

Osimertinib and Capmatinib Combination Therapy to Overcome *MET* Y1003N-Mediated Resistance in *EGFR*-Mutant NSCLC: A Case Report



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ABSTRACT

Osimertinib, a third-generation *EGFR* tyrosine kinase inhibitor, is the frontline standard in the treatment of metastatic *EGFR*-mutant NSCLC. Although osimertinib is effective, disease progression occurs in virtually all patients, mediated by a heterogeneous array of resistance mechanisms. Activation of the *MET* signaling pathway by means of amplification has been implicated in resistance to osimertinib, but activation caused by point mutations in *MET* has not been well described. Here, we present the case of a 65-year-old female with metastatic *EGFR*-mutant NSCLC whose disease progressed on osimertinib owing to emergence of *MET* Y1003N mutation. She subsequently received capmatinib in combination with osimertinib and achieved a partial response. This case illustrates a potential role for dual *EGFR/MET* inhibition in *EGFR*-mutated NSCLC with resistance driven by activating *MET* mutations.

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Keywords: NSCLC; Osimertinib; MET; EGFR; Y1003N; Case report

Introduction

On the basis of results from the phase 3 FLAURA study, the tyrosine kinase inhibitor (TKI) osimertinib is the frontline standard in the treatment of advanced NSCLC with activating alterations in the *EGFR* gene.¹⁻³ Although response rates are robust, acquired resistance is expected for nearly all patients. Mechanisms of

resistance to osimertinib are diverse and include development of secondary *EGFR* mutations, activation of bypass signaling pathways, histologic transformation to squamous or SCLC, and epithelial-mesenchymal transition, among others. Activation of the *MET* pathway by means of gene amplification and, less frequently, emergence of exon 14 skipping alterations have been implicated in resistance to osimertinib,^{4,5} but activation caused by point mutations in *MET* has not been well described.

Here, we describe the case of a patient with metastatic *EGFR*-mutant NSCLC who experienced disease progression on osimertinib owing to the development of a *MET* Y1003N mutation. The patient received

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osimertinib and capmatinib, a potent selective inhibitor of *MET*, with a sustained partial response to treatment. This case illustrates *MET* Y1003N as a point mutation for resistance to osimertinib and the potential role of combination therapy in *EGFR*-mutated NSCLC with secondary resistance driven by *MET* mutations.

Case Presentation

A 65-year-old female with a remote history of hormone receptor-positive infiltrating ductal carcinoma of the left breast diagnosed in 2011 with completion of lumpectomy, radiation therapy, and adjuvant anastrozole was incidentally found to have a 4.5-cm left lower lobe lung mass with mediastinal adenopathy and several small lung nodules bilaterally on a computed tomography (CT) scan in June 2018. Bronchoscopic evaluation result 1 month after revealed lung adenocarcinoma in the right paratracheal lymph node. A positron emission tomography scan result at this time revealed extensive bone metastases involving the L1 vertebral body and sacrum and a lesion in the rectum. Brain magnetic resonance imaging (MRI) result revealed several brain lesions, with the largest measuring $1.8 \times 1.5 \times 1.9$ cm, throughout the cerebrum and one lesion in the right cerebellum measuring $1.9 \times 0.8 \times 0.8$ cm. Colonoscopy result revealed a lesion in the rectum, and disease revealed moderately differentiated rectal carcinoma, a separate primary cancer. Her lung cancer harbored an *EGFR* exon 19 deletion mutation (COBAS *EGFR* mutation test). For stage IV *EGFR*-mutant NSCLC, she was started on osimertinib 80 mg once daily in July 2018 and simultaneously completed stereotactic radiosurgery to the four larger brain lesions, including the right cerebellar and parietal lesion in August 2018. She achieved a partial response to osimertinib with shrinkage of smaller brain lesions not treated with stereotactic radiosurgery and reduction in size of left lower lung mass. For stage III rectal cancer, she received a short course of pelvic radiotherapy in September 2018, followed by low anterior resection with diverting loop ileostomy. Adjuvant chemotherapy was not given for the rectal cancer owing to concern about toxicity in the setting of treatment with osimertinib. Given her history of multiple cancers, she was seen by a genetic counselor. Her hereditary predisposition panel was only notable for an alteration in *RAD51C* (variant of unknown significance).

Nineteen months into treatment with osimertinib, she developed unsteadiness, intermittent headaches, neck pain, and dizziness. A brain MRI scan result revealed an increase in size of a previously irradiated right cerebellar lesion from 0.5 cm to 0.9 cm with surrounding vasogenic edema. She received a two-week course of dexamethasone without improvement in her symptoms. After 3

months, result of a perfusion MRI of the brain revealed a mild enlargement of the right cerebellar lesion with increased blood flow concerning for tumor growth. After multidisciplinary discussion, she underwent resection of the right cerebellar lesion. Pathology revealed a focus of viable carcinoma and normal cerebellar tissue with focal vascular atypia consistent with radiation-induced changes. The cancer cells were positive for TTF-1 and negative for HER2, ER, and PR, consistent with lung adenocarcinoma. There was involvement of the leptomeninges by malignant cells. She underwent a lumbar puncture (LP) owing to persistent neurologic symptoms, and cerebrospinal fluid (CSF) analysis including cytologic evaluation confirmed leptomeningeal disease (LMD) by presence of rare malignant cells. No sufficient tissue from the resected brain sample was available for molecular testing. Targeted next-generation sequencing (NGS; InVisionFirst-Lung, Inivata Inc., Durham, NC) performed on the CSF revealed the *EGFR* exon 19 deletion mutation and additionally *EGFR* amplification and a mutation in *TP53* Q144*. The dose of osimertinib was increased to 160 mg once daily. After 4 months, owing to progressive dizziness and concern about worsening LMD, she was started on carboplatin and pemetrexed plus osimertinib 80 mg once a day. She completed three cycles of chemotherapy plus osimertinib combination without significant side effects. A repeat LP obtained owing to worsening dizziness revealed elevated protein level (118 mg/dL), which was higher than 96 mg/mL on baseline CSF evaluation. NGS performed on the CSF again revealed *EGFR* exon 19 deletion, *EGFR* gene amplification, and *TP53* mutation, with increased variant allele frequencies (VAF) of *EGFR* exon 19 deletion (51.87%) and *TP53* (46.29%), compared with previous VAFs of 35.73% and 25.24%, respectively, in CSF 6 months before.

Three days after the repeat LP, she was admitted with acute kidney injury, hypoxia, nausea, vomiting, and weakness. A CT scan result of the chest obtained on admission revealed an increase in size and density of a right upper lobe (RUL) nodule and new nodules in the right lung (Fig. 1A), with bibasilar peripheral predominant ground-glass opacities. She underwent bronchoscopy, and pathology of a RUL nodule revealed poorly differentiated adenocarcinoma. Blood-based NGS (Guardant, Redwood City, CA) result revealed a novel *MET* Y1003N. Tissue-based NGS result on the RUL nodule revealed *EGFR* G719A and *RAD51C*, but no other alterations, including *MET* Y1003N. Given the emergence of *MET* Y1003N on blood-based NGS suggesting predominant circulating clones contained *MET*-driven resistance, capmatinib 300 mg twice a day was added to osimertinib 80 mg once daily, both of which were titrated up to 400 mg twice a day and 160 mg once daily. Three months

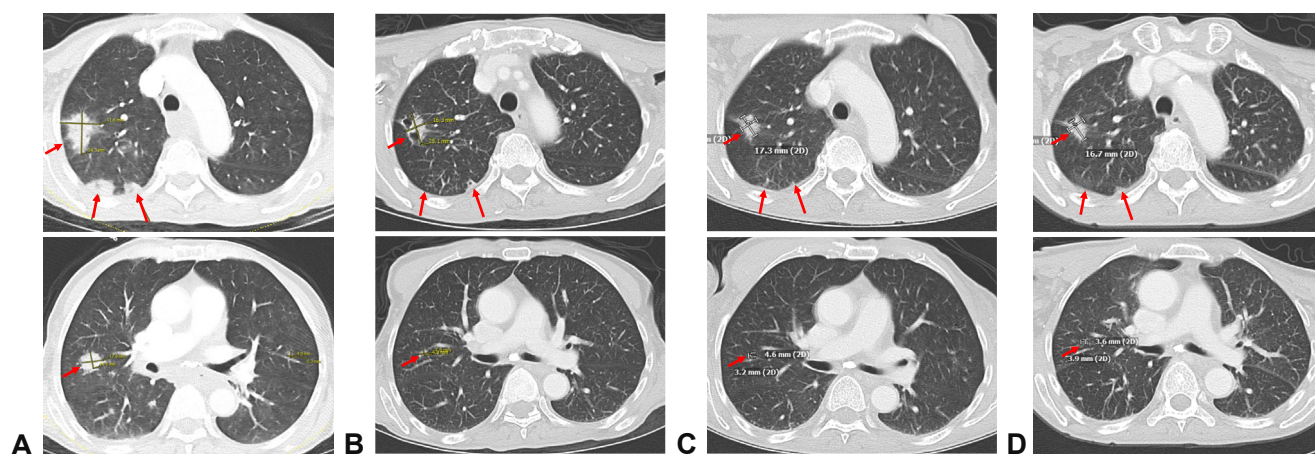


Figure 1. Imaging assessments during treatment. (A) CT chest demonstrating increasing size of RUL nodule with new lobulated pulmonary nodules in the right lung (upper figure) and a new RUL nodule (lower figure); (B) on-treatment CT chest 3 months after capmatinib initiation showing decrease in size of RUL nodules with near resolution of lobulated right lung nodules; (C) with continued response at 6 months; and (D) at 10 months. CT, computed tomography; RUL, right upper lobe.

after initiation of osimertinib and capmatinib, a response was observed in the chest with shrinkage of the right-sided lung lesions (Fig. 1B), which was confirmed on CT scans done at 6 and 10 months (Fig. 1C and D). Despite the improvement in lung lesions, the patient experienced progressive neurologic symptoms, including difficulty with ambulation and speech, owing to worsening of LMD. Eight months into the treatment with osimertinib and capmatinib, bevacizumab was added to the treatment regimen in hopes of improvement in LMD and was given for a total of three doses. The addition of bevacizumab did not provide any meaningful improvement in her neurologic symptoms. Her capmatinib was reduced to 200 mg twice daily owing to lower extremity edema (grade 3). Because of progressive LMD, she enrolled in hospice care 12 months after initiation of osimertinib and capmatinib.

Discussion

Despite the high response rates to EGFR TKIs in EGFR-mutated NSCLC, patients with NSCLC will inevitably develop resistance. Given the wide spectrum of possible resistance mechanisms to osimertinib, tissue- and plasma-based genotyping are crucial to guiding care. MET amplification is a well-established mechanism of acquired resistance to EGFR TKIs, but activating MET mutations have not been well described. Here, we present a case of a patient with metastatic EGFR-mutant NSCLC who experienced disease progression while on osimertinib owing to development of MET Y1003N mutation. This prompted change in therapy to combination osimertinib and capmatinib. This suggests that the MET Y1003N point mutation can mediate resistance to osimertinib and can be overcome by using EGFR and MET co-targeting.

The current data identify MET amplification, including MET exon 14 skipping mutations, as one of the most common mechanisms of resistance to osimertinib. MET amplification was found to occur in up to 10% of patients with EGFR-mutant NSCLC who progress on first-generation EGFR TKIs.⁶ MET-activating point mutations, such as Y1003N, are not as widely reported. In an analysis of resistance mechanisms in 93 patients with osimertinib-resistant NSCLC, mutations including MET P97Q and I865F, in addition to MET amplification, were identified.⁷ MET Y1003N is thought to result in over-activation of MET-mediated signaling by preventing Cbl E3 ligase-mediated degradation, similar to MET exon 14 skipping alterations, leading to cell proliferation and tumor growth.⁸

EGFR TKI plus MET TKI therapies have been studied primarily in the context of MET-amplified, EGFR-mutant NSCLC with progression on previous third-generation EGFR TKI treatment.^{9,10} The TATTON study explored various osimertinib combinations in the setting of differing mechanisms of acquired EGFR TKI resistance. In an expansion cohort of this study that included 180 participants, patients with MET-amplified, EGFR-mutant NSCLC whose disease progressed on a third-generation EGFR TKI were treated with the combination of osimertinib plus savolitinib. Treatment was effective and tolerable, with an overall response rate of 30%.⁸ In addition, crizotinib was found to have efficacy in patients with NSCLC with MET Y1003S point mutation.¹¹

Despite having a response in the lungs with the combination of osimertinib and capmatinib, the patient continued to have progression from her LMD with worsening neurologic symptoms. This is likely due to heterogeneity of resistance; the progressive LMD was probably not driven by the MET Y1003N mutation. The

MET Y1003N mutation was found only on blood-based NGS, and it was not identified on CSF-based NGS.

In addition, this case report highlights the need to develop better monitoring tools for LMD. In the absence of reliable monitoring tools for LMD, her disease status was gauged primarily by clinical symptoms supplemented by repeat LP. CSF analysis is an emerging method for monitoring of LMD. Several studies have revealed the feasibility of NGS on CSF samples.^{12,13} Additional studies are needed to understand the role of serial CSF-based NGS in evaluating the dynamics of LMD.

In summary, we present a novel case of a patient with progressive *EGFR*-mutant NSCLC on osimertinib who was found to have resistance mediated by *MET* Y1003N. To the best of our knowledge, this is the first case describing *MET* Y1003N as a mechanism of resistance to osimertinib. This case suggests a potential role for *EGFR* and *MET* co-targeting in progressive *EGFR*-mutated NSCLC with resistance driven by activating *MET* mutations.

Conclusions

We present the case of a patient with metastatic *EGFR*-mutant NSCLC who developed progression owing to resistance from *MET* Y1003N point mutation. The patient received osimertinib and capmatinib with partial response to therapy, highlighting a potential role of combination therapy in progressive *EGFR*-mutated NSCLC with resistance driven by activating *MET* mutations.

CRedit Authorship Contribution Statement

Molly Wilgucki, Vincent Yeung: Writing—original draft, Writing—review and editing.

Grace Ho, Gabriela L. Bravo Montenegro, Greg Jones, Joshua E. Reuss, Stephen V. Liu: Writing—review and editing.

Chul Kim: Conceptualization, Writing—original draft, Writing—review and editing, Supervision.

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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 national research committee(s) and with the Helsinki Declaration (as revised in 2013).

References

1. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in *EGFR* T790M-positive lung cancer. *N Engl J Med*. 2017;376:629-640.
2. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, *EGFR*-mutated advanced NSCLC. *N Engl J Med*. 2020;382:41-50.
3. Soria J, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated *EGFR*-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378:113-125.
4. Roper N, Brown AL, Wei JS, et al. Clonal evolution and heterogeneity of osimertinib acquired resistance mechanisms in *EGFR* mutant lung cancer. *Cell Rep Med*. 2020;1:100007.
5. Suzawa K, Offin M, Schoenfeld AJ, et al. Acquired *MET* exon 14 alteration drives secondary resistance to epidermal growth factor receptor tyrosine kinase inhibitor in *EGFR*-mutated lung cancer. *JCO Precis Oncol*. 2019;3:PO.19.00011.
6. Frampton G, Ali S, Rosenzweig M, et al. Activation of *MET* via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to *MET* inhibitors. *Cancer Discov*. 2015;5:850-859.
7. Yang Z, Yang N, Ou Q, et al. Investigating novel resistance mechanisms to third-generation *EGFR* tyrosine kinase inhibitor osimertinib in non-small cell lung cancer patients. *Clin Cancer Res*. 2018;24:3097-3107.
8. Socinski MA, Pennell NA, Davies KD. *MET* exon 14 skipping mutations in non-small-cell lung cancer: an overview of biology, clinical outcomes, and testing considerations. *JCO Precis Oncol*. 2021;5:PO.20.00516.
9. Sequist LV, Han JY, Ahn MJ, et al. Osimertinib plus savolitinib in patients with *EGFR* mutation-positive, *MET*-amplified, non-small-cell lung cancer after progression on *EGFR* tyrosine kinase inhibitors: interim results from a multicentre, open-label, phase 1b study. *Lancet Oncol*. 2020;21:373-386.
10. Wang Q, Yang S, Wang K, Sun SY. *MET* inhibitors for targeted therapy of *EGFR* TKI-resistant lung cancer. *J Hematol Oncol*. 2019;12:63.
11. Gao B, Zeng R. Case report: a 91-year-old patient with non-small cell lung cancer harboring *MET* Y1003S point mutation. *Front Med (Lausanne)*. 2022;8:772998.
12. Ge M, Zhan Q, Zhang Z, et al. Different next-generation sequencing pipelines based detection of tumor DNA in cerebrospinal fluid of lung adenocarcinoma cancer patients with leptomeningeal metastases. *BMC Cancer*. 2019;19:143.
13. Cobain EF, Wu Y, Vats P, et al. Assessment of clinical benefit of integrative genomic profiling in advanced solid tumors. *JAMA Oncol*. 2021;7:525-533.