



A rapid and durable response to cabozantinib in an osimertinib-resistant lung cancer patient with *MET* D1228N mutation: a case report

Yukun Kuang^{1,2#}, Jiyu Wang^{1,2#}, Peihang Xu^{1,2#}, Yifan Zheng^{3#}, Lihong Bai^{1,2}, Xue Sun^{1,2}, Zimu Li^{1,2}, Runjing Gan^{1,2}, Huixia Li^{1,2}, Zunfu Ke⁴, Kejing Tang^{1,2^}

¹Division of Pulmonary and Critical Care Medicine, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; ²Institute of Pulmonary Diseases, Sun Yat-sen University, Guangzhou, China; ³Department of Pharmacy, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; ⁴Department of Pathology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

#These authors contributed equally to this work.

Correspondence to: Zunfu Ke. Department of Pathology, The First Affiliated Hospital, Sun Yat-sen University, No. 58, Zhongshan Er Lu, Guangzhou 510080, China. Email: kezunfu@mail.sysu.edu.cn; Kejing Tang. Division of Pulmonary and Critical Care Medicine, The First Affiliated Hospital, Sun Yat-sen University; Institute of Pulmonary Diseases, Sun Yat-sen University, No. 58, Zhongshan Er Lu, Guangzhou 510080, China. Email: tangkj@mail.sysu.edu.cn.

Abstract: Osimertinib has efficacy superior to that of standard epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) for the first-line treatment of patients with EGFR-mutant advanced non-small cell lung cancer (NSCLC). However, patients treated with osimertinib eventually acquire drug resistance. *MET* missense mutations have been demonstrated to mediate resistance to MET-TKIs, such as crizotinib. But the role of *MET* missense mutations in mediating EGFR TKI resistance is undefined. With the increasing use of next-generation sequencing (NGS) at diagnosis, many mechanisms of acquired resistance have been discovered in patients with activated tyrosine kinase receptors. Herein, we report the first case of *MET* D1228N mutation mediating acquired resistance to osimertinib in a MET TKI-naïve NSCLC. The patient with advanced lung adenocarcinoma harboring *EGFR* exon 19 deletion initially responded to osimertinib with progression-free survival (PFS) lasting 11 months and then developed resistance with an acquired mutation of *MET* D1228N. Subsequently, combination therapy of cabozantinib and osimertinib was administered to the patient, and her clinical symptoms were rapidly relieved within one week with good tolerance. She remained on the combined treatment for 10 months. Finally, she achieved an overall survival (OS) of 25 months. Based on our findings, patient with *MET* D1228N mutant lung adenocarcinoma clinically benefited from combinatorial therapy of cabozantinib and osimertinib after osimertinib resistance.

Keywords: Lung adenocarcinoma; osimertinib resistance; *MET* D1228N mutation; cabozantinib; case report

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Introduction

The irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), osimertinib, is a preferred

first-line option for patients with *EGFR*-mutant metastatic non-small cell lung cancer (NSCLC) (1). With the wide application of osimertinib, its resistance mechanisms

[^] ORCID: 0000-0002-5454-4666.

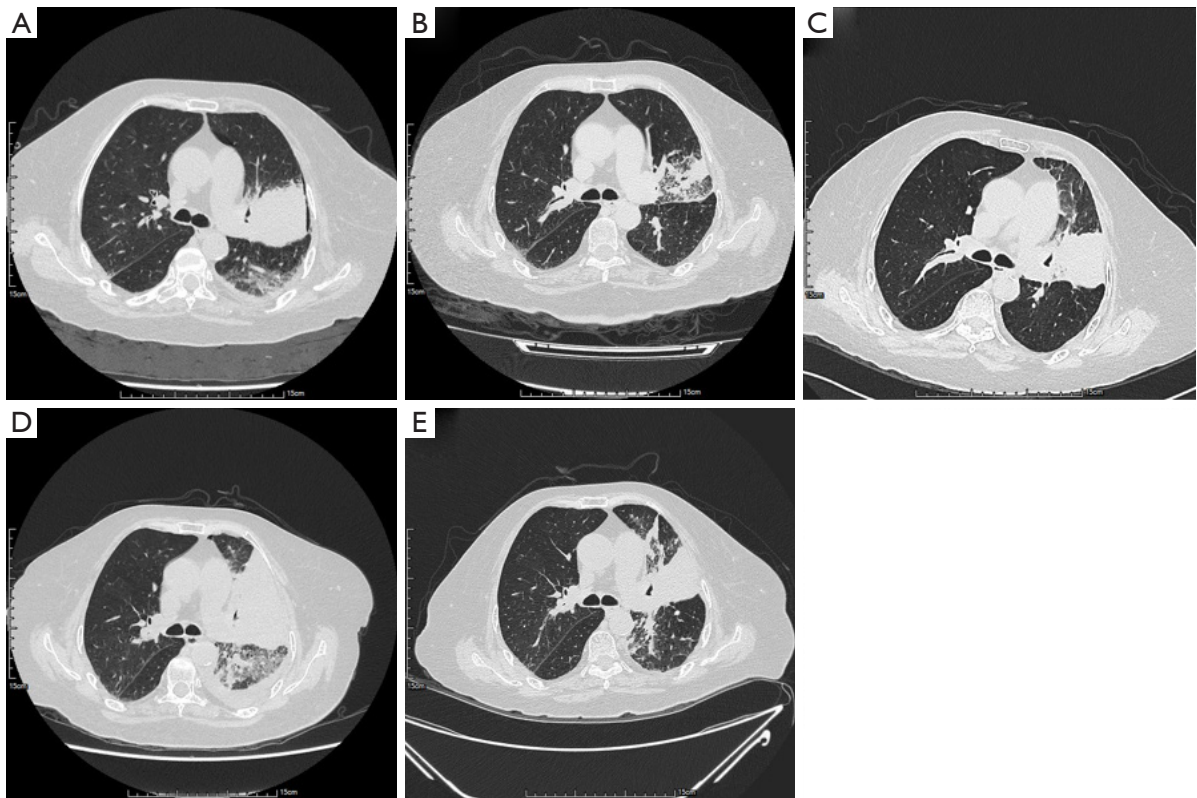


Figure 1 Chest CT images of an advanced NSCLC patient with EGFR exon 19 deletion. (A) At baseline. (B) Confirmed PR after 3 months of osimertinib. (C) Asymptomatic PD after 11 months of osimertinib. (D) Left lung lesion growth with left pleural effusion. (E) Immediate remission after the addition of cabozantinib. CT, computed tomography; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; PR, partial response; PD, progressive disease.

have been well elucidated, among which the activation of the *MET* pathway via *MET* gene activation and amplification is one of the most common bypass pathway mechanisms (2). Combining c-Met inhibitors, such as crizotinib, with osimertinib has been found to be effective in osimertinib-resistant *EGFR*-mutated NSCLC patients harbouring *MET* amplification (3). On the other hand, acquired mutations, including those at positions Y1230 and D1228, can occur over long-term exposure to *MET* inhibitors (4). However, bypass activation of *MET* by missense mutation has not been reported to mediate the resistance to *EGFR* TKIs thus far. In this study, we report the first case of *MET* D1228N mutation as the resistant mechanism to osimertinib in a *MET* TKI-naïve lung adenocarcinoma patient who subsequently benefited from the combinational therapy of *EGFR* and *MET* TKIs. We present the following case in accordance with the CARE reporting checklist (available at <https://dx.doi.org/10.21037/atm-21-3861>).

Case presentation

An 81-year-old female patient presented to the hospital in May 2018 with symptoms of productive cough and shortness of breath for several months. A chest computed tomography (CT) scan showed a 58 mm × 62 mm nodule in the left lung with multiple small nodules, enlarged mediastinal lymph nodes, and pleural effusions (Figure 1A). She was diagnosed with stage IV lung adenocarcinoma and capture-based next-generation sequencing (NGS) with a panel of 168 cancer-related genes (Lung Plasma, Burning Rock, Guangzhou, China) was conducted with a lung biopsy specimen. *EGFR* c.2236_2250del (p.E746_A750del) mutation (abundance 11.52%) was identified, and she thus received osimertinib (80 mg, qd) as the first-line therapy. Her symptoms improved rapidly, and no significant adverse events were observed. A chest CT evaluation 12 weeks later showed a partial response (PR) and the lung lesion significantly decreased (38 mm × 22 mm; Figure 1B). After 11 months

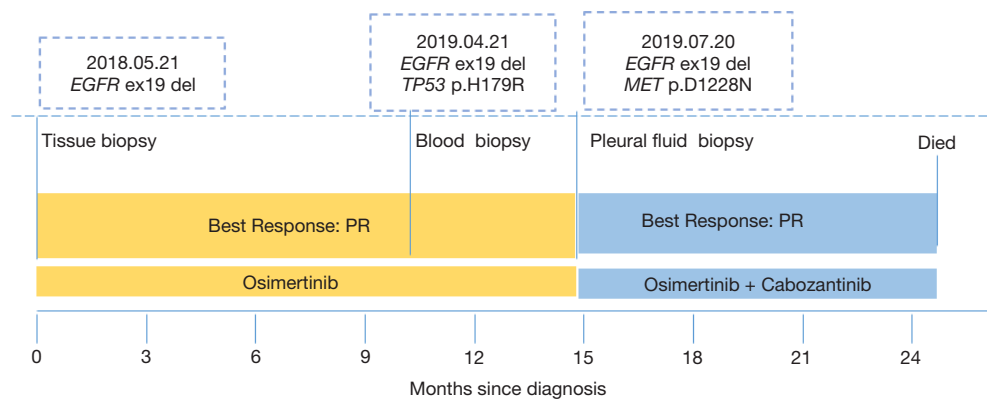


Figure 2 Timeline and duration of each treatment.

of disease control, a CT scan showed an enlarged left lung mass (66 mm × 50 mm; *Figure 1C*). Ultra-deep plasma-derived circulating tumor DNA (ctDNA) NGS revealed *EGFR* E746_A750del (abundance 0.54%) and *TP53* H179R mutation (abundance 1.32%). The patient presented asymptomatic disease progression (PD) and refused chemotherapy, so she continued osimertinib treatment (80 mg, qd). She was readmitted to the hospital with progressive aggravating symptoms in July 2019. Chest CT showed that the mass in the upper lobe of the left lung was enlarged and densified significantly with increased left pleural effusion (97 mm × 67 mm; *Figure 1D*), indicating PD with serious clinical symptoms. Along with intensive respiratory support, the patient received ultrasound-guided pleural puncture and catheterization. Hydrothorax exudate NGS showed *EGFR* E746_A750 deletion (abundance 4.95%) and *MET* D1228N missense mutation (abundance 3.86%). Treatment was subsequently changed to cabozantinib (40 mg, qd) plus osimertinib (80 mg, qd), and she experienced an overall improvement in her clinical symptoms within 1 week. Re-examination of CT 10 days later revealed that the primary lesion of the left lung had dramatically shrunk (65 mm × 65 mm; *Figure 1E*), and the efficacy was evaluated as PR. After discharge, the patient continued the combined treatment of cabozantinib and osimertinib, and no other adverse events occurred except for grade 2–3 diarrhea. Due to personal reasons, the patient did not return regularly. She took cabozantinib and osimertinib until her symptoms worsened again in May 2020. Finally, she died 1 month later with an overall survival (OS) of 25 months. The overall process of diagnosis and treatment is shown in *Figure 2*. All procedures performed in studies involving human participants were in accordance with

the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

The acquired resistance mechanisms to first-line or second-line osimertinib therapy have been illustrated, including *EGFR*-dependent and bypass resistance mechanisms. One of the most frequent causes of bypass pathway activation is *MET* amplification. Furthermore, oncogenic alteration *MET* exon 14 skipping can induce resistance to osimertinib, which has been confirmed in *EGFR*-mutated cell models (5). However, mutations in the *MET* tyrosine kinase domain have rarely been found in NSCLC as a secondary event resulting from exposure to prior therapies, such as TKIs (6).

In a recent case reported by Kang *et al.*, one patient benefited from the combination of osimertinib and cabozantinib after simultaneous development of secondary *MET* mutations upon crizotinib treatment (7). A combination of osimertinib and trastuzumab emtansine (T-DM1), a conjugate of the monoclonal antibody trastuzumab (Herceptin) and the cytotoxic agent DM1, was reported to delay and overcome osimertinib resistance in T790M-positive *EGFR*-mutated NSCLC cell lines that gained *HER2* amplification (8).

In our case, *MET* D1228N mutation, a known resistance mutation to type I *MET* inhibitors, was acquired after first-line osimertinib failure without any prior exposure to *MET* inhibitors. Given that D1228N shows an increased level of

tyrosine phosphorylation with respect to wild-type *MET* (9), we consider it could mediate the resistance to EGFR-TKI osimertinib.

MET D1228N mutation shows resistance to type I *MET* inhibitors, such as crizotinib and capmatinib, but displays sensitivity to type II inhibitors, such as cabozantinib *in vitro* (10). However, in clinical settings, the sensitivity of *MET* D1228N to *MET* inhibitors is equivocal. *MET* D1228N bypass activation was identified as the potential mechanism to crizotinib resistance in a *CD74-ROS1* fusion lung cancer patient. Second-line cabozantinib brought significant improvement and 3 months of progression-free survival for the patient (11). In another report, lung cancer patient who was resistant to osimertinib due to *MET* amplification received crizotinib and osimertinib therapy (7). Upon confirmation of PD, novel acquired *MET* mutations, D1228N/Y, Y1230H, and D1231Y were detected (7). The treatment was changed from crizotinib to cabozantinib, and, after the combinatorial treatment, repeat dynamic liquid biopsy revealed that all *MET* point mutations were undetectable, except for D1228N (7). The allelic fraction of this mutation increased compared to the baseline, suggesting the subclonal lesion bearing this variant was nonresponsive to cabozantinib (7). *MET* D1228N was also reported to be an acquired resistance mutation to crizotinib in an *MET*-amplified advanced triple-negative breast cancer patient. She was treated with cabozantinib for 7 weeks followed by rapid progression (12).

Although the efficacy of cabozantinib to *MET* D1228N mutation remains inconclusive, we treated our patient with cabozantinib and osimertinib after consulting with the patient and her family. Her clinical symptoms were rapidly relieved with 1 week, and she obtained an OS of 25 months. The limitation of this case was loss to follow up during late course of treatment, and the PFS was not available. Collectively, the effectiveness of cabozantinib against *MET* D1228N mutation may differ among patients due to the type of cancer, performance status, and other unknown tumor-intrinsic characteristics. Further investigations are still needed to elucidate the resistance mechanism of acquired *MET* D1228N mutations to develop more efficacious *MET* inhibitors.

Conclusions

Our study was the first to report that *MET* D1228N mutation can also mediate resistance to first-line osimertinib

therapy. Patient with *MET* D1228N mutation clinically benefited from combinatorial therapy of cabozantinib and osimertinib after osimertinib resistance.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://dx.doi.org/10.21037/atm-21-3861>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/atm-21-3861>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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