Editorial

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

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Provenance: This is a Guest Editorial commissioned by the Section Editor Viola Zhu (Memorial Sloan Kettering Cancer Center, New York, NY, USA).

Comment on: Spigel DR, Edelman MJ, O'Byrne K, *et al.* Results From the Phase III Randomized Trial of Onartuzumab Plus Erlotinib Versus Erlotinib in Previously Treated Stage IIIB or IV Non-Small-Cell Lung Cancer: METLung. J Clin Oncol 2017;35:412-20.

Submitted Apr 10, 2017. Accepted for publication Apr 13, 2017.
doi: 10.21037/tlcr.2017.04.06
View this article at: http://dx.doi.org/10.21037/tlcr.2017.04.06

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/CEP*7 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/CEP*7 ratio 2.2 to <5) and in 50% of patients with high-level *MET* amplification (*MET/CEP*7 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.

Acknowledgements

Funding: A. Drilon is supported in part by the NIH under a P30CA008748 core grant.

Footnote

Conflicts of Interests: The authors have no conflicts of interest to declare.

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Cite this article as: Santini FC, Kunte S, Drilon A. Combination MET- and EGFR-directed therapy in MET-overexpressing non-small cell lung cancers: time to move on to better biomarkers? Transl Lung Cancer Res 2017;6(3):393-395. doi: 10.21037/tlcr.2017.04.06

