EDITORIAL

Targeting Co-Occurring Genomic Alterations in *MET* Exon 14 Skipping Mutation-Positive NSCLC

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Recent genomic profiling of lung cancer revealed several clinically important genetic alterations in NSCLC. Multiple inhibitors, including tyrosine kinase inhibitors (TKIs), have been developed to target these genetic alterations in patients with NSCLC. Nevertheless, 20%–30% of those with NSCLC with these genetic alterations do not respond to TKI therapy. For example, the response rate of osimertinib—a third-generation EGFR TKI—for *EGFR*-mutation–positive untreated NSCLC is 80%[1] and that of alectinib—a second-generation anaplastic lymphoma kinase (ALK) TKI—for *ALK*—translocation-positive NSCLC is 82.9%.[2] These findings highlight the clinical importance of primary resistance to TKI therapy.

MET exon 14 skipping mutations define a new subgroup of NSCLC and accounts for 2%–4% of lung adenocarcinoma cases.[3] Exon 14 of *MET* encodes the juxtamembrane domain and Y1003 residue that serves as a binding site for Cbl proto-oncogene, an E3 ubiquitin ligase that regulates MET turnover. Therefore, exon 14 skipping mutation stabilizes MET protein and activates MET signaling.

In this issue, Jamme et al.[4] studied the primary resistance mechanism to MET TKIs in patients with *MET* exon 14 skipping mutations because the response rates of MET TKIs are lower than those for other TKIs against corresponding driver oncogenes, such as *EGFR* or *ALK*. Crizotinib, a MET TKI that received Food and Drug Administration breakthrough designation for use in treatment of NSCLC harboring *MET* exon 14 skipping, was found to have a mild response rate of 32%.[5] Tepotinib, another MET TKI, was found to have a response rate of 42%.[6] These findings indicate considerable prevalence of primary resistance to MET TKIs in *MET* exon 14 skipping mutation-positive lung cancer.

At the molecular level, the PI3K-AKT and RAS-RAF-MEK-ERK (MAPK) pathways play an important role in cancer cell proliferation and survival. Alterations in these signaling pathways can confer primary or acquired resistance to TKIs.

Jamme et al.[4] reported that alterations in the PI3K signaling pathway are often found in *MET* exon 14 skipping mutation-positive NSCLC. Furthermore, they speculated that these alterations might confer primary resistance to MET TKIs. The authors reviewed 65 cases with *MET* exon 14 skipping mutations. PI3K pathway alterations were assessed by targeted next-generation sequencing (mutations) and immunohistochemistry (loss of PTEN). They found *PIK3CA* mutation in two cases (3%) and loss of PTEN in 6 of 26 cases (23%). Moreover, three patients with alterations in the PI3K pathway who were treated with MET TKI had disease progression. Furthermore, they performed preclinical experiments using patient-derived cell lines harboring both a *MET* exon 14 skipping and a PI3K pathway alteration and proposed the preclinical rationale to use combination therapy with a MET TKI and a PI3K inhibitor. Treatment combining capmatinib, a MET TKI, with GDC0941, a specific inhibitor of PI3K caused inhibition of both PI3K and MAPK signaling and restored sensitivity to MET TKI in vitro. These findings highlight the importance of co-occurring genomic alterations for the treatment of lung cancer with *MET* exon 14 skipping mutations.

The role of co-occurring alterations in the MAPK pathway in *MET* exon 14 skipping mutation-positive lung cancer has been previously reported.[7] Target sequencing data were obtained using cell-free tumor

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DNA from 289 patients with *MET* exon 14 skipping mutation-positive NSCLC. Alterations in the MAPK signaling pathway were more often found in *MET* exon 14 skipping mutation-positive NSCLC than in *EGFR*–mutation-positive NSCLC. Moreover, an association between decreased MET TKI treatment response and MAPK pathway co-occurring alterations was found. In a preclinical model expressing a canonical MET exon 14 skipping mutation, KRAS overexpression, or NF1 down-regulation hyperactivated MAPK pathway to promote MET TKI resistance. This resistance was overcome by cotreatment with crizotinib and trametinib, a MEK inhibitor. This study provided the preclinical rationale to use the combination therapy of MET TKI and MEK inhibitor.

These data indicate that a considerable proportion of primary resistance to MET TKIs is caused by co-occurring alterations in either the PI3K or MAPK pathway.

Jamme et al.[4] have proposed two clinically important insights. First, the co-occurring mutation profile can aid in the selection of patients who are most likely to benefit from MET TKIs. This approach can improve the quality of precision medicine-based lung cancer therapy, particularly when information about several hundreds of cancer-associated gene mutations is available for clinicians. Second, the findings propose rationale strategies to overcome primary resistance to MET TKIs for patients with the co-occurring alterations, as found in the preclinical models. It might be reasonable to administer a combination of PI3K or MEK inhibitors with MET TKIs to overcome primary resistance to MET TKIs. Combination therapy of PI3K or MAPK pathway inhibitors with corresponding TKIs has been long proposed in multiple preclinical models. Nevertheless, in the clinical settings, the combination therapy strategies have been hindered by efficacy or safety issues.[8,9] There is a significant gap between preclinical models and clinical results. Therefore, evaluation of the efficacy and safety of the combination therapy in clinical trial is mandatory for its implementation.

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