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TARGETED THERAPIES: Afatinib—new therapy option for EGFR-mutant lung cancer

Helena A. Yu and

Thoracic Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan–Kettering Cancer Center, Weill Cornell Medical College, 300 East 66th Street, New York, NY 10065, USA

William Pao

Division of Hematology/Oncology, Vanderbilt Ingram Cancer Center, 777 Preston Research Building, 2220 Pierce Avenue, Nashville, TN 37212, USA

Abstract

On 15 July 2013, the FDA approved afatinib as a first-line treatment for patients with metastatic non-small-cell lung cancer whose tumours harbour exon 19 deletions or exon 21 (L858R) *EGFR* substitution mutations. We discuss three recent studies investigating afatinib in this molecular subset of patients.

Lung cancers with *EGFR* mutations are dependent on EGFR signalling for survival and proliferation, making them highly sensitive to treatment with EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib or erlotinib. *EGFR* mutations were first described in 2004,¹ more than 5 years after these agents were introduced into the clinic. The official FDA approval of erlotinib for the first-line treatment of patients with *EGFR* mutant non-small-cell lung cancer (NSCLC) took another 9 years, in part because erlotinib and gefitinib were developed as inhibitors of wild-type *EGFR*; pharmaceutical companies had hoped that they would benefit all patients with NSCLC.

The development of erlotinib, a first-generation reversible ATP-competitive inhibitor of EGFR, reflects our evolving understanding of molecularly driven lung cancers. Initially, patients with adenocarcinoma, squamous-cell carcinoma or large-cell carcinoma were treated with either erlotinib alone or erlotinib with concurrent chemotherapy. Erlotinib received FDA approval in 2004 based on data from BR.21, a randomized trial comparing erlotinib to placebo in patients with NSCLC that had disease progression on first-line treatment.² The differences in overall response rates (ORR) and progression-free survival (PFS) were modest at best (9% versus 1% and 10 weeks versus 8 weeks, respectively). After *EGFR* mutations were identified, subsequent studies focused on this molecular subset of

Correspondence to: W. Pao, william.pao@vanderbilt.edu.

Competing interests

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patients.^{3,4} In the EURTAC trial, erlotinib was compared with platinum doublet chemotherapy as first-line treatment for patients with *EGFR*-mutant lung cancers, and erlotinib demonstrated a dramatic improvement in the ORR (58% versus 15%) and median PFS (10 months versus 5 months).⁴ This study was the basis for the 'new' FDA indication on 14 May 2013, for erlotinib in patients with lung cancers harbouring *EGFR* exon 19 deletions and *EGFR* L858R substitutions.

Unfortunately, all patients who initially respond to treatment with *EGFR* TKIs will develop disease progression after a median of 12 months.³ More than half of tumours biopsied following disease progression demonstrate an acquired second-site mutation, *EGFR* T790M.⁵ Afatinib, a 'second-generation' *EGFR* TKI, is an irreversible, covalently-bound inhibitor of *EGFR* that in preclinical studies was shown to be more potent than erlotinib against all forms of *EGFR*, including wild-type, exon 19 deletion, L858R and T790M. Afatinib has been studied as both first-line treatment for patients with *EGFR* mutant lung cancers and as treatment in the *EGFR* TKI acquired resistance setting (Table 1).

In LUX-Lung 3,^{6,7} Sequist, Yang and colleagues compared afatinib 40 mg orally once daily with cisplatin plus pemetrexed as first-line treatment for patients with *EGFR*-mutant lung adenocarcinomas. PFS was 11 months with afatinib versus 7 months with chemotherapy ($P = 0.001$) when including all patients with *EGFR* mutations. When only patients with *EGFR* exon 19 deletions and *EGFR* L858 point mutations were studied, PFS for those treated with afatinib was 14 months. Response rates were more than double with afatinib compared with chemotherapy: 56% versus 23% ($P = 0.001$). Among the patient-reported outcomes, time to deterioration for cough (hazard ratio [HR] 0.60, $P = 0.007$) and shortness of breath (HR 0.68, $P = 0.015$) were longer with afatinib. The adverse effects profiles for the two arms differed, with more fatigue and nausea noted with chemotherapy and more diarrhoea, sore mouth and dysphagia observed with afatinib. This study builds upon previous trials and demonstrates that afatinib is an effective first-line treatment for patients with *EGFR*-mutant lung cancer.

To evaluate afatinib in patients with acquired resistance to *EGFR* TKI, in the LUX-Lung 4 trial,⁸ Katakami and colleagues assessed the drug in Japanese patients with lung adenocarcinomas that had disease progression after being on erlotinib or gefitinib for at least 12 weeks previously. *EGFR* mutation testing was performed on >90% of patient samples, with 73% identified as *EGFR* mutation positive. Five of 61 (8% 95% CI 3–18%) evaluable patients had a partial response, with a disease control rate of 66%. The median PFS was 4 months (95% CI 3–5 months), and the median overall survival was 19 months (95% CI 15 months to not reached). A similar study, LUX-Lung 1, randomly assigned patients who had received prior chemotherapy and an *EGFR* TKI to afatinib (50 mg orally daily) or placebo; this study did not demonstrate an overall survival benefit with afatinib.⁹ The results of LUX-Lung 4 and LUX-Lung 1 suggest that single-agent afatinib has minimal efficacy in patients previously treated with erlotinib or gefitinib.

Acquired resistance to *EGFR* TKI therapy eventually occurs in all patients, and the exact mechanism of resistance could impact the effectiveness of treatment given in the acquired resistance setting. Biopsies at the time of acquired resistance were not required in LUX-

Lung 4, but could have provided insights into the subset of patients that derived greater benefit from afatinib. Possible reasons for a lack of efficacy of afatinib in LUX-Lung 1 and LUX-Lung 4 could be that at lower doses, afatinib inhibits *EGFR* exon 19 deletions and *EGFR* L858R mutants preferentially to *EGFR* T790M, and the doses of drug required to overcome *EGFR* T790M might be unachievable in humans because of toxicity. Combination therapy of afatinib with the anti-EGFR antibody, cetuximab, might provide a way forward in patients with acquired resistance to erlotinib and gefitinib therapy, as a phase IB trial has shown promising activity of this combination with a 32% response rate.¹⁰

For metastatic lung cancer, both the side-effect profile and efficacy must be weighed when considering treatment options for patients. The side-effect profile of EGFR TKIs is distinct from chemotherapy—diarrhoea, rash, dry skin, mucositis and nail changes are most commonly observed with TKIs. Dose reductions of afatinib (standard dose 40 mg orally daily) were required in 52% of patients in the LUX-Lung 3 trial, and treatment-related adverse events of grade 3 occurred in 49% and 48% of patients receiving afatinib and chemotherapy, respectively.⁶ In the OPTIMAL trial,³ 19% of patients required dose reductions of erlotinib (standard dose 150 mg orally daily), and treatment-related adverse events of grade 3 occurred in 17% of patients receiving erlotinib. In total, 8% of patients on afatinib in LUX-Lung 3 required drug discontinuation owing to a treatment-related adverse event, whereas no patients in the OPTIMAL trial required drug discontinuation of erlotinib.

With regards to efficacy, afatinib, erlotinib or gefitinib have not been compared directly, although the median PFS noted in published studies seems to be similar: 11–14 months for afatinib, 8–13 months for erlotinib and 9–11 months for gefitinib. Assuming the costs of each drug are relatively similar, the question remains as to which drug will become the first-line treatment of choice for this patient population. A study comparing gefitinib to afatinib as first-line treatment for patients with metastatic *EGFR*-mutant lung cancer is currently ongoing (LUX-Lung 7, NCT01466660), but a study comparing erlotinib with afatinib is not yet underway. Until superiority of one agent is established, the milder adverse-effect profile of erlotinib might result in its continued use in the USA and Europe as the first-line treatment of choice for patients with *EGFR*-mutant lung cancers.

References

1. Pao W, Chmielecki J. Rational, biologically based treatment of EGFR-mutant non-small-cell lung cancer. *Nat. Rev. Cancer.* 2010; 10:760–774. [PubMed: 20966921]
2. Shepherd FA, et al. Erlotinib in previously treated non-small-cell lung cancer. *N. Engl. J. Med.* 2005; 353:123–132. [PubMed: 16014882]
3. Zhou C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol.* 2011; 12:735–742. [PubMed: 21783417]
4. Rosell R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol.* 2012; 13:239–246. [PubMed: 22285168]
5. Yu H, et al. Analysis of mechanisms of acquired resistance to EGFR TKI therapy in 155 patients with *EGFR*-mutant lung cancers. *Clin. Cancer Res.* 2013; 19:2240–2247. [PubMed: 23470965]

6. Sequist LV, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J. Clin. Oncol.* <http://dx.doi.org/10.1200/JCO.2012.44.2806>.
7. Yang JC, et al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. *J. Clin. Oncol.* <http://dx.doi.org/10.1200/JCO.2012.46.1764>.
8. Katakami N, et al. LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. *J. Clin. Oncol.* <http://dx.doi.org/10.1200/JCO.2012.45.0981>.
9. Miller VA, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol.* 2012; 13:528–538. [PubMed: 22452896]
10. Janjigian YY, et al. Activity of afatinib/cetuximab in patients (pts) with *EGFR* mutant non-small cell lung cancer (NSCLC) and acquired resistance (AR) to EGFR inhibitors [abstract]. *Ann. Oncol.* 2012; 23(Suppl. 9):a12270.

Key points

- Afatinib improves progression-free survival compared with cisplatin and pemetrexed as first-line treatment for patients with *EGFR* mutant lung cancers
- Afatinib monotherapy has limited efficacy in patients with *EGFR*-mutant lung cancers with disease progression on erlotinib or gefitinib
- Erlotinib, gefitinib and afatinib are all viable treatment options for the first-line treatment of patients with *EGFR*-mutant non-small-cell lung cancers

Table 1

An overview of key clinical trials of afatinib in lung cancer

Study	Patient population	Treatment	Primary end point
LUX-Lung 1	EGFR+ AR to EGFR TKI	Afatinib vs placebo	No benefit in overall survival
LUX-Lung 2	EGFR+, 0–1 prior chemotherapies	Afatinib	High response rate (61%)
LUX-Lung 3	EGFR+ first-line	Afatinib vs cis/pem	Improved PFS with afatinib
LUX-Lung 4	EGFR+ AR to EGFR TKI	Afatinib	Low response rate (8%)
LUX-Lung 6	EGFR+ first-line Asian	Afatinib vs cis/gem	Improved PFS with afatinib

Abbreviations: AR, acquired resistance; cis/gem, cisplatin/gemcitabine; cis/pem, cisplatin/pemetrexed; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.