Durable response to afatinib rechallenge in a long-term survivor of non-small cell lung cancer harboring EGFR L858R and L747V mutations

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Abstract
Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors are standard therapeutic agents for non-small cell lung cancer (NSCLC) patients with major EGFR mutations such as exon 19 deletions and a L858R mutation, whereas treatment strategies for cases with uncommon EGFR mutations remain to be fully established. Here, we report a long-term (≥20 years from initial diagnosis) NSCLC survivor carrying EGFR L858R and L747V mutations. The patient received gefitinib monotherapy, systemic chemotherapy/chemoimmunotherapy, and local consolidative therapies for oligometastatic lesions, and responded to afatinib rechallenge with a progression-free survival of 12 months. The current case suggests that afatinib is effective in NSCLC patients with EGFR L858R and L747V mutations and that a therapeutic approach combining appropriately timed systemic therapies with local consolidative therapies for oligometastatic lesions improves long-term survival.

KEYWORDS
afatinib, epidermal growth factor receptor, progression-free survival

INTRODUCTION
Epidermal growth factor receptor (EGFR) mutations are common driver mutations in non-small cell lung cancer (NSCLC). The major EGFR mutations are exon 19 deletions and a L858R mutation, whereas 10% of patients with EGFR-mutated NSCLCs have minor, “uncommon” EGFR mutations.1 Recent advances in next-generation sequencing-based technologies have enabled the detection of a number of rare EGFR mutations, including L747V; therapeutic strategies against NSCLC harboring single or compound uncommon EGFR mutations are under investigation. Here, we report a long-term (≥20 years from the initial diagnosis) NSCLC survivor carrying EGFR L858R and L747V mutations who responded to afatinib rechallenge with a 12-month progression-free survival (PFS).

CASE REPORT
A 32-year-old man who had never smoked was diagnosed with stage IIA (pT2N1M0) primary lung adenocarcinoma in the left S6 and underwent lobectomy in 2001. Two years later, recurrence manifested as multiple pulmonary
metastases. Gefitinib was initiated at 250 mg/day and yielded a complete response. After 7 years of gefitinib treatment, the patient developed a single pulmonary metastasis in the right S4 and underwent partial resection. The tumor was diagnosed as small cell lung cancer (SCLC) harboring the EGFR L858R mutation, indicating resistance to gefitinib due to SCLC transformation. Because of no other recurrent lesions, gefitinib was administered for a total of 9.1 years until the appearance of mediastinal lymph node metastases of SCLC. Subsequently, the patient received cisplatin plus etoposide with concurrent thoracic radiotherapy and achieved a partial response. In 2017, a pulmonary metastatic lesion appeared in the right S6, and the patient underwent segmentectomy. The tumor was an adenocarcinoma. After 8 months, the patient developed mediastinal lymph node metastases of SCLC, and cisplatin plus irinotecan chemotherapy resulted in a partial response. However, after repeated recurrences of regional lymph node metastases, the patient underwent stereotactic radiotherapy. In 2020, the patient showed multiple pulmonary and mediastinal lymph node metastases with SCLC. Atezolizumab plus carboplatin and etoposide was administered, and stable disease was achieved. The patient subsequently showed mediastinal lymph node metastases and received carboplatin plus albumin-bound paclitaxel chemotherapy, achieving a stable disease. Nevertheless, the patient developed metastatic lesions in the lung, mediastinal lymph nodes, and pancreas (Figure 1a–c). The FoundationOne CDx assay (Foundation
Medicine, Inc.) was conducted on the surgical specimen obtained in 2017, revealing 
$\text{EGFR}^{L858R}$ and $\text{L747V}$ mutations accompanied by $\text{EGFR}$ amplification and $\text{TP53}^{R196*}$ mutations. Afatinib was initiated at 40 mg/day causing regression of the metastatic lesions (Figure 1d). However, the dose of afatinib was decreased to 20 mg/day due to intolerable skin toxicities (Figure 2a). Twelve months after afatinib administration, the patient showed pancreatic and right hilar lymph node metastases. At present (August 2022), the overall survival (OS) times from initial diagnosis and gefitinib administration are 20.8 and 18.8 years, respectively, and $\text{EGFR}^{L858R}$ mutations were consistently detected in all samples that underwent genotyping (Figure 2b).

The patient provided informed consent for the publication of this report.

**DISCUSSION**

$L747X$ ($L747P$, $L747S$, and $L747V$) mutations are rare in NSCLC; only 2.2% of all uncommon mutations are $L747X$ mutations. Afatinib has shown better activity against NSCLCs carrying $\text{EGFR}^{L747P/S}$ mutations than gefitinib and erlotinib, which is supported by preclinical studies showing higher sensitivities of afatinib to $L747P$- or $L747S$-mutant cells.6,7 Regarding $L747V$ mutations, a lung adenocarcinoma patient with $\text{EGFR}^{L858R}$ and $L747V$ mutations achieved a 6-month PFS with erlotinib,8 while another patient with lung adenocarcinoma harboring $\text{EGFR}^{G719A}$ and $L747V$ mutations responded to afatinib with a 25-month PFS.9 The clinical effectiveness of EGFR-tyrosine kinase inhibitors (TKIs) against $\text{EGFR}^{L747X}$-mutated NSCLCs in previous reports is summarized in Table S1. Together with the findings in our case, afatinib appears to be clinically active against $\text{EGFR}^{L747V}$-mutated NSCLC.

Our patient was administered gefitinib for 9.1 years, and the OS from gefitinib initiation was 18.8 years. Hirsch et al. analyzed long-term (>10 years) survivors of NSCLC treated with gefitinib, showing that the median duration of gefitinib treatment was 11.1 years and the 15-year survival rate from gefitinib initiation was 59%.10 A previous study suggests that salvage surgery, which is defined as the resection of relapsed residual tumors within the thorax, after TKI treatment is safe and feasible and may contribute to prolonged OS time.
by reducing the local tumor burden. Furthermore, local consolidative therapies improve the OS in stage IV NSCLC with ≤3 synchronous metastases. Thus, local consolidative therapy for oligometastatic lesions may be a valid approach to prolong the survival of patients with EGFR-mutated NSCLC in combination with EGFR-TKI therapies.

The transformation from NSCLC to SCLC is a mechanism of resistance to EGFR-TKIs. Marcoux et al. investigated the clinical outcomes of EGFR-mutated lung adenocarcinomas transforming to SCLC, showing that the median OS since the time of SCLC transformation was 10.9 months, whereas another report described long-term survival with an OS of 58 months from SCLC transformation. In comparison with these reports, our patient survived for more than 142 months from the initial diagnosis of SCLC transformation, which may be partly attributed to repeated salvage surgeries and stereotactic radiotherapy along with systemic therapies.

In summary, the current case suggests that afatinib rechallenge is effective in NSCLC patients with EGFR L858R and L747V mutations and that a therapeutic approach that combines appropriately timed systemic therapies with local consolidative therapies for oligometastatic lesions improves long-term survival.

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CONFLICT OF INTEREST
The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.