Combination MET- and EGFR-directed therapy in MET-overexpressing non-small cell lung cancers: time to move on to better biomarkers?

Fernando C. Santini¹, Siddharth Kunte², Alexander Drilon¹,³

¹Thoracic Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; ²Department of Internal Medicine, Mount Sinai St. Luke's West Hospital, New York, NY, USA; ³Weill Cornell Medical College, New York, NY, USA

Correspondence to: Alexander Drilon, M.D. Thoracic Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, 885 2nd Avenue 10th floor, New York, NY 10017, USA. Email: drilona@mskcc.org.

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The MET pathway and combination targeted therapy

MET is a well described proto-oncogene. It was first identified in the 1980s, and its ligand, hepatocyte growth factor (HGF), was later identified in the early 1990s. MET is activated when HGF binds to the receptor, inducing homodimerization and phosphorylation of intracellular tyrosine residues. Various cytoplasmic effector proteins, including GAB1, GRB2, phospholipase C, and SRC are subsequently recruited, activating the downstream RAF/ERK/MAPK, PI3K/AKT, Wnt/β-catenin, and STAT signaling pathways. After activation, MET is internalized through endocytosis and is either recycled to the plasma membrane or degraded. Depending on the cellular context, these downstream pathways can drive cell proliferation, survival, migration, motility, invasion, angiogenesis, epithelial-to-mesenchymal transition (EMT), and generation and maintenance of cancer stem cells. In the wild-type state, HGF-MET signaling is essential for regeneration in liver and skin, and can control the EMT during development (1).

In non-small cell lung cancers (NSCLCs), MET pathway dysregulation potentially occurs via mechanisms including amplification, rearrangement, mutation, and overexpression, and functional crosstalk between the MET receptor and other transmembrane receptors such as EGFR is well described. Both EGFR and MET use an overlapping repertoire of signaling adaptors and downstream effector pathways, highlighting their ability to co-drive oncogenic signaling, as has been observed in non-small cell lung cancer models. More importantly, MET pathway activation via amplification has been associated with acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) in lung cancer patients with activating EGFR mutations. This data initially provided a reasonable rationale for combining MET- and EGFR-directed targeted therapy in the management of advanced NSCLCs (2,3).

Onartuzumab and erlotinib in MET-overexpressing NSCLC

The exploration of the activity of the combination of onartuzumab, a humanized monovalent monoclonal antibody against MET, and erlotinib, a first-generation EGFR TKI, provides an important example of the utility of such an approach. Spiegel et al. conducted a global, randomized, placebo-controlled, phase 2 study in patients with recurrent NSCLC evaluating erlotinib with or without onartuzumab (4). MET expression was measured mainly on archival tissue by a MET immunohistochemistry (IHC) scoring system using the CONFIRM SP44 anti-
MET monoclonal antibody. MET positivity was defined as a score of +2 or +3 (≥50% of tumor cells with strong or moderate staining). In a retrospective analysis of this study by Koeppen et al., a positive correlation between IHC score and MET mRNA levels was found (5). The co-primary end points were progression-free survival (PFS) in the intent-to-treat (ITT) and MET-positive populations. While there was no improvement in PFS or overall survival (OS) in the ITT population, MET IHC-positive patients treated with erlotinib plus onartuzumab showed improvements in both PFS (HR=0.53; P<0.04) and OS (HR=0.37; P=0.002) compared to those treated with erlotinib alone, sparking interest in the further use of MET overexpression by IHC as a potential predictive biomarker of response for the combination.

Several factors should be pointed out to put these results into context. First, there was an imbalance in the prevalence of activating EGFR mutations in both groups. These mutations were more prevalent in tumors from patients who received combination therapy in comparison to those that received erlotinib alone (20% vs. 7%). Second, type II error was set at 50%, and it is well recognized that low statistical power increases the risk of a false negative result. However, low statistical power also leads to increased risk that significant results will be falsely positive, for any given P value (6). Lastly, as will be pointed out later, the molecular features of these tumors beyond EGFR were not clear.

Regardless, the improvement in survival in MET-overexpressing NSCLCs with combination therapy in this trial fueled further interest in the development of this combination, and a phase 3 study, the METLung trial, was mounted, the results of which were recently published by Spiegel and colleagues (7). In contrast to the prior phase 2 trial, only patients with MET IHC-positive NSCLCs were enrolled. Patients were stratified by MET IHC score, number of prior lines on therapy, histology, and EGFR mutation status. Key exclusion criteria included prior treatment with an EGFR inhibitor. The primary endpoint was OS in the ITT population and 499 patients were randomly assigned to receive onartuzumab plus erlotinib (n=250) or placebo plus erlotinib (n=249). Unfortunately, unlike the subset analysis of the prior phase 2 trial in MET-overexpressing lung cancers, after the first interim analysis, the trial did not meet its primary endpoint (8). In fact, OS was numerically shorter in the combination onartuzumab and erlotinib arm, compared with erlotinib alone in patients with MET-overexpressing NSCLC. Furthermore, there was a signal for potential harm in patients with EGFR-mutant lung cancers.

**Biomarker selection for MET-directed targeted therapy strategies**

The disappointing experience with onartuzumab and erlotinib in MET-overexpressing NSCLCs underscores the fact that, in isolation, MET overexpression is not an optimal predictive biomarker of response to MET-directed antibody therapy, an observation that likely extends to MET TKI therapy as well. For combination MET- and EGFR-directed therapy, ongoing efforts have begun to shift towards molecularly enriching for patients with EGFR-mutant lung cancers. As mentioned previously, a proportion of EGFR-mutant lung cancers acquire MET amplification after progression on EGFR TKI therapy, and already, responses to combination therapy for this genomic subset have been reported (9,10).

Moreover, data on the utility of single-agent MET-directed therapy in MET-amplified and MET exon 14-altered lung cancers continues to emerge. MET amplification is found in a small subset of patients with NSCLCs, and high levels of amplification (MET/CEP7 ratio ≥5 by FISH) are thought to potentially represent a driver state of its own, given its lack of overlap with other drivers (11). On the PROFILE 1001 phase 1 study of crizotinib, patients with MET-amplified advanced NSCLCs were treated. Response was observed in 16.7% of patients with intermediate-level MET amplification (MET/CEP7 ratio 2.2 to <5) and in 50% of patients with high-level MET amplification (MET/CEP7 ratio ≥5) (12).

MET mutations that affect the juxtamembrane domain and result in alterations involving exon 14 lead to tumor growth. This occurs secondary to decreased degradation of the MET receptor mediated by loss of a c-Cbl E3 ubiquitin ligase binding site. MET exon 14 alterations are detected in 3–4% of lung adenocarcinoma samples, with a higher incidence in pulmonary sarcomatoid carcinomas (13). On an expansion cohort of the same PROFILE 1001 trial, response to crizotinib was achieved in 39% of patients, with a median duration of response of 9.1 months [95% confidence interval (CI): 5.9–10.5] and a median PFS of 8.0 months (95% CI: 6.9–10.8). In patients who had central testing for both MET amplification and MET exon 14 alterations, two partially overlapping states, MET amplification was only observed in one patient, highlighting how MET exon 14 alterations are independent predictors of benefit from MET tyrosine kinase inhibition. Conversely,
Caparica et al. reported responses to crizotinib in high-level MET-Amplified NSCLC that did not harbor MET exon 14 alterations (14).

In terms of ongoing and future trials of MET-directed therapy, appropriate molecular selection is key, and that selecting patients on the basis of tumor MET overexpression alone is unlikely to represent a viable strategy for accrual. Prospective trials of MET-directed targeted therapy should focus on accruing patients with MET exon 14 alterations and MET amplification, and trials of combination MET- and EGFR-directed targeted therapy should enrich for patients with EGFR-mutant lung cancers with acquired resistance mediated by the acquisition of MET amplification.

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Footnote

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