MET in the Driver's Seat: Exon 14 Skipping Mutations as Actionable Targets in Lung Cancer

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The receptor tyrosine kinase MNNG-HOS transforming gene (MET) and its ligand hepatocyte growth factor play an important role in normal cell biology as well as in a number of cancers. MET has been shown to be overexpressed, amplified, mutated, or be unable to be degraded in several tumors.[1] Previous clinical results with MET inhibitors did not meet their end points in phase 3 trials, and therapeutics such as onartuzumab and tivantinib did not go forward as therapeutically efficacious.[2–4] As is true for many clinical trials of this kind, there are usually some responders; however, even larger studies often underestimate or neglect the impact of rather rare molecular changes that can affect or drive disease progression. Initial trials utilized expression as a biomarker; however, as we have learned from *EGFR* and anaplastic lymphoma receptor tyrosine kinase gene (*ALK*), it is important to determine the molecular changes for the particular gene for potentially targeting. To arrive at the true value of a MET-driven therapeutic, we must understand the molecular alterations of MET. The number of patients (11,205) in the cohort studied by Schrock et al. in this issue[5] is impressive and has yielded important information about the molecular epidemiology of *MET* exon 14 (*MET*ex14) alterations in lung cancer. *MET*ex14 alterations are known to be transforming in preclinical disease models, and 298 patients (2.7%) with these alterations were identified in this large cohort. A related study by Liu et al. that is also published in this issue[6] and looks for *MET*ex14 alterations in 1296 Chinese patients with NSCLC found a frequency of only 0.9 % (12 cases). This may be a reflection of ethnic differences, as it is also true for the higher frequency of EGFR tyrosine kinase mutations in East Asian patients with NSCLC.[7] In the most comprehensive study thus far, 38,028 cancer specimens were analyzed for *MET*ex14 alteration and identified with a frequency of 0.6% (221 cases).[8] *MET*14ex14 alterations were most frequently found in 3% of adenocarcinoma, which is comparable to the frequency observed in this lung cancer study. Similarly to the results of previous studies,[9,10] amplifications were associated with approximately 15% of patients with *MET*ex14 NSCLC. However, it is unclear from this study whether the *MET* amplifications described were preexisting or whether they were the result of mechanisms of resistance to therapeutics such as EGFR inhibitors. Notably, individual *MET*ex14 alterations were not associated with a particular histologic subtype, but acinar features (23.8%) and solid component (21.4%) in general were more frequently associated with these changes.

The main purpose of studying *MET*ex14 is to define the response to MET inhibition in this patient population. Even though with eight patients the pool that was analyzed for clinical outcomes in response to the MET inhibitor crizotinib here is small, the results are nonetheless impressive. Of the patients evaluated, six had partial or complete responses, one experienced stable disease, and one experienced a change to resectable disease. These data are an important validation of previous data by Paik et al. demonstrating positive results in a cohort of four patients with *MET*ex14 and stage IV adenocarcinoma and by Frampton et al. in three *MET*ex14-positive patients.[8,11] Larger clinical trials focused on *MET*ex14 alterations are expected to give a much clearer picture of the true response in a bigger cohort. Additional known disease-driving mutations were found to be associated with *MET*ex14 alterations,

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including mutations in *KRAS*, *EGFR*, *BRAF*, and *ALK*, and it would be of interest to know whether these genetic changes alter the efficacy of MET-targeted approaches. In these future trials it will also be important to obtain additional information about the smoking status and the stage of the disease. If the clinical results hold true, there clearly is a need for careful assessment of *MET*ex14 alterations. The molecular changes within exon 14 are diverse and may require in-depth molecular profiling of all patients with lung cancer, irrespective of additional disease-driving mutations. The data would also warrant a second look at other *MET* mutations[12,13] independent of exon 14 and evaluation of their potential as actionable targets. Interestingly, the data do not hint at a strong role for *MET* amplifications within the *MET*ex14 disease process, in particular, as it relates to late-stage disease. Even though an association of *MET* amplification with increased mutation burden was found, more studies are needed to define its significance. Few data are available that correlate the disease response to MET inhibition in patients with *MET* amplification, but it appears that at least a subset of patients may be able to benefit from this treatment.[14]

The presumptive molecular mechanism that leads to dysregulation of MET function is likely to involve altered function of the ubiquitin E3 ligase Casitas B-lineage lymphoma (CBL), with MET as one of its targets.[1] CBL is thought to bind to MET at phospho-Y^{1003}, allowing for ubiquitination and subsequent degradation of the receptor tyrosine kinase.[15] During normal signaling this process would allow for a controlled shutoff of the receptor. This process appears to be disrupted in *MET*ex14 alterations and would be predicted to lead to dysregulated or prolonged MET signaling. As CBL has oncogenic potential and can also be mutated in lung cancer,[16] a careful analysis of the entire MET/CBL pathway may be warranted. In head and neck squamous cell carcinoma, MET is frequently overexpressed and genetic variations of c-CBL as well as the relationship between CBL and MET expression have been defined.[17] Elevated MET expression and concurrent low CBL expression was detected in 73 tumor specimens. Ectopic expression of wild-type CBL in a cell line model led to direct downregulation of MET and reduced viability. Thus reduced CBL expression may increase MET expression and contribute to MET-dependent tumorigenesis. Increasing the degradation of MET or other receptor tyrosine kinases by CBL-dependent mechanisms would be expected to enhance the efficacy of kinase inhibitors that specifically target this class of proteins. The tumor cell microenvironment through stromal cell interactions plays a truly underappreciated role in this process, as it can provide the ligand that initiates MET signaling[18–20] and thus the recruitment of CBL. Future therapies may be expanded to not only disrupt MET signaling but also prevent ligation of the receptor through stromal cells.

This study clearly underlines the fact that there are a small but significant number of patients with lung cancer and *MET*ex14 alterations, initially described by us in SCLC and thereafter in NSCLC, who can benefit from MET inhibition.[12,13] Our goal should be to further define this patient population and not leave any patient with any actionable mutation behind. MET-targeted therapies have come a long way since our initial characterization of a novel MET kinase prototype small molecule inhibitor, and now multiple highly efficacious MET inhibitors have been tested in clinical trials as well.[1,21,22] As immunotherapy in lung cancer is showing increasing yet limited success, additional therapeutic options are needed to have an ever greater impact on overall survival. Introducing MET inhibitors for targeted therapy, as adjuvant therapy, in combination with traditional therapy, or in combination with chemotherapy as well as with radiation therapy, would be expected to benefit patients with *MET*ex14 alterations. What is required here is a much closer collaboration between the clinic and diagnostic laboratories to move personalized therapies forward.

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