CASE REPORT

Acquired Resistance to Osimertinib Plus Savolitinib Is Mediated by *MET*-D1228 and *MET*-Y1230 Mutations in *EGFR*-Mutated *MET*-Amplified Lung Cancer

Andrew J. Piper-Vallillo, MD,[a] Brian T. Halbert, MD,[a] Deepa Rangachari, MD,[a] Susumu S. Kobayashi, MD, PhD,[a,b] Daniel B. Costa, MD, PhD[a,*]

[a]*Department of Medicine, Division of Medical Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts*
[b]*Division of Translational Genomics, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center, Kashiwa, Chiba, Japan*

Received 10 June 2020; accepted 11 June 2020
Available online - 20 June 2020

Introduction

MET gene amplification is an established mechanism of acquired resistance to all classes of EGFR tyrosine kinase inhibitors (TKIs) in *EGFR*-mutated lung cancer. Novel strategies to target *EGFR*-mutated *MET*-amplified tumors in clinical trials have reported promising results, with a clear activity of the combination of osimertinib and savolitinib reported from the TATTON trial (NCT02143466) in 2020.[1] Savolitinib is a type IB–selective MET kinase inhibitor in the same class as capmatinib and tepotinib (Table 1).[2,3] There is a paucity of data on the mechanisms of acquired resistance to combination therapy with osimertinib and savolitinib. Here, we report a case of *EGFR*-mutated and *MET*-amplified lung adenocarcinoma that developed resistance to a combination therapy of osimertinib and savolitinib owing to MET-dependent mechanisms. The clinical, genomic, radiographic, and retrospective outcome data used for this case report have been compiled under an ongoing institutional review board–approved protocol at our institution with an appropriate waiver of consent.

Case Presentation

A 61-year-old Asian man with a previous 5-pack-year history of smoking initially presented with early stage node-positive lung adenocarcinoma. After initial management with lobectomy and adjuvant platinum doublet chemotherapy, within 1 year he developed widespread metastatic recurrence harboring *EGFR* delL747_T751 mutation. He was treated with oral erlotinib daily for 14 months before developing disease progression in his liver. Targeted biopsy revealed metastatic lung adenocarcinoma with *EGFR*-delL747_T751 (exon 19 deletion) and *MET* amplification (FoundationOne, Foundation Medicine). The MET:centrome_probe_SE7 ratio was 7.73 (cMET FISH Kreatech assay, Integrated Genetics, LabCorp), confirming high-level amplification.

*Corresponding author.

Drs. Piper-Vallillo and Halbert contributed equally to this work.

Disclosure: Dr. Costa reports receiving personal fees (consulting fees and honoraria) and nonfinancial support (institutional research support) from Takeda/Millennium Pharmaceuticals, AstraZeneca, and Pfizer; and nonfinancial support (institutional research support) from Merck Sharp & Dohme Corporation, Merrimack Pharmaceuticals, Bristol-Myers Squibb, Clovis Oncology, Spectrum Pharmaceuticals, and Tesaro outside of the submitted work. Dr. Rangachari reports receiving nonfinancial support (institutional research support) from Bristol-Myers Squibb, Novocure, and AbbVie/Stemcentrx, all outside of the submitted work. Dr. Kobayashi reports receiving research support from Boehringer Ingelheim, MiNA Therapeutics, and Taiho Therapeutics; and personal fees (honoraria) from Boehringer Ingelheim, Bristol-Myers Squibb, and Takeda Pharmaceuticals outside of the submitted work. The remaining authors declare no conflict of interest.

Address for correspondence: Daniel B. Costa, MD, PhD, Department of Medicine, Division of Medical Oncology, Beth Israel Deaconess Medical Center, 330 Brookline Ave., Boston, MA 02215. E-mail: dbcosta@bidmc.harvard.edu

Cite this article as: Piper-Vallillo AJ, et al. Acquired Resistance to Osimertinib Plus Savolitinib Is Mediated by *MET*-D1228 and *MET*-Y1230 Mutations in *EGFR*-Mutated *MET*-Amplified Lung Cancer. JTO Clin Res Rep 1:100071

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2020.100071

Table 1. MET TKI Activity Against MET Wild-Type and Activating Loop Mutations

Type	Name	MET Wild-Type	MET-D1228H	MET-D1228N	MET-D1228V	MET-Y1230C	MET-D1230H
Ia	Crizotinib	Sensitive	Resistant	Resistant	Resistant	Resistant	Resistant
Ib	Savolitinib	Sensitive	Resistant	Resistant	Resistant	Resistant	Resistant
Ib	Capmatinib	Sensitive	Resistant	Resistant	—	Resistant	Resistant
II	Cabozantinib	Sensitive	—	Sensitive	Sensitive	—	Sensitive
II	Glesatinib	Sensitive	Sensitive	Sensitive	—	Sensitive	Sensitive

Note: References numbers 2 to 6 were used to generate the modified heat map. Green indicates sensitivity whereas red indicates resistance, with the intensity of color indicating higher or lower preclinical inhibitory patterns. —, indicates data not available.
TKI, tyrosine kinase inhibitors.

Suspecting *MET* amplification as the mechanism of resistance to the EGFR TKI, he was transitioned to oral osimertinib 80 mg daily in combination with oral savolitinib 300 mg daily under the clinical trial TATTON;[1] he achieved partial response for 18 months before developing progressive disease (Fig. 1). Tissue biopsy confirmed adenocarcinoma, and next-generation sequencing of circulating tumor DNA (FoundationOne Liquid, Foundation Medicine) revealed *EGFR*-delL747_T751 mutation (allele frequency [AF] 3.3%), lack of *EGFR*-T790M and *EGFR*-C797S, *MET* amplification, and *MET* mutations (D1228H AF 15.6%, D1228N AF 1.8%, D1228Y AF 1.6%, and Y1230C AF 0.98%). Off-label oral cabozantinib 60 mg daily was added to oral osimertinib 80 mg daily in an effort to target these *MET* mutations (Table 1). Although he achieved stable disease (Fig. 1), he developed considerable fatigue, gastrointestinal toxicity, and cytopenias on dual-inhibitor therapy, thus requiring cessation of cabozantinib. A repeat liquid biopsy revealed the original truncal *EGFR* mutation, *MET*

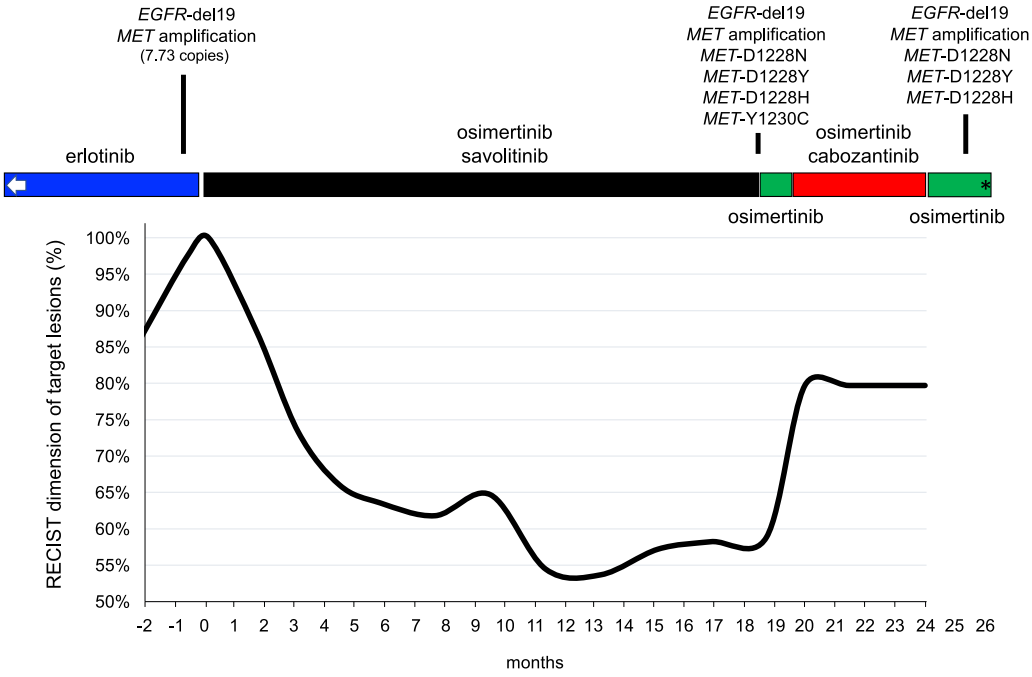

Figure 1. The clinical, radiographic, and genomic course of *EGFR*-mutant NSCLC with *MET*-mediated resistance before, during, and after osimertinib plus savolitinib therapy. Graphical representation of RECIST target lesion measurements in percentage (baseline set at 100% at the time before the commencement of osimertinib plus savolitinib) over the course of therapy. Noted are different types of kinase inhibitors targeting EGFR (erlotinib and osimertinib) or targeting MET (savolitinib and cabozantinib). The results of tissue-based and liquid biopsy–based comprehensive genomic profiling results are highlighted in accordance with the course of therapy. The tissue-based comprehensive genomic profiling test (FoundationOne) at the time of erlotinib resistance also revealed additional genomic aberrations, including *TP53* N239I, *FGF14* amplification, and *IRS2* amplification. The liquid biopsy–based (FoundationOne Liquid) tests after osimertinib and savolitinib also identified the *TP53* N239I mutation. *EGFR*-del19 indicates *EGFR* exon 19 deletion (delL747_T751). The left white arrow indicates previous periods of erlotinib use; * indicates the time of death. A note is made that this occurred during the COVID-19 pandemic in Massachusetts and no autopsy or SARS-CoV-2 testing was performed. COVID-19, coronavirus disease 2019; RECIST, Response Evaluation Criteria in Solid Tumor; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

amplification, and the known *MET*-D1228X mutations (Fig. 1). He was continued on osimertinib but died after 3 months.

Discussion

MET amplification is a frequently observed (5%–20% of cases) mechanism of resistance to EGFR TKIs. The EGFR plus MET coinhibition strategy of osimertinib plus savolitinib is undergoing final regulatory approval for *EGFR*-mutated plus *MET*-amplified advanced lung cancer in the SAVANNAH trial (NCT03778229). Resistance to combined EGFR and MET inhibition is poorly understood but can be expected to occur should this strategy gain wide appeal. Our report highlights MET-dependent resistance mechanisms (rather than EGFR-dependent mechanisms) mediated by *MET* kinase mutations in a pattern similar to the one seen in a previous case report.[4] Single-agent savolitinib has been associated with *MET*-D1228X and Y1230X resistance mutations in other *MET*-amplified tumor types.[5] Cabozantinib is a multikinase type II MET kinase inhibitor with putative preclinical activity against type I MET inhibitor resistance mutations, including MET-D1228X and Y1230X activation loop mutations (Table 1)[4,6] and offers a potential treatment strategy as seen in a previous case treated with oral erlotinib 100 mg daily plus oral cabozantinib 60 mg daily[4] but has significant toxicity that may limit widespread combinatory use as seen in our case report. Understanding the true frequency of *MET* mutations as a mechanism of resistance to osimertinib plus savolitinib will help define the need to develop novel MET inhibitors with broader activity against *MET* mutations and additional therapies to delay or prevent the heterogeneity of on-target and off-target resistance to EGFR TKIs.

Acknowledgments

This work was funded in part through the National Institutes of Health/ National Cancer Institute grants R37 CA218707 (Dr. Costa), R01 CA169259 (Dr. Kobayashi), R01 CA240257 (Dr. Kobayashi) plus Department of Defense LC170223 (Dr. Kobayashi).

References

1. 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.
2. Engstrom LD, Aranda R, Lee M, et al. Glesatinib exhibits antitumor activity in lung cancer models and patients harboring *MET* exon 14 mutations and overcomes mutation-mediated resistance to type I MET inhibitors in nonclinical models. *Clin Cancer Res*. 2017;23:6661–6672.
3. Collie GW, Koh CM, O'Neill DJ, et al. Structural and molecular insight into resistance mechanisms of first generation cMET inhibitors. *ACS Med Chem Lett*. 2019;10:1322–1327.
4. Bahcall M, Sim T, Paweletz CP, et al. Acquired METD1228V mutation and resistance to MET inhibition in lung cancer. *Cancer Discov*. 2016;6:1334–1341.
5. Frigault MM, Markovets A, Nuttall B, et al. Mechanisms of acquired resistance to Savolitinib, a selective MET inhibitor in *MET*-amplified gastric cancer. *JCO Precis Oncol*. 2020;4:222–232.
6. Li A, Yang JJ, Zhang XC, et al. Acquired *MET* Y1248H and D1246N mutations mediate resistance to MET inhibitors in non-small cell lung cancer. *Clin Cancer Res*. 2017;23:4929–4937.