Differential Pattern of Resistance and Sensitivity to Different Classes of MET Inhibitors for *MET*-Amplified Tumors With *MET*-D1228X or *MET*-Y1230X Mutations

Andrew J. Piper-Vallillo, MD
Division of Medical Oncology, Department of Medicine
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, Massachusetts

Susumu S. Kobayashi, MD, PhD
Division of Medical Oncology, Department of Medicine
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, Massachusetts
Division of Translational Genomics
Exploratory Oncology Research and Clinical Trial Center
National Cancer Center
Kashiwa, Japan

Daniel B. Costa, MD, PhD
Division of Medical Oncology, Department of Medicine
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, Massachusetts

To the Editor:

We thank Drs. Fujino and Mitsudomi[1] for their interest in our description of *MET* mutations as a mechanism of resistance to dual EGFR-MET inhibition in *EGFR*-mutated plus *MET*-amplified lung cancer.[2] The ongoing approvals and late-stage development of multiple type I MET tyrosine kinase inhibitors—such as capmatinib, tepotinib, savolitinib, and crizotinib—have paved the way for the use of these therapies in the clinical care of patients with tumors driven by *MET* aberrations.[1,3-5]

However, the widespread use of type I MET inhibitors will also highlight the inherited vulnerability of tumor adaptation mediated by on-target resistance through *MET* kinase domain mutations, including *MET*-D1228X and *MET*-Y1230X mutations.[2] Some type II MET inhibitors (i.e., cabozantinib, merestinib, and glesatinib) have preclinical activity against *MET*-amplified tumors co-harboring *MET*-D1228X or *MET*-Y1230X mutations.[1,2] Fujino and Mitusudomi[1] eloquently highlighted the preclinical differences in the inhibitory profiles of these two mutations and pointed toward the need for the development of more potent MET inhibitors with an enhanced pattern of activity against MET kinase domain mutations.

Acknowledgments

This work was funded in part through National Institutes of Health/National Cancer Institute grants R37 CA218707 (to Dr. Costa).

References

1. Fujino T, Mitsudomi T. Acquired resistance mechanism for MET-TKI. *JTO Clin Res Rep*. 2021;2:100134.
2. Piper-Vallillo AJ, Halbert BT, Rangachari D, Kobayashi SS, Costa DB. 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*. 2020;1:100071.
3. Wolf J, Seto T, Han JY, et al. Capmatinib in MET exon 14-mutated or MET-amplified non-small-cell lung cancer. *N Engl J Med*. 2020;383:944-957.
4. Paik PK, Felip E, Veillon, et al. Tepotinib in non-small-cell lung cancer with MET exon 14 skipping mutations. *N Engl J Med*. 2020;383:931-943.
5. Drilon A, Clark JW, Weiss J, et al. Antitumor activity of crizotinib in lung cancers harboring a MET exon 14 alteration. *Nat Med*. 2020;26:47-51.

Address correspondence to: Daniel B. Costa, MD, PhD, 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. Differential Pattern of Resistance and Sensitivity to Different Classes of MET Inhibitors for *MET*-Amplified Tumors With *MET*-D1228X or *MET*-Y1230X Mutations. JTO Clin Res Rep 2021;2:100133

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2020.100133