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**[ CASE REPORT ]**

## Successful Treatment with Ramucirumab Plus Erlotinib following Osimertinib-induced Interstitial Lung Disease

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**Abstract:**

Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) are key drugs for patients with EGFR mutation-positive non-small cell lung cancer, and osimertinib is the standard treatment. Although drug-induced interstitial lung disease (ILD) is a remarkable adverse event of EGFR-TKIs, evidence regarding the continuation and re-challenge of EGFR-TKIs after drug-induced severe ILD is lacking. This is the first report of successful switching to ramucirumab plus erlotinib after osimertinib-induced severe ILD in an 81-year-old woman with stage IV lung adenocarcinoma harboring the EGFR L858R mutation in exon 21. These findings suggest that ramucirumab plus erlotinib may be a viable treatment option for osimertinib-induced severe ILD.

**Key words:** ramucirumab, erlotinib, osimertinib, drug-induced interstitial lung disease, lung adenocarcinoma

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### Introduction

Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) are key drugs for treating patients with EGFR mutation-positive non-small cell lung cancer (NSCLC). Osimertinib, a third-generation EGFR-TKI, has shown better outcomes than other EGFR-TKIs (1, 2). However, drug-induced interstitial lung disease (ILD) is recognized as a remarkable adverse event associated with EGFR-TKIs, especially osimertinib (1-3).

We herein report a case of successful switching to ramucirumab plus erlotinib after osimertinib-induced severe ILD in an 81-year-old woman with stage IV lung adenocarcinoma harboring the EGFR L858R mutation in exon 21.

### Case Report

An 81-year-old woman without a history of smoking visited the Department of Dermatology at our hospital because of chronic eczema managed with an antiallergic drug.

She was diagnosed with stage IV lung adenocarcinoma with a mass in the right lower lobe of the lung, pleurisy, and bone metastases (cT2aN2M1c) (Figure A). Genetic test-

ing using multiplex polymerase chain reaction (PCR) revealed an EGFR L858R mutation in exon 21. Although she had chronic eczema, there was no evidence of a connective tissue disorder in the autoimmune antibody test. The Eastern Cooperative Oncology Group performance status was 1, and she received osimertinib at a dose of 80 mg daily as first-line treatment.

After 44 days of osimertinib treatment, the patient complained of dyspnea on exertion. Her body temperature (36.4°C), blood pressure (122/81 mmHg), pulse rate (89 beats/minute), and respiratory rate (16 breaths/minute) were measured. Percutaneous oxygen saturation was within 90% (room air), and oxygen was administered at a rate of approximately 2 L/min (via a nasal cannula). Laboratory tests showed slightly elevated C-reactive protein (0.90 mg/dL), and elevated Krebs von den Lugen-6 (518 U/mL).

Chest computed tomography (CT) showed diffuse ground-glass opacities in both lungs, although primary lung cancer and cancer pleurisy slightly decreased (Figure B). Differential diagnoses of viral infections such as COVID-19, heart failure, or drug-induced ILD were considered. She had no symptoms of a common cold, such as runny nose, sore throat, or cough, and COVID-19 PCR was negative. There were no findings suggestive of heart failure, such as leg



**Figure.** (A) Chest computed tomography (CT) before osimertinib initiation showed a mass on the right lower lobe of the lung and right pleural effusion. (B) Chest CT, 44 days after osimertinib initiation, showed diffuse ground glass opacities (GGOs) in both lungs. (C) Chest CT before erlotinib initiation showed improvement of the GGOs and increase in tumor size and pleural effusion.

edema or weight gain. No drugs other than osimertinib that could cause drug-induced ILD had been initiated in the past few months. Therefore, the patient was diagnosed with grade 3 osimertinib-induced ILD.

Osimertinib was discontinued immediately, and intravenous pulses of methylprednisolone (1,000 mg daily) were initiated. After 3 days of intravenous methylprednisolone pulses, oral prednisolone (1 mg/kg daily) was initiated. After initiating ILD treatment, her breathing and oxygen requirements improved promptly, allowing the gradual tapering of prednisolone. When the dose of prednisolone was tapered to 5 mg, CT showed an improvement in ILD; however, the primary lung cancer and right pleural effusion increased (Figure C). Therefore, sequential treatment was required.

There was no decline in her performance status (1), and the patient preferred to use EGFR-TKIs rather than cytotoxic chemotherapy. Informed consent regarding the risk of ILD recurrence was obtained from the patient. Therefore, we decided to treat her with ramucirumab and erlotinib. Erlotinib was initiated at a dose of 100 mg daily without ramucirumab, in consideration of her age and chronic skin disease. No adverse events were observed during the first month after starting erlotinib; therefore, ramucirumab (10 mg/kg daily) was added to erlotinib. The patient had been receiving treatment with ramucirumab plus erlotinib for one year without disease progression or recurrence of ILD.

## Discussion

To our knowledge, this is the first report of a successful switch to ramucirumab plus erlotinib following osimertinib-induced severe ILD. EGFR-TKIs are key drugs for patients with EGFR mutation-positive NSCLC, and osimertinib is the standard treatment for such patients (1, 2). However, drug-induced ILD is an important adverse event associated with EGFR-TKIs, and the incidence of osimertinib-induced ILD is higher than that of other EGFR-TKIs, especially in the Asian subset (1-3).

The incidence of osimertinib-induced ILD is approximately 12% in Japanese individuals (4). However, despite its high incidence, osimertinib-induced ILD usually responds to steroid therapy (4). Although the strategy of treatment after

osimertinib-induced ILD is important, evidence regarding the continuation and re-challenge of osimertinib after osimertinib-induced severe ILD is lacking. Sequential treatment options for patients with osimertinib-induced ILD are re-administration of osimertinib, switching to another EGFR-TKI, or switching to cytotoxic chemotherapy. A previous retrospective study showed that when osimertinib was re-administered to 33 patients after osimertinib-induced ILD (grade 1-2, except for a single patient), 5 (15%) had recurrence of osimertinib-induced ILD (5). In our case, the patient had grade 3 ILD; therefore, readministration of osimertinib was considered difficult.

Consequently, switching to another EGFR-TKI was considered. Several cases of successful switching to afatinib after osimertinib-induced ILD have been reported (6). In addition, a previous retrospective study showed that the risk of recurrent ILD was lower with switching to erlotinib than with osimertinib rechallenge after severe osimertinib-induced ILD (7).

Vascular endothelial growth factor (VEGF) is suggested to be involved in the exacerbation of interstitial pneumonia. Patients with idiopathic pulmonary fibrosis or progressive fibrosing ILD are treated with VEGF receptor inhibitors such as nintedanib (8, 9). Antibodies against VEGF, such as bevacizumab or ramucirumab, can be used in combination with chemotherapy. A previous retrospective study reported that chemotherapy regimens combined with bevacizumab for patients with pre-existing ILD might reduce the incidence of interstitial pneumonia exacerbation compared with chemotherapy regimens without bevacizumab (10). The phase 3 RELAY study revealed significant improvement in the progression-free survival with ramucirumab plus erlotinib compared to placebo plus erlotinib in untreated EGFR-mutation-positive NSCLC (11). In that study, the incidence of drug-induced ILD in the erlotinib group was 3.1%, whereas that in the ramucirumab plus erlotinib group was 1.8%, which was not significantly different but trended lower (11). In a phase 2 study comparing osimertinib plus bevacizumab with osimertinib, the incidence of drug-induced ILD of any grade was lower with osimertinib plus bevacizumab (3%) than with osimertinib alone (18%) (12). In contrast, a phase 2 study comparing docetaxel plus ramu-

circumab with docetaxel revealed that the incidence of severe drug-induced ILD was similar between the two groups (13). Another phase 2 study comparing osimertinib plus bevacizumab with osimertinib in EGFR T790M mutation-positive patients also revealed that the incidence of drug-induced ILD was similar between the two groups (14). Although there are conflicting results, we consider that combining an antibody against VEGF with chemotherapy may reduce the risk of drug-induced ILD.

In the RELAY study, the incidence of dermatitis acneiform was similar between the two groups, but the incidence of grade  $\geq 3$  adverse events, including dermatitis acneiform, was higher with ramucirumab plus erlotinib than with erlotinib (15, 16). In the ramucirumab plus erlotinib group, the incidence of grade  $\geq 3$  adverse events was higher in patients  $\geq 70$  years old than in those  $< 70$  years old (15). In our case, given the patient's age of 81 years old, the high risk associated with ramucirumab plus erlotinib, and the reduction effect of ILD with the addition of ramucirumab, we decided to start erlotinib without ramucirumab and sequentially add ramucirumab.

## Conclusion

Here, we describe a case of successful switching to ramucirumab plus erlotinib after osimertinib-induced severe ILD. Our case showed that ramucirumab plus erlotinib may be a viable treatment option for osimertinib-induced severe ILD.

## Author's disclosure of potential Conflicts of Interest (COI).

Motoko Tachihara: Honoraria, Eli Lilly Japan.

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