCLC cell lines with the T790M resistance mutation (Table 1)[49] and in cell lines with the less common secondary resistance mutation T854A.[35] Finally, afatinib has shown activity in xenograft models with EGFR L858R/T790M double-mutant murine lung tumor.[49]

The recommended phase II dose of afatinib is 50 mg orally daily based on phase I trials in patients with advanced solid tumor malignancies as well as specifically in patients with advanced NSCLC.[50,53,54] At 50 mg, more than 90% of patients experienced a treatment-related adverse event, but dose-limiting adverse events were experienced in an acceptable number of patients.[50,53] Because the severity (but not the overall incidence) of adverse events increases

Table 1 Inhibition of EGFR cell lines by afatinib compared to erlotinib as shown by EC_{50} values

	Wild-type	L858R mutation	L858R + T790M
Afatinib	60	0.7	99
Erlotinib	110	40	>4000
Gefitinib	157	5	>4000

Notes: Units in nM.

Abbreviations: EGFR, epidermal growth-factor receptor; EC_{50}, half maximal effective concentration.

with dose increases from 40 mg daily to 50 mg daily, some phase II trials begin at a starting dose of 40 mg daily.[54–56]

To maximize plasma drug concentrations, afatinib should be taken while fasting.[50] Maximal plasma concentrations are attained 3–6 hours after drug administration.[50,57] With once-daily dosing, afatinib reaches a steady state after 7 days[50] and has a half-life of 30–40 hours.[53] Afatinib undergoes minimal metabolism and has no identified major circulating metabolites. It does not require dose adjustment for renal impairment. Unlike erlotinib, there is no detectable cytochrome P450-mediated metabolism of afatinib.[58]

Safety and tolerability

EGFR is expressed in the epithelium; it helps maintain mucosal integrity and promote mucosal repair in the gut and maintains the protective barrier of the skin.[56,57] Therefore, the most common treatment-related adverse events of EGFR-TKIs in general, and afatinib in particular, are gastrointestinal (GI) and cutaneous side effects, specifically diarrhea and rash.[22,55]

Almost all patients experience at least one treatment-related adverse event when receiving afatinib therapy, with 90% of patients experiencing either a GI or cutaneous adverse event.[50,53,55,57] GI side effects include diarrhea (95%), nausea, vomiting, stomatitis, and decreased appetite. Cutaneous adverse events include rash, acne, dry skin, folliculitis, and palmar-plantar disorders. The rash is usually located on the face and trunk; when severe, it can cause ulceration and desquamation.[57] In combined data of treatment-related adverse events from recent phase II/III trials, 88% of patients had diarrhea and 81% experienced a rash (n = 489).[55,61] Of these patients, the majority (>80%) had grade 1 or 2, and none had grade 4, adverse events.[55,61] Both GI and cutaneous adverse events are usually manageable with supportive care, dose reduction, or interruption of treatment.[50,57,59] Afatinib was associated with possible treatment-related interstitial lung disease (4/129 patients) in only one study,[55] similar to the infrequent reports of interstitial pneumonia, pneumonitis, acute respiratory distress syndrome, pulmonary fibrosis, and alveolitis associated with erlotinib.[60] In phase II/III trials, afatinib is associated with a dose-reduction rate of 38%–67%[55,56,61] and a drug-discontinuation rate of 8%–20%.[55,62]

Efficacy studies

Clinically, afatinib has shown promise in the LUX-Lung series of trials. The complete series of afatinib trials in advanced NSCLC is summarized in Table 2.

LUX-Lung 1 was a phase IIb/III study of 585 patients with stage IIIb or IV NSCLC (adenocarcinoma) who progressed on chemotherapy including at least one platinum-based regimen and at least 12 weeks of erlotinib or gefitinib.[61] Patients were randomized to afatinib 50 mg/day plus BSC or placebo plus BSC. Patients were treated until disease progression or undue toxicity. While the primary end point of OS was not statistically significant, OS of 10.78 months in the afatinib group versus 11.96 months in the placebo group (hazard ratio [HR] 1.077, $P = 0.74$), there was a statistically significant difference in the secondary end point of PFS in favor of afatinib. Median PFS in the group receiving afatinib was 3.3 months versus 1.1 months for patients who received placebo (HR 0.38, $P < 0.0001$). Partial RR was 7% in the afatinib group versus 0.5% in the placebo group ($P < 0.01$). Disease-control rate was 58% in the afatinib group versus 19% in the placebo group ($P < 0.0001$).

There are several potential reasons why LUX-Lung 1 did not show a difference in OS for afatinib. First, the study design was based on the assumption that the control-group OS would be a median of 4.7 months, as observed in the second-line and third-line phase III trial of erlotinib,[16] but instead OS survival in the placebo group surprisingly exceeded 10 months. This could be attributable to the additional therapies given after progression on the trial. Notably, more patients in the placebo group (79% versus 68%) received additional chemotherapy upon progression. In an exploratory analysis of the 191 patients who did not receive subsequent systemic treatment upon progression on this trial, there was a survival advantage for patients who received afatinib over placebo (5.8 vs 4.6 months, HR 0.65).

It is important to note that EGFR mutation status was not required for study entry, and so the number of patients with EGFR mutations is unknown. Less than half of the patients in the study had complete or partial response to previous reversible EGFR-TKI therapy, less than would be expected if they all had EGFR-activating mutations. Indeed, a more robust improvement in PFS was seen in the 96 patients who were known to harbor EGFR-activating mutations. Similarly, when analyzing patients who met Jackman criteria for acquired resistance,[29] the PFS difference was 4.5 months for those treated with afatinib versus 1.0 month for those who received placebo, suggesting that afatinib may have its greatest impact in subgroups of patients with EGFR mutations.[61]

LUX-Lung 2 was a phase II open-label, single-arm trial in 129 patients with stage IIIb/IV adenocarcinoma of the lung with confirmed EGFR-activating mutations.[55] Sixty-one patients received afatinib as first-line treatment, and 68 patients received afatinib as second-line treatment

Table 2 Clinical trials investigating afatinib for advanced stage non-small cell lung carcinoma

Trial (NCI #)	Phase	EGFR mutation status	Line of therapy	Study design	Primary end point	Publications/ presentations
Intermittent, high-dose afatinib (NCT01647711)	I	Must have known T790M mutation	2nd/3rd line after progression on 1st-generation EGFR-TKI	Afatinib at pulsatile, high doses	MTD	None, trial ongoing
Afatinib + cetuximab (NCT01090011)	Ib/II	Not required	2nd/3rd line after progression on 1st-generation EGFR-TKI	Afatinib + biweekly cetuximab	DLT	Janjigian et al[48]
LUX-Lung 4 (NCT00711594)	I/II	Not required	2nd/3rd line after platinum-based chemotherapy and 1st-generation EGFR-TKI	Afatinib monotherapy	Safety, RR	Murakami et al[53]
LUX-Lung 2 (NCT00525148)	II	Activating mutation required	1st and 2nd line (after chemotherapy only, no prior EGFR-TKI)	Afatinib monotherapy	RR	Yang et al[55]
Afatinib + simvastatin (NCT01156545)	II	Not required	2nd/3rd line after chemotherapy but no TKI	Afatinib + simvastatin + afatinib	RR	None, trial ongoing
LUX-Lung 7 (NCT01466660)	IIB	Activating mutation required	1st line	Afatinib vs gefitinib	PFS, DCR	None, trial ongoing
Afatinib (NCT01003899)	II	Wild-type status required	3rd line after platinum-containing regimen	Afatinib	RR	None, trial completed
LUX-Lung 1 (NCT00656136)	III	Not required	2nd/3rd line after platinum-based chemotherapy and 1st-generation EGFR-TKI	Afatinib + best supportive care (BSC) vs placebo + BSC	OS	Miller et al[61]
LUX-Lung 3 (NCT00949650)	III	Activating mutation required	1st line	Afatinib vs cisplatin/ pemetrexed	OS	Yang et al[63]
LUX-Lung 5 (NCT01085136)	III	Not required	2nd line after chemotherapy and/or 1st-generation EGFR-TKI	Investigator's choice of chemotherapy vs weekly paclitaxel + afatinib	OS	None, trial ongoing
LUX-Lung 6 (NCT01121393)	III	Activating mutation required	1st line	Afatinib vs cisplatin/ gemcitabine	PFS	None, trial ongoing
LUX-Lung 8 (NCT01523587)	III	Not required	2nd/3rd line after platinum-containing regimen, squamous cell histology	Afatinib vs erlotinib	PFS	None, trial ongoing

Abbreviations: BSC, best supportive care; DLT, dose limiting toxicity; DCR, disease control rate; EGFR, epidermal growth-factor receptor; MTD, maximum tolerated dose; PFS, progression free survival; OS, overall survival; RR, response rate; TKI, tyrosine kinase inhibitor.

after progressing following cytotoxic therapy. No patients had been exposed to prior EGFR-TKIs. The patients continued on afatinib 50 mg/day (later decreased to 40 mg/day for improved tolerability) until progression or undue toxicity.

At median follow-up of 22 months, planned analysis was performed. The primary end point, overall RR, was 61%. Notably, 66% of those with exon 19 deletion or exon 21 L858R mutations had a response to treatment, while only 39% of those with less common EGFR mutations did. The vast majority (87%) of responses occurred within 8 weeks. There was no difference in RR based on prior chemotherapy. The median response duration was 12.9 months by independent assessment and 14 months by investigator assessment. Median PFS was slightly shorter in the subset of patients with less common mutations, 10.1 months (95% CI 8.12–13.80 months), and slightly longer in those for whom afatinib was first-line treatment. These results are similar to those seen in analogous trials of first-generation EGFR-TKIs. The median OS was 23.3 months (95% CI 18.53–38.01 months) in those patients receiving afatinib in the second-line setting and was not reached for patients who received afatinib as first-line treatment.

The results of the LUX-Lung 3 trial were presented at the annual American Society of Clinical Oncology meeting in June 2012. In this phase III trial, 345 patients with EGFR mutation-positive advanced NSCLC were randomized to receive afatinib or cisplatin/pemetrexed as first-line therapy. After a median follow-up of 8 months, PFS in the afatinib group was 11.1 months compared to 6.9 months in the chemotherapy arm (HR 0.58, $P = 0.0004$). Among the 308 patients with the common mutations exon 19 deletion or exon 21 L858R mutation, the difference in PFS was even more striking: 13.6 months with afatinib compared to 6.9 months in the chemotherapy group (HR 0.47, $P < 0.0001$). OS data will be available in 2 years.[62]

Upcoming and ongoing trials of afatinib include additional single-agent afatinib trials in the LUX-Lung series (Table 2) as well as a phase II trial of afatinib in the third-line treatment of EGFR wild-type advanced NSCLC[63] and a phase Ib/II combination trial with afatinib and cetuximab after progression on a first-generation EGFR-TKI. Thus far, results have been promising in this latter trial, with disease control reported in the first 26 patients, including 36% with partial responses and four out of 13 responses in T790M-mutated patients.[64]

Patient-focused perspectives

Despite the frequency of side effects, patients report improved quality of life with afatinib treatment.[59,61] When compared with placebo, patients with advanced, non-small cell lung cancer treated with afatinib (vs placebo) reported statistically significant improvement in cough (46% vs 25%), dyspnea (51% vs 36%), and pain (50% vs 32%).[61] Preliminary results from LUX-Lung 3 comparing afatinib versus cisplatin and pemetrexed as first-line treatment in patients with advanced lung adenocarcinoma demonstrate a statistically significant delay in onset of cough (HR 0.60) and dyspnea (HR 0.68) with afatinib treatment.[62] LUX-Lung 3 also demonstrated improvement in health-related quality of life with afatinib compared to chemotherapy. A higher proportion of patients treated with afatinib (vs placebo) had a 10-point or more improvement in cough (67% vs 60%), dyspnea (64% vs 50%), and pain (59% vs 48%) when analyzed using the European Organisation for Research and Treatment of Cancer (EORTC) standardized quality-of-life questionnaire for lung cancer (QLQ-LC13).[65] Quality of life and its determinants were evaluated using the EORTC QLQ-C30 questionnaire, and patients treated with afatinib experienced improvements in their overall well-being and physical, cognitive, and role functioning compared with chemotherapy ($P < 0.05$).[65]

Conclusion

The first-generation reversible EGFR-TKIs erlotinib and gefitinib have yielded impressive clinical benefits for patients with EGFR-mutated NSCLC. Unfortunately, these benefits are transient due to the mutability of tumor-cell genomes and the resultant resistance that develops to these agents. Thus, additional treatments that can overcome or prevent resistance are needed. Just as erlotinib and gefitinib are most effective in patients with EGFR-activating mutations, irreversible EGFR-TKIs such as afatinib likely have their own particular niche. At the present time, afatinib's role is not yet defined. It may be best utilized as a second- or third-line TKI in patients with the most common resistance mutations. Or it may simply prove to be a third EGFR-TKI option for patients with EGFR-activating mutations.

At a minimum, afatinib appears comparable to current first-generation EGFR-TKI options. In the first-line treatment of patients with common activating mutations, phase III studies show PFS of 9.7–13.1 months with erlotinib,[22,23] 9.2–9.4 months with gefitinib,[25,27] and 11.1 months with afatinib.[62] Admittedly, cross-trial comparisons do not take into account different patient characteristics such as EGFR mutation status, thus a head-to-head comparison would be prudent. In the meantime, continued efforts to determine the molecular subtype of patients who will most benefit from afatinib are ongoing.

Disclosure

The authors report no conflicts of interest in this work.

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