Targeting *MET* Exon 14 Skipping Alterations: Has Lung Cancer MET Its Match?

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The treatment landscape of NSCLC has been transformed by the approval of molecularly targeted agents against critical drivers in this disease, including EGFR, anaplastic lymphoma kinase, and ROS1.[1] Several other targets are showing great promise in clinical trials, including the receptor tyrosine kinase MET proto-oncogene receptor tyrosine kinase (MET). Although initial studies undertaken with MET inhibitors were disappointing, the recent emergence of splicing alterations of MET proto-oncogene receptor tyrosine kinase gene *MET* exon 14 (*MET*ex14) in NSCLC as a primary driver has reinvigorated interest in the development of MET inhibitors in this disease.[2] *MET*ex14 alterations are complex and diverse, and they are comprehensively reviewed in the article by Drilon et al. in this edition of the *Journal of Thoracic Oncology*. *MET*ex14 alterations occur at a prevalence of approximately 3% to 4% in lung adenocarcinoma compared with 2% in squamous cell lung cancer.[3,4] These aberrations tend not to be observed in younger patients with NSCLC and seem to be enriched in pulmonary pleomorphic/sarcomatoid carcinomas.[5,6] Interestingly, concurrent *MET* amplification is observed in approximately 20% of *MET*ex14-aberrant NSCLC, and such tumors have also been shown to harbor a significantly total higher mutational burden.[7]

Several bona fide MET inhibitors with varying potencies, specificities, and underlying mechanisms of action are currently in clinical trials.[8] The MET inhibitors currently being assessed in phase II studies involving patients with *MET*ex14-aberrant NSCLC include the type I inhibitors crizotinib (Xalkori [Pfizer, New York, NY]) and capmatinib (INC280 [Novartis, Basel, Switzerland]), as well as the type II inhibitors cabozantinib (Cabometyx [Exelixis, Inc., South San Francisco, CA]), tepotinib (MSC2156119J, [Merck Serono, Darmstadt, Germany]), and glesatinib (MGCD265 [Mirati Therapeutics, San Diego, CA]). These small molecule MET inhibitors are all adenosine triphosphate–competitive, but whereas type I MET inhibitors bind to the MET unique autoinhibitory conformation through the interaction of the aromatic ring of the inhibitor (π-stacking) with Y1230 in the MET activation loop, type II inhibitors bind to the adenosine triphosphate adenine binding site. Of these agents, it is likely that crizotinib will be the first to obtain U.S. Food and Drug Administration approval for this molecularly selected patient population, adding to its registration for use in anaplastic lymphoma receptor tyrosine kinase gene (*ALK*)- and *ROS1*-rearranged NSCLC. Early data from the PROFILE-1001 study reported a 44% overall response rate in 18 patients with evaluable treatment-naive or chemotherapy-refractory *MET*ex14-aberrant NSCLC.[9] Other phase II crizotinib studies involving this indication are ongoing, including the NCI-MATCH trial (NCT02465060) in the United States and the National Lung Matrix Trial (NCT02664935) in the United Kingdom.

One of the key challenges with molecularly targeted agents is understanding and addressing the inevitable development of drug resistance. In vitro studies have already identified several predominant resistance mutations in MET-dependent tumors after treatment with type I MET inhibitors such as crizotinib, including *MET* Y1230 and D1228 mutations.[10] Any mutations (Y1230 or D1228) that directly or indirectly weaken the interactions between these type I inhibitors and the MET

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activation loop may potentially lead to drug resistance. In this edition of the *Journal of Thoracic Oncology*, Ou et al. report the detection of a *MET* Y1230C mutation that appears to confer resistance to crizotinib in a patient with *MET*ex14 (D1010H)-aberrant NSCLC who had a durable response for 13 months.[11] In this study, although it was not possible to make a direct comparison between the mutational allele frequencies of the different aberrations detected because baseline and disease progression sampling involved different tissue (tumor versus circulating plasma DNA [cpDNA]), the presence of the *MET* Y1230C mutation at reportable levels in cpDNA at disease progression is compelling. Whether this was a preexisting versus acquired mutation will require larger studies to characterize and validate such mutations and other resistance mechanisms in the clinic through the increased analysis of biopsy samples and cpDNA collected before treatment and after treatment at disease progression. Therefore, the significance of this potential de novo *MET* Y1230C mutation in two of 762 sequencing reads (well below reportable levels of the assay) before therapy is currently unknown but seems to bear striking similarity to the gatekeeper *EGFR* T790M mutation in providing tumors with a growth advantage. For example, de novo *EGFR* T790M mutation "degrades" the response of first- and second-generation EGFR inhibitors, suggesting that the *MET* Y1230C mutation may have similar effects on MET inhibitors. An acquired critozitnib resistance mutation in the MET kinase domain D1228N has also recently been described in a patient with advanced *MET*ex14-aberrant NSCLC treated with crizotinib.[12]

Although it may be possible that switching from type I to type II MET inhibitors may overcome such *MET* Y1230 and D1228 resistance mutations, it is likely that second-generation inhibitors specifically targeting such MET aberrations will ultimately be required. Another important approach to consider pursuant to delaying single-agent resistance will be the combination of small molecule MET inhibitors with hepatocyte growth factor antibodies or antibodies that inhibit ligand binding to the MET receptor or block its dimerization, so as to achieve "total blockade" of the MET axis. To address such challenges in the clinic, we need to redesign clinical trials to consider type I to II MET inhibitor switching, novel combination therapies, and the incorporation of both tumor and serial cpDNA tissue sampling to monitor mutation allele frequencies of MET aberrations and identify putative resistance mechanisms in an efficient manner. From a practical point of view, such trial designs should include patients with lung adenocarcinomas and squamous cell lung carcinomas, as well as patients with lung pleomorphic/sarcomatoid carcinomas, without limitations on lines of prior therapies, to optimize accrual.

In view of its great diversity, a major challenge for the development of MET inhibitors is the development of a robust, sensitive, and rapid analytically validated companion diagnostic for routine detection of *MET*ex14 alterations. It is unlikely that MET expression through immunohistochemistry assays will suffice. Current molecular testing mainly involves nonstandardized DNA-based hybrid capture next-generation sequencing, which is not sufficiently comprehensive to capture the wide range of *MET*ex14 alterations.[7] Also, The Cancer Genome Atlas has also reported that certain *MET*ex14 alterations detected have resulted in incomplete *MET*ex14 skipping.[13] It is therefore imperative that confirmatory assays, such as quantitative reverse-transcriptase polymerase chain reaction or direct RNA sequencing, be utilized to confirm *MET*ex14 skipping alterations. However, given the typical small sizes of diagnostic NSCLC biopsy specimens, the amount of tissue available after initial DNA-based next-generation sequencing may ultimately be insufficient for further RNA-based assays. The use of serial cpDNA sampling will provide a practical and relatively less invasive method for the detection of resistance mutations, such as *MET* Y1230 or D1228 alterations, but it will likely be affected by false-negatives. Ultimately, as both *MET*ex14 alterations and MET amplification are relatively rare events, the development of a cpDNA assay to rapidly screen patients with NSCLC for such aberrations will be important.

At the present time, the incidence of brain metastases at diagnosis and frequency of intracranial failure with MET inhibitors in patients with *MET*ex14-altered NSCLC is unknown. In this issue, Klempner et al. present a compelling case of a patient with known *MET*ex14-aberrant NSCLC with intracranial progression while receiving crizotinib despite ongoing extracranial response.[14] Upon switching to cabozantinib because of crizotinib-induced grade 4 transaminitis, the patient achieved a complete intracranial response and maintained a systemic response, providing the first evidence of central nervous system (CNS) penetration and activity of cabozantinib in a patient with prior exposure to crizotinib, potentially suggesting "reversal of resistance" after a switch from type I to a II MET inhibitors. Because crizotinib is likely to be the first MET inhibitor approved for *MET*ex14-altered NSCLC, in view of its poor CNS penetration, there will still be an unmet need for a potent CNS-penetrant type II MET inhibitor. Whether the current cadre of type II MET inhibitors, such as cabozantinib, will fulfill this niche role remains to be assessed.

Apart from *MET*ex14-altered NSCLC, it is now clear that MET inhibitors will also play a critical role in the treatment of patients with *MET*-amplified NSCLC. In this

issue, Caparica et al. report two patients with high-level *MET* amplification (*MET/CEP7* ratio $\geq$5) without concomitant *MET*ex14 alterations who responded to crizotinib, supporting its importance as a true NSCLC driver.[15] These findings imply that any companion diagnostic for MET inhibitors in NSCLC should also include testing for high-level *MET* amplification. Moving forward, studies should also assess the significance of *MET* amplification clonality in predicting antitumor responses to MET inhibitors by evaluating the degree of heterogeneity using in situ heterogeneity mapping of fluorescence in situ hybridization.[16]

We have come a long way from the previous dispiriting negative NSCLC phase III trials of tivantinib (ARQ197 [ArQule, Burlington, MA/Daiichi Sankyo, Tokyo, Japan]) and onartuzumab (MetMab [Roche, Basel, Switzerland]) in combination with erlotinib.[1] The present data confirm that *MET* remains a key oncogenic driver in NSCLC with definite therapeutic viability. Priority must now be given to achieving rapid regulatory approval by designing registration trials to assess single-agent MET inhibitors using a robust molecular profiling assay in tumor and cpDNA for the selection and monitoring of *MET*-addicted patients with *MET*-amplified and/or *MET*ex14-altered NSCLC. Expectations must be met!

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