CASE REPORT

Intracranial Activity of Osimertinib Plus Capmatinib in a Patient With *EGFR* and *MET*-Driven Lung Cancer: Case Report

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Received 19 February 2021; revised 23 February 2021; accepted 26 February 2021
Available online - 9 March 2021

ABSTRACT

We previously published in the *Journal of Thoracic Oncology* the case of a patient with *EGFR* and *MET*-driven lung cancer and extracranial response to capmatinib and osimertinib. Here, we report on a second patient treated with the same combination, revealing complete and durable intracranial response. Adding capmatinib to osimertinib seems to be an effective salvage therapy for patients with *EGFR*-mutant lung cancer and acquired *MET* amplification.

Keywords: Lung cancer; Targeted therapy; Capmatinib; Osimertinib; Case report

Introduction

Osimertinib has superior activity against brain metastases over other tyrosine kinase inhibitors.[1] Dose increase may delay progression in the central nervous system; however, long-term survival is limited, because tumors activate alternative signaling pathways.[2] One of the most frequent molecular mechanisms of osimertinib resistance is *MET* amplification.[3] Clinical trials are ongoing to test osimertinib in combination with MET inhibitors, including savolitinib or tepotinib. The MET inhibitor capmatinib as a single agent is approved for the treatment of patients with lung cancer and *MET* exon 14 skipping mutation.[4] In the *Journal of Thoracic Oncology*, we previously published a case report of a patient with durable remission of pulmonary metastases on capmatinib plus osimertinib, on the basis of high-level *MET* amplification at the time of progression on osimertinib alone.[5] The patient had previous irradiation of multiple brain metastases, and the disease is controlled for more than 22 months now, which encouraged us to treat a second patient with the same combination.

Case Presentation

The second patient described here is a 69-year old female never smoker, diagnosed with having metastatic lung adenocarcinoma and *EGFR* deletion 19 in 2017. She had initial therapy with osimertinib plus stereotactic radiosurgery for a solitary brain metastasis, and developed disseminated liver metastases, and hilar lymph node metastases in August 2019. Bronchoscopic rebiopsy result revealed high-level *MET* amplification, with gene copy number of 20, MET immunohistochemistry of 3 plus, and MET-to-CEN7 ratio of greater than 5 (Fig. 1*A* and *B*). Osimertinib was stopped, the patient received chemotherapy with carboplatin and pemetrexed, but the disease progressed systemically and with disseminated brain metastases. In January 2020, the patient was enrolled in the early access program of

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Disclosure: Prof. Dr. Gautschi is a consultant for Amgen and Eli Lilly and attended advisory boards for Eli Lilly and Bayer. Dr. Diebold declares no conflict of interest.

Cite this article as: Gautschi O, Diebold J. Intracranial Activity of osimertinib plus capmatinib in a patient with EGFR and MET-driven lung cancer: case report. *JTO Clin Res Rep*. 2021;2:100162.

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ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2021.100162

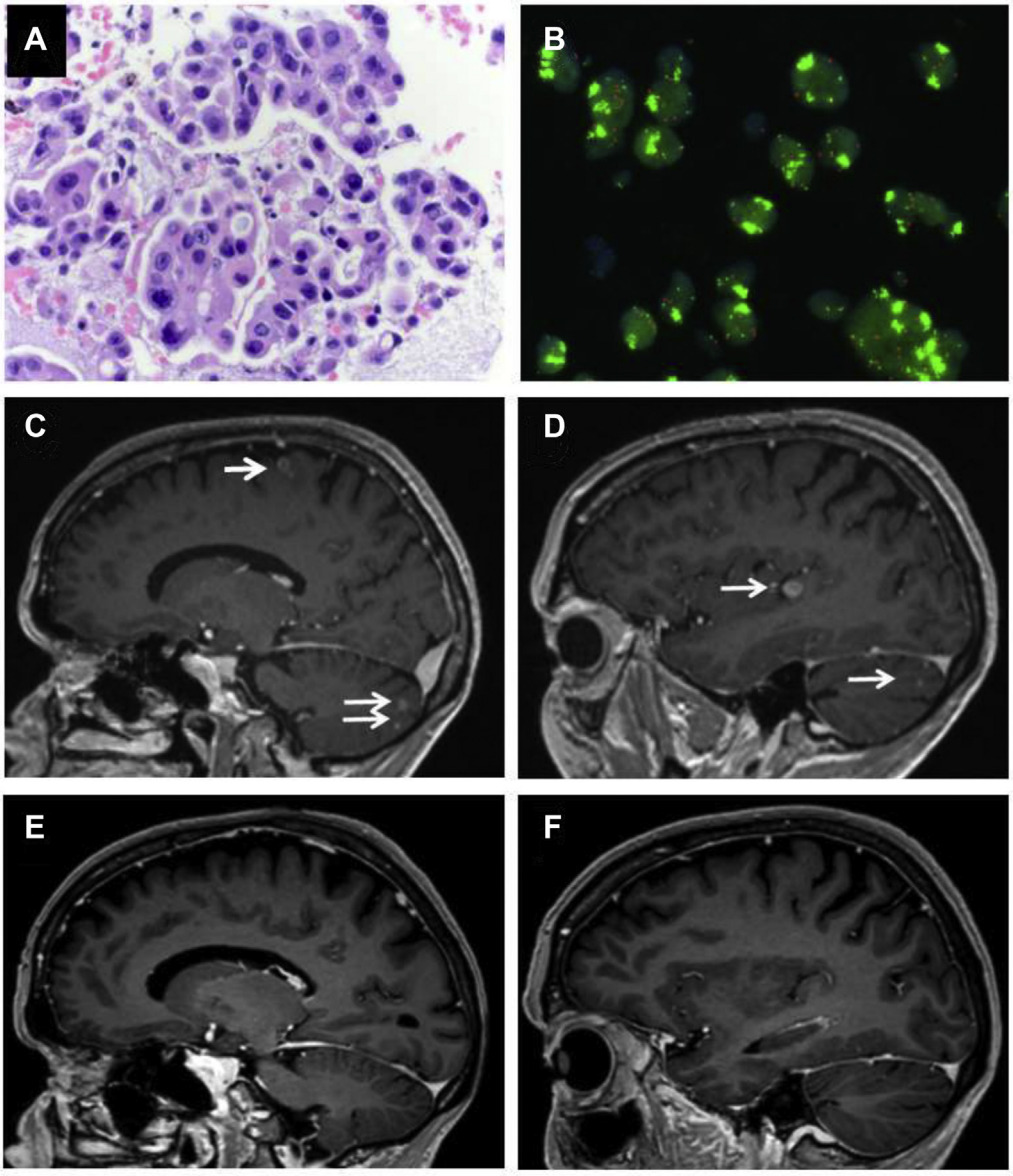

Figure 1. Tumor rebiopsy result revealing (*A*) lung adenocarcinoma, (*B*) MET-FISH result with clusters of green signals indicating high-level MET amplification. Brain MRI at the time of (*C*, *D*) tumor progression after osimertinib and chemotherapy, revealing multiple brain metastases (arrows), and (*E*, *F*) after 4 months of therapy with capmatinib plus osimertinib, revealing complete intracranial response. FISH, fluorescence in situ hybridization; MRI, magnetic resonance imaging.

Novartis, in which capmatinib 200 mg twice daily (50% of the recommended single-agent dose, on the basis of our previous patient) was started together with osimertinib 80 mg, leading to complete remission of all brain metastases (Fig. 1*C*–*F*). The patient remains on capmatinib (200 mg once daily) and osimertinib 80 mg for more than 12 months now (last imaging on January 2021). Tolerability is good, with grade 1 peripheral edema and grade 1 serum creatinine elevation.

Discussion

Addition of low-dose capmatinib to full-dose osimertinib is feasible and can induce durable remission of intracerebral and extracerebral metastases from tumors with *EGFR* mutation and acquired resistance to osimertinib associated with *MET* amplification. Rechallenge with osimertinib alone may also induce tumor remission to some extent, but brain metastatic tissue or serial blood samples were not available for the testing of *MET* and drug plasma levels. Rebiopsy

under chemotherapy was not feasible, because the condition of the patient required immediate therapy. However, the extent and durability of intracranial and extracranial response on capmatinib plus osimertinib, and the absence of skin and mucosal toxicity suggest that intracranial response is indeed mediated by dual target inhibition, rather than by osimertinib alone, or by elevated osimertinib plasma level by capmatinib.

Conclusion

Combination therapy with capmatinib and osimertinib seems to be an effective salvage therapy for patients with osimertinib-resistant lung cancer and acquired *MET* amplification. Clinical trials combining MET inhibitors with osimertinib are ongoing.

Acknowledgments

The patient provided consent to this publication. The authors thank Dr. Mannhard (Cham, Switzerland) for patient referral, Dr. Roos and A. Hirschmann from our institution for the images, and Novartis (Basel, Switzerland) for capmatinib and approval of this report.

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