Targeting MET in NSCLC: looking for a needle in a haystack

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Non-small cell lung cancer (NSCLC) remains the leading cause of cancer related death worldwide, with a median survival that rarely exceeds 12 months in unselected patients with metastatic disease treated with conventional chemotherapy. In the last decade, the identification of key genetic events driving tumor growth and metastatic spread led to postulate the concept of oncogene-addiction. According to this model, the inhibition of certain molecular drivers by targeted agents could be effective in reducing tumor burden and improving patients outcome. In this context, due to its central role in cancer proliferation and metastasis, mesenchymal-epidermal transition (MET) has recently emerged as a potential tumor-driver and also as a promising therapeutic target in several malignancies, particularly in NSCLC where *MET* is often deregulated by overexpression, gene amplification or mutations (1). Furthermore, preclinical data showed a potential cross-talk between MET and epidermal growth factor receptor (EGFR) pathways. Indeed, these receptors are often co-expressed and their functional transactivation potentiates downstream signaling (1). In addition, *MET* gene amplification has been recognized as one of the mechanisms responsible for EGFR-Tyrosine Kinase Inhibitor (TKI) secondary resistance in *EGFR* mutant NSCLC (2,3). As a consequence, there is a strong rationale to combine dual MET/EGFR inhibition in NSCLC.

In 2013, Spigel *et al.* published the results of a randomized phase II trial exploring the activity of the combination of erlotinib and onartuzumab (or MetMab), a monovalent monoclonal antibody directed against the extracellular domain of MET receptor, in 137 molecularly unselected NSCLC patients who failed at least one prior chemotherapy regimen (4). Archival tumor tissue was required to evaluate levels of MET expression by using immunohistochemistry (IHC) and considering as MET positive those samples having ≥50% of tumor cells with moderate (2+) or high (3+) staining intensity (MET diagnostic positive). Additional evaluation included *MET* gene copy number (GCN) assessed by fluorescent in situ hybridization (FISH) and adopting a cut-off of mean ≥5 copies per cell to define positivity. Co-primary end points of the trial were progression-free survival (PFS) in intent-to-treat (ITT) population and in IHC diagnostic positive population. In ITT population neither PFS (HR, 1.09; P=0.69) nor overall survival (OS; HR, 0.80; P=0.34) favored the experimental arm. However, in MET diagnostic positive disease the combination onartuzumab-erlotinib was superior to erlotinib-placebo in both PFS and OS (HR, 0.53; P=0.04; HR, 0.37; P=0.002, respectively), whereas a detrimental effect was noted in the MET diagnostic negative subgroup. Interestingly, *MET* GCN was not predictive for onartuzumab sensitivity.

Moving from these promising findings, the same authors conducted a large, randomized, confirmatory phase III trial aiming to demonstrate a survival improvement for the combination of onartuzumab and erlotinib in MET diagnostic positive NSCLC. The results of this study have been presented this year at the annual meeting of the American Society of Clinical Oncology (5). The study, enrolling a total of 490 subjects, failed to replicate the results observed in the phase II trial. Particularly, neither OS (6.8 *vs.* 9.1 months, HR, 1.27; P=0.07) nor PFS (2.7 *vs.* 2.6 months, HR, 0.99; P=0.92), the secondary end-point of this study, differed between the two arms. Notably, subset analyses for both OS and PFS confirmed the lack of superiority of onartuzumab-erlotinib combination, with similar results across all stratification factors, including histology (non-squamous versus squamous), number of previous therapy lines (1 versus 2), *EGFR* mutational status (mutated versus wild type) and *MET* status even when assessed by IHC (2+ versus 3+) or FISH (positive versus negative).

Although several factors could be responsible for the negative results of the study, it is possible that the potential benefit produced by the anti-MET agent was not detected because of a non-optimal patient selection. In fact, the cut-off of ≥5 *MET* copies per cell adopted for discriminating FISH positive versus FISH negative demonstrated a significant association with patient prognosis with no evidence of any predictive value (1). Recently, Camidge *et al.* presented the preliminary results of the ongoing phase I PROFILE 1001 study, in which the activity of crizotinib, a potent anti MET inhibitor, was evaluated exclusively in *MET* amplified NSCLC patients (6). In this study, *MET* FISH positivity was defined as a ratio of *MET*/centromere ≥1.8. By using this cut-off, patients were stratified on the base of levels of amplification within three categories as low (*MET/CEP*7 ratio ≥1.8-≤2.2) amplification, intermediate (*MET/CEP*7 ratio >2.2-<5) amplification and high (*MET/CEP*7 ratio ≥5) amplification. Interestingly, patients with intermediate and high levels of *MET* amplification were current smokers. Crizotinib did not result particularly effective in the small group of patients with low levels of amplification, whereas a marked anti-tumor activity was observed in both intermediate/high *MET* amplified groups (RR =50%). These findings are consistent with those reported in preclinical data (7,8). Indeed, in an *in vitro* model of gastric cancer, Japanese investigators demonstrated that only gastric cancer cell lines displaying high levels of amplification were sensitive to a potent anti MET inhibitor PF665752 (7). In another preclinical model, crizotinib induced apoptosis only in the two NSCLC cell lines with high levels of amplification (8). In addition, cell lines harboring *EGFR* mutations with acquired resistance to EGFR TKIs became *MET* addicted only in presence of high levels of *MET* amplification (3). Therefore, these data overall indicated that anti-MET strategies should be focused exclusively in patients which tumor display high levels of *MET*-amplification.

Identification of patients potentially sensitive to anti-MET agents is of crucial relevance. In 2009 we analyzed a cohort of more than 430 surgically resected NSCLC, aiming to evaluate the prognostic impact of *MET* amplification, and we found that an increase GCN of >5 copies per cell discriminated patients with different prognosis (1). By applying the same criteria adopted in the study by Camidge *et al.*, we observed that among patients included onto the analysis only a small percentage had intermediate (3%) or high levels (0.6%) of *MET* amplification, clearly indicating that the proportion of patients population potentially sensitive to anti-MET agents is relatively small. In addition, we observed that *MET* amplified patients are generally former or current smokers and approximately one third of them have squamous histology. Moreover, clinical characteristics of *MET* amplified patients do not reflect the typical population of NSCLC generally screened for biomarkers in clinical practice. In the MetMab trial, the main method used for selecting patients was IHC (5). Several evidences indicated that such method is not optimal for patient selection. Looking at mechanisms of MET deregulation, it is clear that even restricting the analysis to patients with high expression (MET 3+), they represent approximately 10% of all NSCLC, while patients with *MET* amplification are only 3-4% of cases. Recently, Arriola *et al.* showed that although *MET* amplified NSCLC invariably displayed high levels of protein expression (3+), a consistent proportion of MET 3+ by IHC was FISH negative (9). That implies that presence of *MET* amplification should be confirmed by FISH, even in MET 3+ patients.

In conclusion, *MET* remains a relevant target driving tumor growth in NSCLC but realistically in a small fraction of patients with gene amplification. In addition, as *MET* amplification have been identified mainly in individuals with smoking history and also in squamous cell histology, looking for patients potentially sensitive to anti MET agents means to focus on a category of patients that is normally less considered for biomarkers assessment. All available data clearly demonstrated that IHC or *MET* GCN are not optimal for identify patients potentially sensitive to anti-MET agents. Furthermore, as IHC is less expensive and less time-consuming than FISH test, its use could be proposed to screen on a large scale those individuals more likely to have *MET* amplification. At the present time, a phase II Italian trial (METROS trial, Eudract number 2014-001263-12) is ongoing with the aim of assessing crizotinib sensitivity in patients with intermediate or high levels of *MET* amplification. The results of this study will provide evidence on the role of anti-MET agents in selected NSCLC and will define the best cut-off of *MET* amplification discriminating sensitive versus resistant population. If sensitivity is not confined to individuals with high levels of amplification, more than one needle could be found in the haystack.

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