Acquired Resistance Mechanism for MET Tyrosine Kinase Inhibitor

To the Editor:

We read with great interest the article entitled "Acquired resistance to osimertinib plus savolitinib is mediated by *MET* D1228 and Y1230 mutations in *EGFR*-mutated, *MET*-amplified lung cancer" by Piper-Vallillo et al.[1] recently published in *JTO Clinical and Research Reports*. In this article, the authors postulated that *MET* D1228N/Y/H and Y1230C secondary mutations could be the mechanisms of acquired resistance to type I MET inhibitor, savolitinib, along with EGFR tyrosine kinase inhibitor (TKI) treatment. There are two types of MET TKI, which are as follows: type I (e.g., capmatinib, tepotinib, and savolitinib) that binds to an active form of MET and type II (e.g., cabozantinib, merestinib, and glesatinib) that binds to an inactive form of MET. We previously reported that MET D1228 and Y1230 are the hotspots for the secondary resistant mutation for type I MET TKIs for NSCLC carrying *MET* exon 14 skipping mutation using in vitro models.[2] Concentrations that inhibit 50% (IC_{50}s) of most of the type I TKI to D1228X and D1230X were more than several 100 folds of that of the wild-type MET. Piper-Vallillo et al.[1] noted that this was also true for the combination therapy of type I MET TKI and EGFR TKI for *EGFR*-mutated, *MET*-amplified NSCLC. We also reported that switching from type I to type II MET TKI may be effective to overcome *MET* D1228 and Y1230 mutations.[2] However, Piper-Vallillo et al.[1] also reported that the treatment with a type II MET inhibitor, cabozantinib, could only eliminate Y1230C, whereas D1228N/Y/H mutant alleles remained. Similarly, in earlier reports on the sequential treatment of type I to type II MET TKI for patients with MET-driven NSCLC on resistance from D1228X and Y1230X,[3–5] biopsies at the time of disease progression were found to carry D1228X. Altogether, these facts indicate that D1228X is more resistant than Y1230X to the currently available type II inhibitors. Indeed, the analysis of our in vitro data suggested that the IC_{50}s of cabozantinib to D1228Y, merestinib to D1228Y, or glesatinib to D1228A was 78-fold, 18-fold, or 10-fold of the corresponding IC_{50}s to wild-type MET, respectively, whereas the IC_{50}s for any Y1230X was a maximum of threefold increase.[2] Because the clinical development of type I MET TKIs preceded that of type II TKIs for MET-driven lung cancer, we will often witness the proclamation of *MET* D1228X and Y1230X as resistance mechanisms in the near future. Hence, the establishment of an effective treatment against D1228X is urgently awaited.

Toshio Fujino, MD
Tetsuya Mitsudomi, MD
Division of Thoracic Surgery
Department of Surgery
Kindai University Faculty of Medicine
Osaka-Sayama, Japan

References

1. Piper-Vallillo AJ, Halbert BT, Rangachari D, Kobayashi SS, Costa DB. Acquired resistance to osimertinib plus savolitinib is mediated by MET-D1228 and Y1230 mutations in EGFR mutated MET amplified lung cancer. *JTO Clin Res Rep*. 2020;1:100071.
2. Fujino T, Kobayashi Y, Suda K, et al. Sensitivity and resistance of MET exon 14 mutations in lung cancer to eight MET tyrosine kinase inhibitors in vitro. *J Thorac Oncol*. 2019;14:1753–1765.
3. 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.
4. Kang J, Chen HJ, Wang Z, et al. Osimertinib and cabozantinib combinatorial therapy in an EGFR-mutant lung adenocarcinoma patient with multiple MET secondary-site mutations after resistance to crizotinib. *J Thorac Oncol*. 2018;13:e49–e53.
5. Recondo G, Bahcall M, Spurr LF, et al. Molecular mechanisms of acquired resistance to MET tyrosine kinase inhibitors in patients with MET exon 14-mutant NSCLC. *Clin Cancer Res*. 2020;26:2615–2625.

Address correspondence to: Tetsuya Mitsudomi, MD, Department of Thoracic Surgery, Kindai University Faculty of Medicine, 377-2 Ohno-Higashi, Osaka-Sayama 589-8511, Japan. E-mail: mitsudom@med.kindai.ac.jp

Cite this article as: Fujino T and Mitsudomi T. Acquired Resistance Mechanism for MET Tyrosine Kinase Inhibitor. JTO Clin Res Rep 2021;2:100134

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2020.100134