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Case Report

# Promising Combination Therapy with Bevacizumab and Erlotinib in an EGFR-Mutated NSCLC Patient with MET Amplification Who Showed Intrinsic Resistance to Initial EGFR-TKI Therapy

Nobuhiko Seki Maika Natsume Ryosuke Ochiai Terunobu Haruyama Masashi Ishihara Yoko Fukasawa Takahiko Sakamoto Shigeru Tanzawa Ryo Usui Takeshi Honda Shuji Ota Yasuko Ichikawa Kiyotaka Watanabe

Division of Medical Oncology, Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan

**Keywords**
Lung cancer · EGFR mutation · MET amplification · Erlotinib · Bevacizumab

**Abstract**
In lung cancer, several potential mechanisms of intrinsic and acquired resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have been explored, including mesenchymal-epithelial transition factor (MET) signaling pathway activation. On the other hand, vascular endothelial growth factor (VEGF) production of EGFR-mutated lung cancer cells is stimulated by predominantly activated MET signaling pathway. Therefore, the inhibition of VEGF axis as the downstream target of MET signaling pathway seems promising. Here, for the first time, we report the potential efficacy of combination therapy with bevacizumab and erlotinib in an EGFR-mutated NSCLC patient with MET amplification who showed intrinsic resistance to initial EGFR-TKI therapy. The patient was a 60-year-old male smoker, showing performance status (PS) 2, who presented with stage IV lung adenocarcinoma (cT4N2M1a)

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Nobuhiko Seki, MD, PhD
Division of Medical Oncology, Department of Internal Medicine
Teikyo University School of Medicine, 2–11–1, Kaga
Tokyo 173–8606 (Japan)
E-Mail nseki@med.teikyo-u.ac.jp

harboring the EGFR exon 19 deletion mutation. He was started on gefitinib at 250 mg/day. However, by 28 days, his symptoms further deteriorated along with the increased tumor size, resulting in PS 3. Then, repeat biopsy was performed, showing the positive MET amplification and the preserved EGFR exon 19 deletion mutation. Therefore, on the basis of the potential efficacy for activated MET signaling pathway as well as the confirmed safety by the known phase II trial for EGFR-mutated patients, the patient was started on combination therapy with bevacizumab at 15 mg/kg every 3 weeks plus erlotinib at 150 mg/day. By 21 days, his symptoms gradually improved along with the decreased tumor size, resulting in better PS with no severe toxicities.



## Introduction

Sensitizing mutations in the epidermal growth factor receptor (EGFR) gene are associated with marked responses to EGFR tyrosine kinase inhibitors (TKIs), such as gefitinib, erlotinib, and afatinib, in advanced non-small-cell lung cancer (NSCLC) patients [1]. However, up to 20% of NSCLC patients show poor initial clinical response to EGFR-TKIs although they harbor a sensitizing EGFR mutation [2]. These patients represent a subgroup that is intrinsically resistant to EGFR-TKI treatment, and several potential mechanisms of intrinsic resistance to EGFR-TKIs have been explored, including mesenchymal-epithelial transition factor (MET) signaling pathway activation [2]. To date, several novel strategies have been developed to target activated MET signaling pathway [2]. However, efficacy of bevacizumab in combination with erlotinib has not been reported in EGFR-mutated NSCLC patients with MET amplification who showed intrinsic resistance to initial EGFR-TKI therapy. Here, we report the promising efficacy of combination therapy with bevacizumab and erlotinib to such a case.

## Case Report

A 60-year-old male smoker presented with persistent cough and severe right-back pain. His performance status (PS) was 2 by the pain despite opioid use in palliative care. In the imaging test of full body, chest X-ray and chest CT revealed a large lung mass, extending to posterior chest wall and vertebral body, surrounded by lymphangitic carcinomatosis in the right lower lung as well as multiple lymphadenopathy and right pleural effusion (Fig. 1a, b). Bronchoscopic biopsy of the tumor lead to a diagnosis of primary lung adenocarcinoma (cT4N2M1a, stage IV) harboring the EGFR exon 19 deletion mutation. No other molecular analysis was performed. The patient was started on gefitinib at 250 mg/day for the treatment of lung adenocarcinoma. However, by 28 days after the start of gefitinib therapy, his symptoms further deteriorated along with the increased tumor size, resulting in PS 3 (Fig. 2a, b).

Then, repeat biopsy was performed from the lung tumor. First, in addition to the preserved EGFR exon 19 deletion mutation, EGFR T790M mutation was analyzed, resulting in negative status. Second, as a possible molecular alteration next to EGFR T790M mutation, fluorescence in situ hybridization (FISH) analysis for MET amplification was analyzed, resulting in positive status (mean MET per cell = 6.7, MET/CEP7 [centromeric enumeration probe for chromosome 7] ratio = 2.5). At this point, cytotoxic chemotherapy was not a candidate for treatment due to his poor PS. Furthermore, although crizotinib was known as potential MET inhibitor as well as anaplastic lymphoma kinase (ALK) inhibitor, combination therapy with crizotinib and EGFR-TKI was considered to lack the evidences about safety. Therefore,

combination therapy with bevacizumab and erlotinib was selected on the basis of the potential efficacy for activated MET signaling pathway as well as the confirmed safety by the JO25567 phase II clinical trial [3].

The patient was started on erlotinib at 150 mg/day plus bevacizumab at 15 mg/kg every 3 weeks. By 21 days after the start of this combination therapy, his symptoms gradually improved along with the decreased tumor size, resulting in better PS with no severe toxicities (Fig. 3a, b). However, after 2 cycles of bevacizumab administration, he unfortunately fractured his face from falling down during the rehabilitation to improve the deteriorated activity of daily life (ADL). Then, he underwent open reduction and fixation of his face fracture under general anesthesia. Eventually, he was forced to quit this promising combination therapy.

## Discussion

Resistance to EGFR-TKIs includes intrinsic (primary) and acquired (secondary) resistance. Intrinsic resistance is generally defined as a de novo inefficacy of EGFR-TKIs, whereas acquired resistance is generally defined as relapse of the tumor after a period of clinical response.

Recently, valuable insights have been gained into the molecular mechanisms of acquired resistance to EGFR-TKIs, including EGFR secondary mutations (e.g., T790M), phenotypic changes (e.g., small-cell lung cancer), and upregulation of bypass signaling pathways [4]. Among bypass signaling pathways, MET amplification is a well-characterized genetic alteration which drives erb-b2 receptor tyrosine kinase 3–dependent activation of downstream phosphoinositide 3-kinase/protein kinase B signaling, bypassing the inhibited EGFR [4]. On the other hand, although little is known about EGFR-TKI intrinsic resistance, major molecular mechanisms include EGFR T790M mutations, EGFR exon 20 insertions, BIM deletions, and upregulation of bypass signaling pathways (e.g., HGF overexpression and MET amplification) [2]. Acquired MET amplification accounts for approximately 5% to 10% of the resistant cases, whereas de novo MET amplification accounts for approximately 3% of EGFR-mutated NSCLC patients before treatment [5]. In our case, FISH analysis for MET amplification before EGFR-TKI treatment was not performed. However, according to the clinically-remarkable de novo resistance to initial EGFR-TKI, MET amplification seems to have existed as the intrinsic resistant mechanism.

Preclinical reports suggest that combined EGFR and MET inhibition is necessary to overcome resistance caused by concurrent MET amplification [6, 7, 8]. However, clinical reports regarding successful combination of EGFR and MET inhibitors in EGFR-mutated/MET-amplified NSCLC patients are limited [9, 10]. Here, for the first time, we have reported the potential efficacy of combination therapy with bevacizumab and erlotinib in an EGFR-mutated NSCLC patient with MET amplification who showed intrinsic resistance to initial EGFR-TKI therapy.

Regarding the rationale of combining bevacizumab with erlotinib, bevacizumab is an anti-angiogenic monoclonal antibody for vascular endothelial growth factor (VEGF), a key mediator of angiogenesis. VEGF production of EGFR-mutated lung cancer cells is stimulated by predominantly activating the MET/Gab1 axis, where Gab1 is known to be an important adaptor protein for MET signaling pathway [6]. Therefore, the inhibition of VEGF axis as the downstream target of MET signaling pathway seems promising. Actually, bevacizumab enhanced the antitumor activity of erlotinib in EGFR-mutated/MET-amplified NSCLC xenograft models, showing that combination therapy with bevacizumab and erlotinib significantly inhibited the tumor growth rate by approximately 50% compared with erlotinib alone [6, 7, 8].

In the clinical settings, the results of phase III study comparing bevacizumab plus erlotinib with erlotinib in patients with untreated NSCLC harboring a sensitizing EGFR mutation were presented at 2018 ASCO Annual Meeting as median PFS of 16.9 months in bevacizumab plus erlotinib arm and 13.3 months in erlotinib arm (HR 0.605, $p = 0.0157$) [11]. Furthermore, in this study, initial clinical response (some kind of shrinkage) was observed in all the patients treated with bevacizumab plus erlotinib. Therefore, this regimen is now considered as a new standard first-line treatment in EGFR-mutated NSCLC patients.

In conclusion, we have shown the promising combination therapy with bevacizumab and erlotinib in an EGFR-mutated NSCLC patient with MET amplification who showed intrinsic resistance to initial EGFR-TKI therapy.

## Statement of Ethics

The authors have no ethical conflicts to disclose.

## Disclosure Statement

The authors declare that they have no relevant financial interests.

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**Figure 1A**

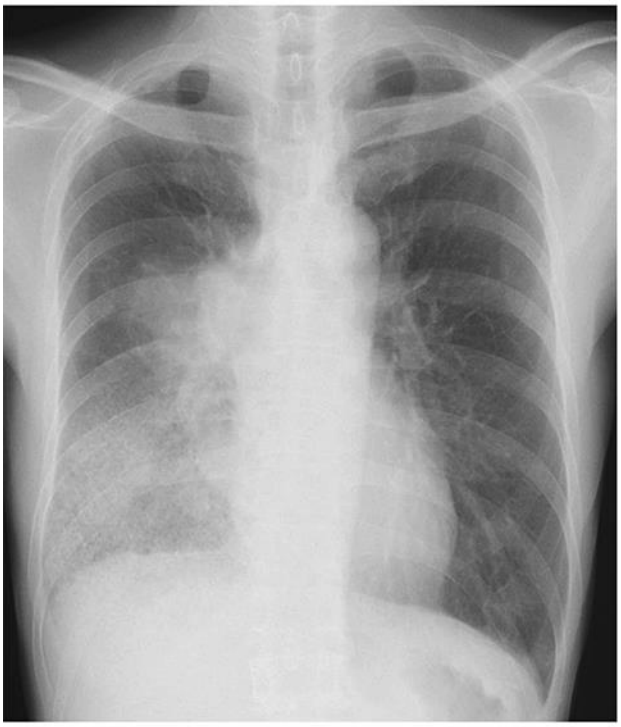


**Figure 1B**

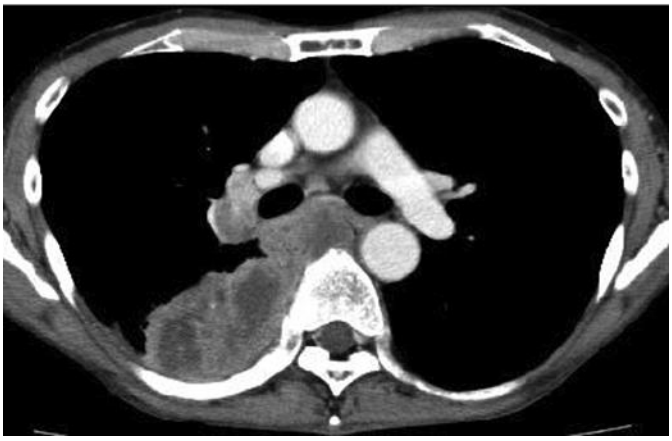
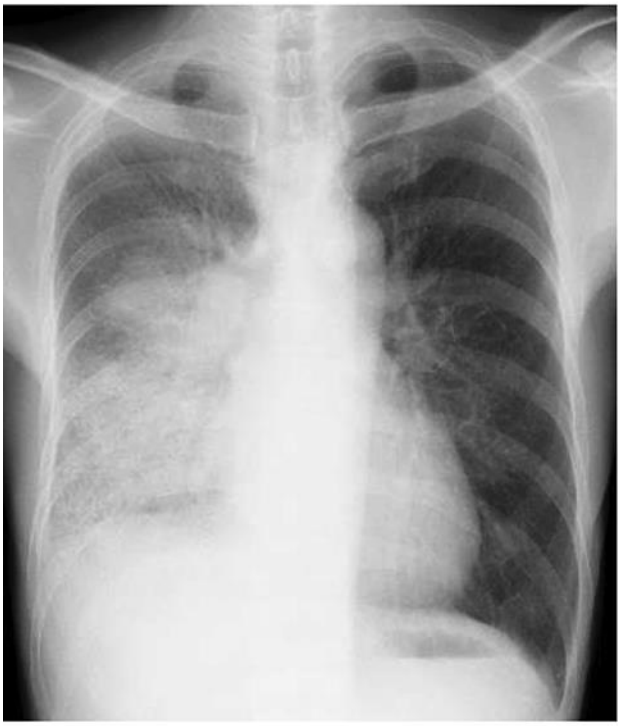


**Fig. 1.** Chest X-ray and chest CT images before initial EGFR-TKI treatment. (**a**) Chest X-ray image showed a right hilar mass followed by lymphangitic carcinomatosis in the right lower lung field. (**b**) Chest CT image showed a large lung mass, extending to posterior chest wall and vertebral body, in the right lower lung as well as multiple lymphadenopathy and right pleural effusion.

**Figure 2A**



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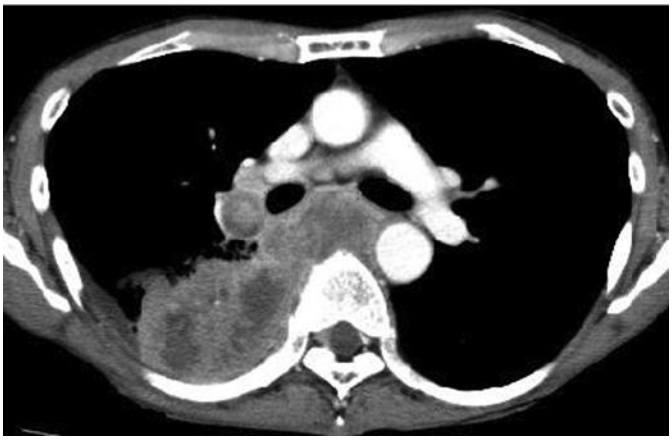

**Fig. 2.** Chest X-ray and chest CT images after 28 days of gefitinib therapy. (**a**) Chest X-ray image showed the increased right hilar mass and the worsened lymphangitic carcinomatosis. (**b**) Chest CT image showed interval progression of the lung mass and the lymphadenopathy.

**Figure 3A**

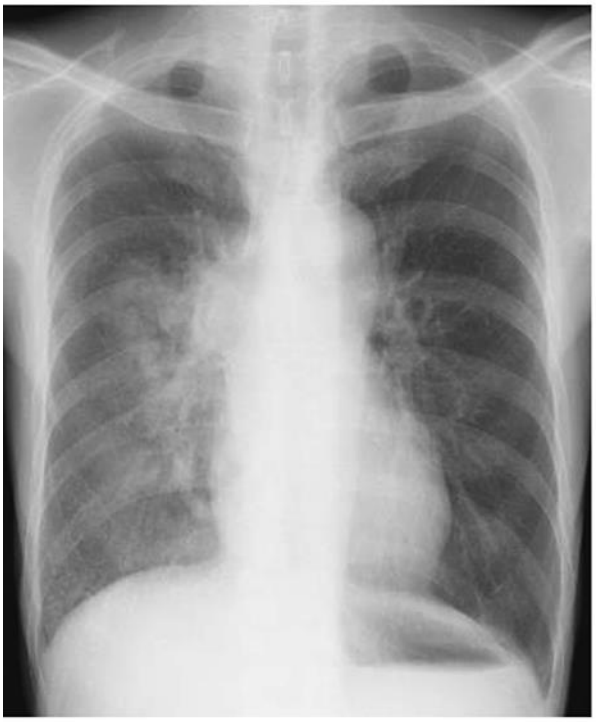

**Figure 3B**

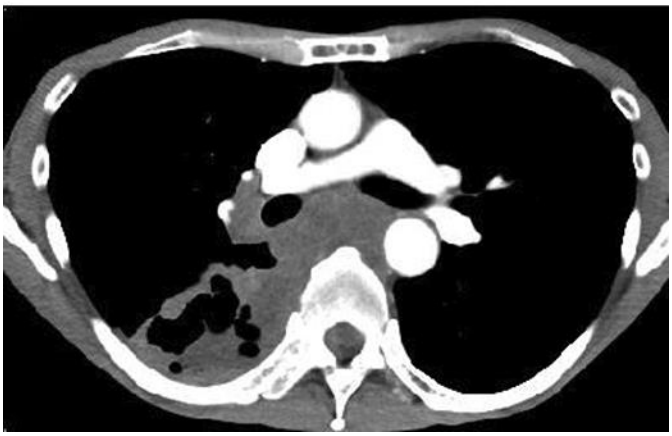

**Fig. 3.** Chest X-ray and chest CT images after 21 days of combination therapy with bevacizumab and erlotinib. (**a**) Chest X-ray image showed the decreased right hilar mass and the improved lymphangitic carcinomatosis. (**b**) Chest CT image showed interval response of the lung mass and the lymphadenopathy. Especially, cavitation of the lung mass as bevacizumab-specific response was observed.