


# Long-term response to second-line afatinib treatment for advanced squamous cell carcinoma non-small cell lung cancer: a rare case report

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## Abstract

The ErbB family is composed of four cell membrane receptors: ErbB-1 (epidermal growth factor receptor or human epidermal growth factor receptor [HER]1), ErbB-2 (HER2), ErbB-3 (HER3), and ErbB-4 (HER4). All members of the ErbB family play a critical role in regulating cell growth, proliferation and migration of tumours. Afatinib is an irreversible ErbB family inhibitor that is approved for second-line treatment of advanced squamous cell carcinoma (SqCC) that has progressed following platinum-based chemotherapy. Here we describe the case of a 56-year-old male Chinese patient with SqCC who had previously failed chemotherapy and radiotherapy and was subsequently enrolled in the LUX-Lung 8 study. The patient responded well to treatment with afatinib (40 mg/day). His disease stabilised after 8 weeks and a complete response was achieved after 12 weeks of treatment. Follow-up of this patient is ongoing; he is still alive and has not experienced disease progression in the 7 years since initiation of afatinib. The long-term response and prolonged survival in this patient provide additional evidence for second-line treatment with afatinib in patients with SqCC.

## Keywords

Afatinib, squamous cell carcinoma, non-small cell lung cancer, long-term response, case report, ErbB inhibitor

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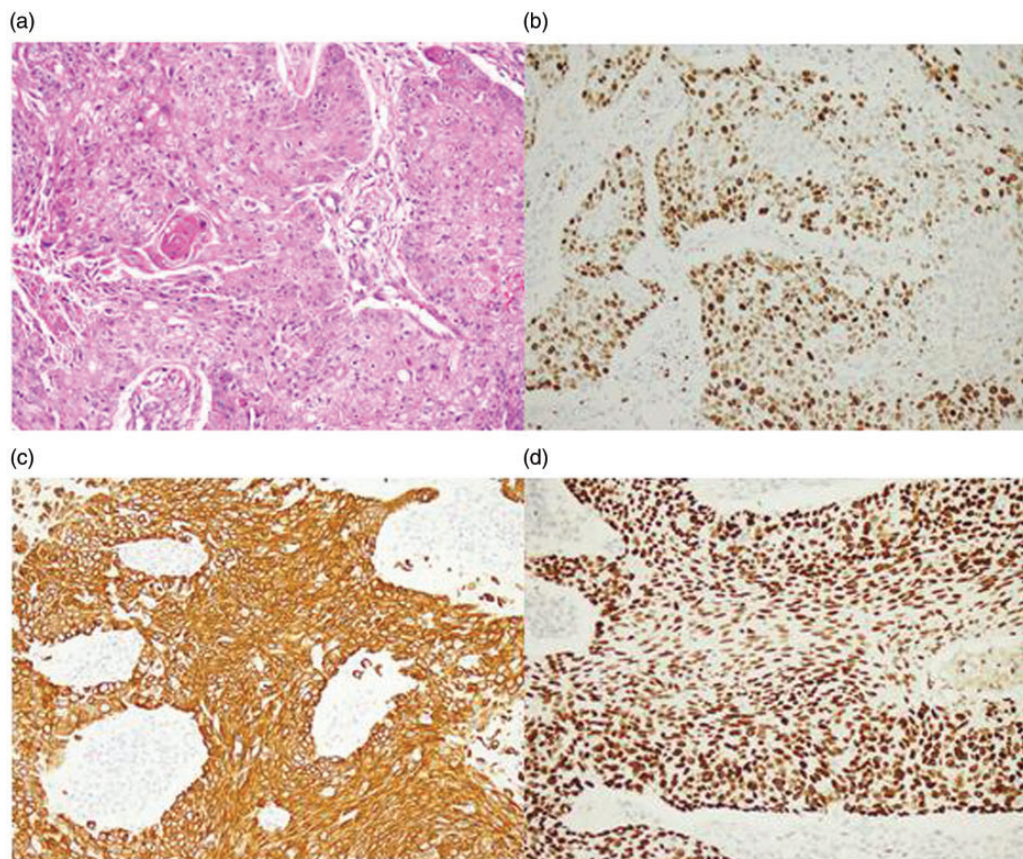
## Introduction

Squamous cell carcinoma (SqCC) has significant heterogeneity and a complex genetic map. SqCC accounts for 25% to 30% of non-small cell lung cancers (NSCLCs).<sup>1,2</sup> Compared with other NSCLC subtypes, SqCC is often diagnosed at a more advanced stage and in older patients, contributing to poorer prognoses.<sup>1,2</sup> A lack of defined molecular targets and high frequency of comorbidities<sup>1</sup> prevent patients with SqCC benefiting from the advances that have improved outcomes for other subtypes of NSCLC. As a result, median survival for patients with SqCC is 9 to 11 months,<sup>3</sup> shorter than that of patients with other NSCLC subtypes. Platinum-based doublet chemotherapy is the primary first-line therapy for SqCC.<sup>2,4</sup> However, several new treatment options have recently emerged for patients with SqCC who progress following chemotherapy. These include afatinib, necitumumab, three checkpoint inhibitors (nivolumab, pembrolizumab, atezolizumab), docetaxel with or without ramucirumab, and erlotinib.<sup>1,4</sup> In China, afatinib is approved for second-line treatment of SqCC, while nivolumab was recently approved for second-line treatment of NSCLC. In a randomised, controlled trial conducted in patients with stage IIIB/IV SqCC (LUX-Lung 8), treatment with second-line afatinib had significant clinical benefits in both the study population<sup>5</sup> and the Chinese subgroup.<sup>6</sup> Here we describe a Chinese patient with SqCC who received second-line afatinib in the LUX-Lung 8 study and achieved a long-term response to treatment.

## Case report

A 56-year-old male patient with a 30-year history of smoking (7.5 pack-years, 1–9 cigarettes per day) first presented in our hospital in November 2011 with a productive

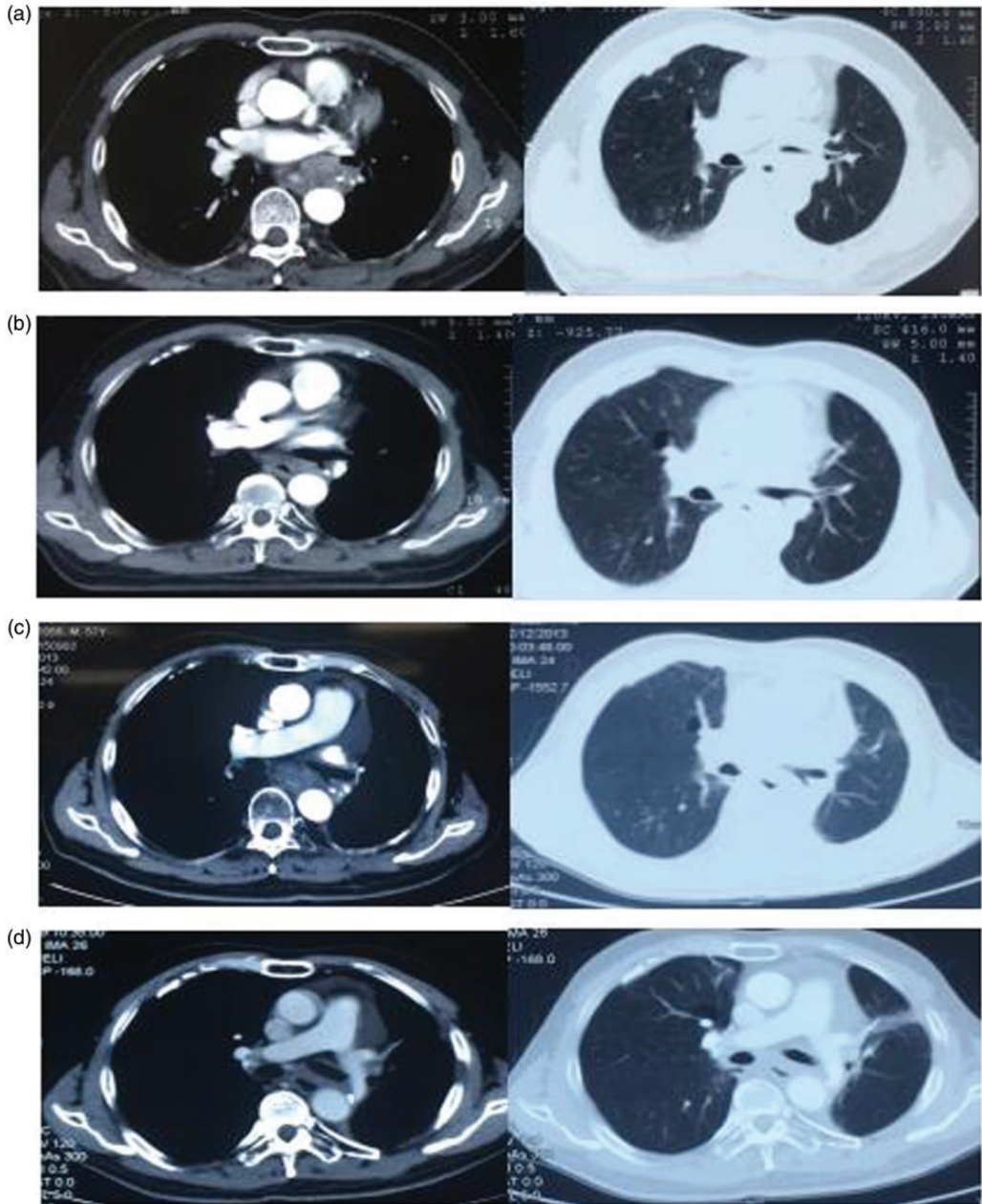
cough and left chest pain persisting for 2 months. Physical examination revealed dry and moist rales on the left lower lobe of the lung. A computed tomography (CT) scan of the lungs revealed a large mass on the basal segment of the left lower lobe as well as multiple swelling lymph shadows in the mediastinum. The tumour biopsy showed a moderately differentiated SqCC (Figure 1a). Immunohistochemistry showed that Ki67, CK5/6 and P40 were expressed (Figure 1b–d). The initial radiological assessment did not detect distant metastases and no abnormalities were found in his initial laboratory data. The patient was diagnosed with SqCC of the left lung (cT2N2M0, IIIA). Between November and December 2011, the patient received four cycles of neoadjuvant chemotherapy with gemcitabine (3.6 g) and cisplatin (120 mg) every 21 days. His symptoms of cough and chest pain were relieved although he occasionally experienced chemotherapy-related gastrointestinal discomfort. In January 2012, a surgical resection of the left lower lung lobe together with dissection of the mediastinal lymph nodes was performed. Post-operative pathology showed SqCC with blood vessel infiltration, and a metastasis to the subcarinal lymph nodes was detected (pT1N2M0, IIIA). Adjuvant chemotherapy with gemcitabine plus cisplatin was administered (two cycles) 1 month after surgery. The patient responded well to the above treatments with no discomfort. Following 12 months of disease-free survival, the patient developed a recurrent cough without any abnormal physical signs. Chest CT scans showed swelling of the mediastinal lymph nodes and stenosis of the lumen of the left main bronchus and upper lobe bronchus, suggestive of disease progression (Figure 2a). Squamous-type carcinoma was confirmed again by bronchoscopy with transbronchial lung biopsy and no signs of distant metastases were observed on



**Figure 1.** Histology images in (a) show moderately differentiated squamous cell carcinoma (SqCC). Immunohistochemistry for SqCC showed that (b) Ki-67, (c) CK5/6 and (d) P40 were expressed in tumour cells ( $\times 200$  original magnification).

imaging analysis. All laboratory data were within the normal range. Thus, one cycle of radiotherapy was administered (January–March 2013) and a partial response was achieved (Figure 2b). This was followed by four cycles of gemcitabine plus cisplatin at the previous dose and frequency (April–June 2013), which resulted in stable disease. In May 2013, the patient developed chest tightness, which was judged as pneumonia-related with radiotherapy by multidisciplinary experts. After 5 days of treatment with methylprednisolone (40 mg/day), his symptoms improved significantly and chemotherapy was continued.

However, the patient failed to continue chemotherapy because of thrombocytopenia in June 2013. In August 2013, the patient developed symptoms of shortness of breath during light activity. He had weakened breath sounds on the left lobe when auscultating. Additionally, elevated serum squamous cell carcinoma antigen was detected, although there were no abnormalities in other laboratory data. A chest CT scan revealed thickening of the rear wall of the left main bronchus, corresponding thickening of the horizontal oesophagus wall, and local enlargement of the mediastinal space. These findings suggested disease



**Figure 2.** Chest computed tomography (CT) images from the case. The image in (a) shows disease progression after surgery and four cycles of adjuvant chemotherapy in January 2013. The image in (b) shows a partial response after one cycle of radiotherapy and four cycles of chemotherapy in June 2013. The image in (c) shows disease progression following chemoradiotherapy in August 2017. The image in (d) shows complete response after 12 weeks of afatinib treatment.

progression following a progression-free survival (PFS) time of 7 months (Figure 2c).

The patient was enrolled in the LUX-Lung 8 study on August 23, 2013. He provided written informed consent and commenced second-line therapy with afatinib (40 mg/day). Following 8 weeks of afatinib therapy, his shortness of breath was significantly relieved. The patient had no detectable baseline target disease, with stable non-target disease. After 12 weeks of afatinib treatment, the patient was in good condition without any symptoms or drug-related adverse events. Physical examination revealed normal breath sounds and CT imaging showed that the subcarinal lymph node metastasis and left lower lobe lesions had disappeared, indicating a complete response to treatment (Figure 2d). Follow-up of the patient is continuing: he undergoes a whole-body imaging examination every 6 months to 1 year, including chest and abdominal CTs, brain magnetic resonance imaging, radionuclide bone scanning, and lymph node colour ultrasound. The patient is still alive, and his disease has not progressed for 7 years. He has experienced no drug-related adverse events since the initiation of afatinib treatment.

## Discussion

Here, we described a patient with advanced SqCC who achieved a complete response after 12 weeks of second-line treatment with afatinib. This response has been sustained for over 5 years. At the time of writing, the patient is still alive and shows no evidence of disease progression. This suggests that the prognosis for this patient was more favourable than that of most patients in the LUX-Lung 8 study, for whom median PFS and overall survival (OS) following afatinib therapy were 2.6 and 7.9 months, respectively.<sup>5</sup> It has been reported previously that afatinib is associated with long-term survival. Yang et al.<sup>7</sup>

described 15 patients in the LUX-Lung 8 study who experienced prolonged survival while receiving more than 12 months of treatment with afatinib. Median OS in these 15 patients was 23.1 months (range 12.9–31.6 months), shorter than for our patient. Moreover, in patients with advanced NSCLC harbouring epidermal growth factor (EGFR) mutations, median PFS following first-line afatinib treatment was 11.0 to 13.6 months.<sup>8</sup> In patients with exon 19 deletions in EGFR, prolonged OS of 31.7 months has been observed.<sup>9</sup> Regardless of whether PFS or OS is measured, the efficacy of second-line afatinib in our patient was superior to the results of first-line treatment.

The mechanism of action of afatinib in patients with SqCC is still unclear. In SqCC, multiple genetic mutations have been identified in various downstream signalling molecules of the ErbB receptors, while EGFR mutations are rare (<5%).<sup>10</sup> In a comprehensive analysis of SqCC, overexpression of EGFR and abnormal expression of ErbB receptors were the predominant pathological mechanisms identified. Afatinib irreversibly inhibits signalling of all ErbB heterodimers and homodimers, enhancing the blockade of downstream signals. In addition to EGFR, afatinib inhibits multiple ErbB family members simultaneously, including ErbB2 (human epidermal growth factor receptor [HER]2), ErbB3 and ErbB4.<sup>11–13</sup> In a retrospective analysis of the tumour mutation profiles of patients in the LUX-Lung 8 study, second-generation sequencing results showed that 50% of patients with long-term responses to afatinib (12 months of treatment) were positive for ErbB mutations. In addition, patients with ErbB mutations in the afatinib-treated group had longer PFS and OS than those with non-ErbB mutations (4.9 months vs 3.0 months and 10.6 months vs 8.1 months, respectively).<sup>14</sup> Therefore, it is highly possible that the primary pharmacological mechanism

underlying response to afatinib in patients with SqCC is broad-spectrum inhibition of the ErbB family pathway.

Regrettably, ErbB gene spectrum results for this patient were not available because the patient refused to undergo sequencing analysis after progressing on first-line treatment. We believe that the significant efficacy of afatinib is closely related to wide inhibition of the ErbB pathway. Tumour mutation profiling of patients in the LUX-Lung 8 study revealed that benefit from afatinib therapy was predominantly associated with mutations in HER3 and HER4, and particularly HER2. Outcomes did not appear to be related to EGFR overexpression.<sup>14</sup> It seems conceivable that an alternative pathway may exist that could be strongly inhibited by afatinib, for example, one enabled by mutations in HER2. Moreover, it is also possible that the wide and sustained inhibition seen with afatinib therapy in these cases is related to the presence of co-expressed mutations in multiple ErbB family members. Therefore, next-generation sequencing of ErbB family members in SqCC may be useful to help predict the efficacy of afatinib and identify SqCC patients who may benefit from second-line afatinib therapy. Whether ErbB family members may be useful as predictive biomarkers for the treatment of patients with SqCC requires more clinical data and further investigation into the mechanism of action of afatinib in these patients.

## Conclusion

We reported the case of a patient with SqCC of the lung who derived remarkable benefit from second-line treatment with afatinib. Long-term response to afatinib in this case provides an important reference for the treatment of patients with advanced SqCC. Larger studies of patients with SqCC are needed to further verify long-term

responses to afatinib, and to identify potential biomarkers.

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## Declaration of conflicting interest

The authors declare that there is no conflict of interest.


## Ethics and informed consent

The Ethics Committee of The Jilin University First Hospital approved this study. The patient provided informed consent for publication of this case.

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