Editorial

Negative results of METLung study: an opportunity to better understand the role of MET pathway in advanced NSCLC

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The negative results of the global METLung phase III trial recently presented at American Society of Clinical Oncology (ASCO) were clearly unexpected (1). The trial assessed the impact on overall survival (OS) of adding onartuzumab, a monovalent monoclonal antibody against mesenchymal-epithelial transition (MET) factor receptor tyrosine kinase (RTK), to erlotinib in second or third-line therapy of advanced non-small cell lung cancer (NSCLC) patients with MET overexpression. There was a strong rationale behind this phase III trial: dysregulation of MET signaling in cancer is responsible for cell proliferation, cell cycle progression, cell dissociation, motility, spreading and invasion, overexpression of MET is linked to a worse prognosis for both early and late stages of NSCLC, and crosstalk with other RTKs including EGFR can lead to synergistic activation of downstream pathways. Moreover, amplification of MET seems to be involved in a significant proportion of patients with *EGFR* mutations developing acquired resistance to EGFR inhibitors.

The design of the METLung phase III trial was mainly based on the findings of a randomized phase II trial (2), suggesting that combination of onartuzumab to erlotinib was only effective in patients with high level of MET expression for both progression free survival (PFS) and OS. MET expression was centrally assessed on archival samples by immunohistochemistry (IHC) with an anti-MET antibody using a scoring system evaluating both staining intensity and prevalence of these intensities in tumor cells (score from 0 to 3+). The study first confirmed the negative prognostic impact of MET overexpression in patients treated in second or third-line setting with erlotinib (plus placebo) in the control arm. If there was no difference for PFS or OS in the whole population of patients (N=137), the study mostly showed a significant PFS (HR, 0.53; 95% CI: 0.28-0.99) and OS improvement (HR, 0.37; 95% CI: 0.19-0.72) in patients with MET-positive tumors (score of 2+ or 3+). This benefit remained significant after removal of MET-positive patients with known *EGFR* mutations. On the other hand, MET gene copy number determined by FISH (<5 versus ≥5) was not predictive of ornartuzumab sensitivity (2).

The METLung global phase III trial included patients with previously treated stage IIIB or IV NSCLC and a good performance status (PS 0-1). Only tumors with high MET expression were eligible; EGFR testing and MET overexpression (score from 2+ to 3+) were centrally confirmed on archival samples. Patients were randomized (1:1) to receive a combination of either both erlotinib 150 mg/day and onartuzumab 15 mg/kg given intravenously once every 3 weeks or erlotinib plus placebo. Randomization was stratified by EGFR mutational status, treatment line (2nd line versus 3rd line), MET score (2+ versus 3+) and histology. The primary objective was to demonstrate a prolongation of OS.

METLung was stopped early at the time of a planned interim analysis after inclusion of 499 patients because the futility boundary was crossed. Enrolled patients have similar demographics to those in the phase II study: about two-thirds of patients had PS 1 and were in second-line therapy; median age was 62 and 86% of patients had non-squamous carcinoma. Eleven percent of patients had *EGFR* mutations and 21.5% a MET score of 3+. Addition of onartuzumab to erlotinib did not prolong OS with a median survival of 6.8 *vs.* 9.1 months for erlotinib plus placebo (HR, 1.27; 95% CI: 0.98-1.65). Consistently, there was no response rate or PFS improvement in the combined arm, with a median PFS of 2.7 and 2.6 months for erlotinib plus onartuzumab and erlotinib plus placebo, respectively. Subgroup analysis

did not reveal any subgroup of patients benefiting from addition of onartuzumab to erlotinib; notably, there was no PFS or OS improvement in the small subgroup of patients with *EGFR* mutations (N=57) for which the combination of onartuzumab to erlotinib might be deleterious in terms of OS (HR, 4.68; 95% CI: 0.97-22.63) (1).

Several reasons can be taken into consideration to account for these surprisingly negative results. The first one concerns the biological rationale of the study. Even if preclinical data strongly suggest that there is crosstalk between MET and EGFR, the role of amplification of *MET* in the development of resistance to erlotinib has been clinically observed only in patients with *EGFR* mutations after prior treatment with EGFR tyrosine kinase inhibitor (TKI) and not in all comers mostly harboring wild-type *EGFR*. Moreover, this mechanism of resistance seems to be involved in only from 4% to 20% of acquired resistance to EGFR TKIs in case of EGFR mutation. It is unknown if the addition of an anti-MET therapy to front-line EGFR TKI treatment would prevent the emergence of secondary resistance depending on *MET* amplification and even so it was the case, it is unlikely that this small proportion of patients would have driven a survival benefit in the METLung trial.

The second reason might be related to a too optimistic interpretation of the phase II study results (2). Indeed, the lack of stratification according to MET expression status might have led to imbalances in prognostic or predictive factors, especially for *EGFR* mutations (patients receiving erlotinib in both arms), 7/35 patients in the onartuzumab arm and 2/31 patients in the placebo control arm harboring EGFR mutation. Even if the OS benefit in the onartuzumab arm remained positive after removing from analysis the patients with *EGFR* mutations, the number of remaining patients was very small (N=57), with possible imbalances in other prognostic factors that may have accounted for OS differences (for instance, *KRAS* and *EGFR* status were unknown for five and four patients in the control arm and in the experimental arm, respectively). The fact that the magnitude of OS improvement was higher than that of PFS was also indicative of a possibly inadequate distribution of prognostic factors in the MET positive patients. Therefore, the level of confidence in the magnitude of PFS and OS benefit obtained with the addition of onartuzumab to erlotinib in MET positive patients may have been excessive.

Another reason may be linked to reproducibility of the IHC testing or scoring for assessing MET expression. However, the test has been centrally performed in the same conditions than in the phase II study and it seems unlikely that MET scoring is responsible for the disparity of results between the phase II and the phase III studies.

The most credible explanation accounting for the METLung trial failure is that MET overexpression might not be an appropriate target for onartuzumab in the majority of NSCLC patients. Dysregulation of MET pathway in NSCLC can come from *MET* amplification, rare *MET* mutations that can concern the extracellular domain involving HGF binding, the tyrosine kinase domain leading to a constitutive MET activation or the juxtamembrane domain causing a disruption in negative regulation of MET signaling, autocrine or paracrine loop due to overexpression of HGF in the tumor cells or in the stroma (3). Nevertheless, the most frequent cause of increased protein expression appears to result from transcriptional up-regulation of *MET* in absence of gene amplification or mutation that can be due to other oncogenes or hypoxia with activation of transcription factor hypoxia-induced factor 1α (HIF-1α). In contrast to the situation of oncogene addiction, this inappropriate MET signaling is a secondary event as a consequence rather than the cause of the cell transformation. However, some rare tumors seem to be addicted to sustained MET activity for their growth and survival; in NSCLC, such addiction to MET functioning as a primary driver appears to result from *MET* true amplification (and not from polysomy as assessed by gene copy number in the METLung trial), occurring in a small proportion of patients (up to 5-7%) (4). True amplification assessed by FISH is a continuous variable (as determined by *MET*/centromere ratio on chromosome 7) with an unknown cut-point to detect addiction to MET pathway. The recently reported results of the crizotinib phase I study in 14 patients with *MET* amplification showed a 0%, 17% and 67% response rate in the low- (*MET*/CEP ratio ≥1.8 and ≤2.2), intermediate- (*MET*/CEP ratio >2.2 and <5) and high *MET* amplification (*MET*/CEP ratio >5) groups, respectively (5). Interestingly, high level of *MET* amplification leading to durable response to MET tyrosine kinase inhibitors seems to mainly occur in smokers (5). It is unknown if monoclonal antibodies targeting the extracellular domain of MET would reproduce the crizotinib results in tumors addicted to *MET* true amplification.

Recent results of clinical trials are therefore helpful to better understand different scenarios for MET signaling in NSCLC. In most cases, overexpression of the MET protein is a late event consecutive to the transformed phenotype, deriving from transcriptional up-regulation or ligand-dependent autocrine or paracrine mechanism. *MET* true amplification does seem to be involved in the

large majority of NSCLC, except perhaps for *EGFR* mutant patients resistant to EGFR TKIs. Targeting MET pathway in these tumors harboring overexpression of MET assessed with IHC will probably not result in large PFS or survival benefits and the optimal therapeutic approach in this case (MET TKIs versus monoclonal antibodies) remains undetermined. The exploratory subgroup analysis of the negative phase III study evaluating the addition of tivantinib (a MET tyrosine kinase inhibitor) in patients with MET overexpression might suggest a PFS and OS benefit (6), contrary to the negative METLung results with onartuzumab. Conversely, a small proportion of patients with *MET* mutation or *MET* true amplification may represent a new targetable subtype of NSCLC, notably in smokers, but even if FISH actually appears as the most promising method, the optimal biomarker for defining this subset of patients remains to be defined.

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