



Durable response to crizotinib in an advanced lung adenocarcinoma patient harboring rare *CD47-MET* fusion: a case report

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Background: *MET* fusion is a rare type of structure rearrangement, reported only in 0.26% of non-small cell lung cancer (NSCLC). Some uncommon genomic variants, including *MET* fusions, have been detected with advanced detection technology. Therapeutic option for *MET*-rearranged NSCLC remains largely uncovered.

Case Description: Herein, we described a 72-year-old male patient with a 10-year history of smoking who presented to our hospital with coughing, blood-tinged sputum, chest distress, and anhelation. He was diagnosed with stage IV lung adenocarcinoma harboring a *CD47 (EX7)-MET (EX15)* fusion, detected by next-generation sequencing (NGS). After one month of crizotinib treatment, the patient showed partial re-expansion of the collapsed right lower lobe, shrinkages of lymph node lesions, and reduced right pleural effusion. The patient achieved partial response (PR) to first-line treatment of crizotinib with a progression-free survival (PFS) of 8 months. Cabozantinib was subsequently administered, and a short-term PR of fewer than three months was observed. The patient retained *CD47-MET* fusion and acquired *MET* D1228E at cabozantinib progression.

Conclusions: This case provided the first clinical evidence for the efficacy of crizotinib in *CD47-MET* rearranged NSCLC and suggested *MET* D1228E as a resistance mechanism. NGS is a powerful tool for identifying rare *MET* gene variants in patients with NSCLC, which should be encouraged in clinical practice.

Keywords: Non-small cell lung cancer (NSCLC); *CD47-MET* fusion; *MET* D1228E; cabozantinib; case report

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Introduction

MET gene, located on chromosome 7q21-31, encodes a receptor tyrosine kinase, activated by the binding of hepatocyte growth factor (HGF). Activating alterations in *MET*, achieved mainly via overexpression, amplification, mutations, or alternative splicing, have been discovered in non-small cell lung cancer (NSCLC). The activity of *MET* tyrosine kinase inhibitors (TKIs), such as crizotinib, capmatinib, tepotinib, and savolitinib, varies by *MET* mutation category (1,2). *MET* fusion, a rare type of structure

rearrangement initially described in a few cases (3-5), has recently been reported in 0.26% of NSCLCs (6). Although sporadic cases have suggested the efficacy of crizotinib in NSCLC with *MET* fusion (3-5), the therapeutic relevance of this type of alteration remains largely uncovered and warrants further evidence. Herein, we presented a case of an advanced lung adenocarcinoma patient with *CD47-MET* fusion, who achieved a durable response of 8 months to crizotinib. We present the following case in accordance with the CARE reporting checklist (available at <https://tcr>.

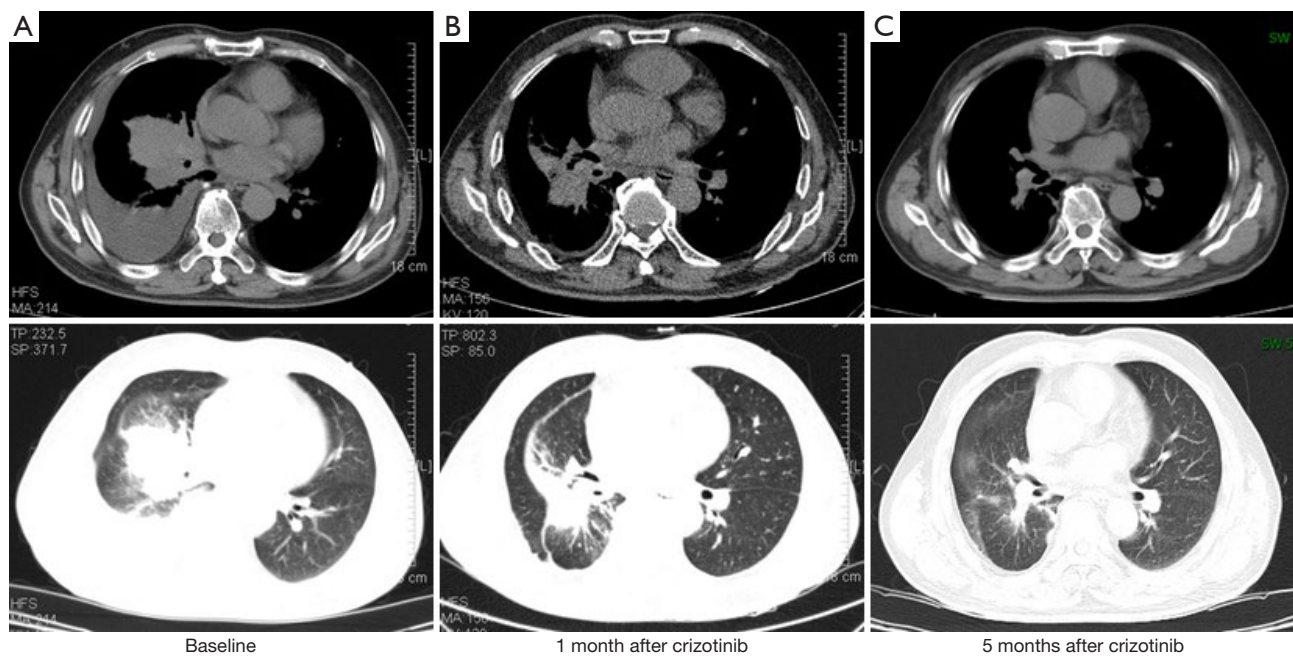


Figure 1 Tumor response to crizotinib treatment. (A) Baseline before treatment; (B) 1 month after crizotinib; (C) 5 months after crizotinib.

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Case presentation

In April 2019, a 72-year-old male with a 10-year history of smoking presented to our hospital with coughing and blood-tinged sputum accompanied with chest distress and anhelation for 2 weeks. Physical examinations reported no abnormal symptoms except for diminished breath sounds. Imaging results were shown in *Figure 1*. Chest computed tomography (CT) scan revealed multiple scattered nodules on both lungs, atelectasis of right lower lobe, a mass near the hilum of lung, multiple enlarged lymph nodes on right lung hilum and mediastinum, and right pleural effusion (*Figure 1A*). No brain metastases were observed. CT-guided percutaneous biopsy was performed for histopathological examination, which indicated stage IV lung adenocarcinoma. Immunohistochemistry results showed positive expression of PD-L1, and the tumor proportion score (TPS) was 5%. The biopsied tissue was sent for next-generation sequencing (NGS) using a 520-gene panel (Burning Rock Biotech, Guangzhou, China) and a *CD47 (EX7)-MET (EX15)* rearrangement (*Figure 2*) was identified with an allele frequency (AF) of 9.75%. No other mutation was detected. The results also revealed a tumor mutational burden (TMB) of 2.4 mutations/Mb and a microsatellite

stable status (MSS). Subsequently, crizotinib (250 mg/b.i.d. orally) was administrated starting from May 2019. After 1 month of treatment, the patient showed partial re-expansion of the collapsed right lower lobe, shrinkages of lymph node lesions, and reduction in right pleural effusion (*Figure 1B*). After 5 months of treatment, the patient remained as partial response (PR) (*Figure 1C*) with minimal side effects and eventually achieved a progression-free survival (PFS) of 8 months.

After progression on crizotinib, the patient was switched to cabozantinib in Feb 2020 with an initial dosage of 100 mg for 3 weeks, followed by a reduced dosage of 62.5 mg. A repeated chest CT performed in another hospital due to the COVID 19 pandemic in April 2020 (data was not available) revealed a significant shrinkage of the tumor lesion. Disease progressed in May 2020, and the patient was subsequently treated with a combination of pemetrexed and bevacizumab. A re-biopsy of the pulmonary lesion at cabozantinib progression was sent for NGS using a 168-gene panel (Burning Rock Biotech, Guangzhou, China), and results showed that the patients retained *CD47-MET* fusion (AF: 5.71%) and acquired a *MET D1228E* mutation (AF: 5.94%). No other mutation was identified. After two cycles of pemetrexed and bevacizumab treatment, the patient achieved a stable disease (data was not available). All procedures performed

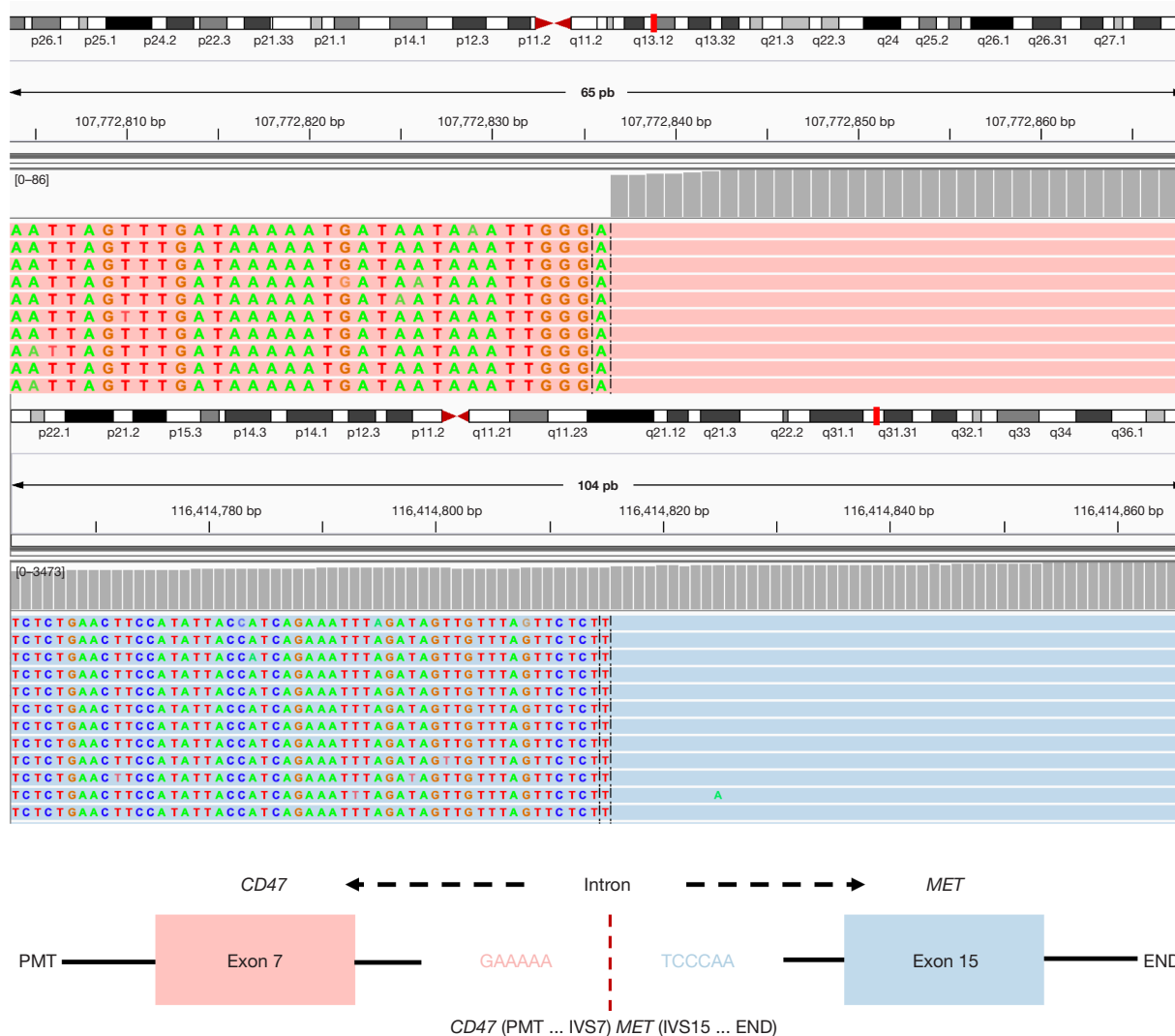


Figure 2 Illustration of *CD47-MET* fusion. The *CD47-MET* rearrangement had breakpoints in the *CD47* intron 7 and *MET* intron 14, which conferred the fusion of *CD47* exon 7 to *MET* exon 15. PMT, promoter; IVS, intervening sequence.

in this study 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 *CD47-MET* rearrangement identified in our case had breakpoints in the *CD47* intron 7 and *MET* intron 14,

which conferred the fusion of *CD47* exon 7 to *MET* exon 15 (Figure 2). This fusion was first identified in a stage IA lung adenocarcinoma patient who underwent surgical resection (7). However, the therapeutic relevance of this fusion has not been reported. Our study provides the first clinical evidence for the efficacy of crizotinib in *CD47-MET* rearranged NSCLC, which is in line with previous case reports on responses of *MET* fusions to crizotinib, including *HLA-DRB1-MET*, *MET-ATXN7L1*, *KIF5B-MET*, *STARD3NL-MET*, and *MET-UBE2H* (3-5,8,9). The response duration reported in these studies ranged from 4 months to 12 months with a median duration of 8 months,

consistent with the PFS of 8 months observed in our case.

Crizotinib, originally developed as a MET inhibitor, has now been approved by the FDA only for *ALK* or *ROS1* rearranged NSCLC patients. However, numerous studies have revealed clinical benefits with crizotinib in patients harboring *MET* amplification or *MET* exon 14 skipping mutation (10,11). Our case further supports that *MET* fusion represents a novel molecular target for crizotinib in NSCLC. The utility of MET TKIs was not fully understood in *MET* fusion-positive cancers, especially in NSCLC. Besides some isolated cases that have shown responses to crizotinib in *MET* fusion-positive NSCLC and gliomas (5,8,12), some clinical trials are underway to assess the efficacy of MET TKIs in cancers including those with *MET* fusions. At present, a phase II trial (NCT01639508) is underway to evaluate the effectiveness of cabozantinib in advanced NSCLC patients, including those with *MET* fusions. The efficacy of tepotinib, FDA approved for application in metastatic NSCLC patients with the METex14 mutation, was assessed with or without other TKIs in MET-driven NSCLC (NCT04739358). The safety and efficacy of TPX-0022, a MET/CSF1R/SRC inhibitor, are being evaluated in patients harboring *MET* fusions in a phase 1 study (NCT03993873). Another phase I clinical trial (NCT02978261) of a c-Met inhibitor PLB1001 was conducted in patients with PTPRZ1-MET fusion gene-positive recurrent high-grade gliomas.

MET D1228E mutation was identified at disease progression on second-line cabozantinib. Acquired *MET* D1228N/H/V has been reported to mediate resistance to type I MET TKIs (including crizotinib) through impaired drug binding (13,14). Since the genomic profile at crizotinib progression was unknown in our case, *MET* D1228E is more likely to emerge as a resistance mutation to crizotinib. *In vitro* and preliminary clinical evidence revealed that *MET* D1228V/H retained sensitivity to the type II MET inhibitor cabozantinib, while D1228N might confer resistance to it (13,14). Interestingly, *CD47-MET* fusion and *MET* D1228E were present at similar frequencies (5.71% and 5.94%, respectively) in the re-biopsy of the pulmonary lesion at cabozantinib progression, suggesting that the two mutations might be on the same allele of the *MET* fusion gene. However, they were located in exon 15 and exon 19, respectively, and we can't confirm it by DNA-based NGS. In our study, the response to cabozantinib was initially observed but failed to sustain. Both *CD47-MET* fusion and *MET* D1228E were retained at cabozantinib progression. Therefore, the

responsiveness of *CD47-MET* fusion and *MET* D1228E to cabozantinib remains inconclusive and requires further exploration.

In conclusion, we described the first case for the efficacy of crizotinib in *CD47-MET* rearranged NSCLC and suggested *MET* D1228E emerging as a putative resistance mechanism. Our study highlights the therapeutic actionability of *MET* fusion and paves the way for establishing therapy for *MET*-rearranged NSCLC.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-141/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-141/coif>). 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 this study 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 provided by the patient for publication of this case report and any accompanying images.

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