Mutations at the splice sites of exon 14 of *MET* gene: a new target for sarcomatoid carcinomas?

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The pulmonary sarcomatoid carcinoma (SC) represents less than 1% of non-small cell lung cancer (NSCLC). Its prognosis is worse than that of other histological subtypes, by its particular aggressiveness and resistance to conventional therapies (1,2). Therefore, alternative therapies are sought, via immunotherapy or targeting molecular abnormalities. Liu *et al*. performed in Asian patients whole exome sequencing of 10 samples from SC followed by targeted sequencing of a set of five key genes on a validation cohort with 26 samples (3). The first analysis of the 10 samples showed two samples with mutations at the splice sites of exon 14 of *MET*. Subsequent targeted mutation screening of all 36 tumors confirmed these 2 mutations and identified 6 additional tumors with DNA alterations leading to exon 14 skipping.

The *MET* oncogene is a gene encoding a tyrosine kinase receptor whose ligand is hepatocyte growth factor (HGF). Upon activation, MET induces cell mitogenesis, motility, invasion, and morphogenesis. Pathological activation through gain in gene copy number or kinase domain point mutations induces tumor proliferation, invasive growth and angiogenesis. In NSCLC, *MET* kinase domain mutations have not been described whereas *MET* gene can be amplified, particularly during acquired resistance to EGFR targeting therapies in EGFR-mutated NSCLC. Recently, mutations leading to diverse exon 14 splicing alterations, as described to be highly frequent by Liu *et al*. (3). are emerging as a new hope for subsets of patients likely to derive benefit from targeted therapies, especially those with SC.

In the manuscript reported by Liu *et al*. in SC, mutations identified in *MET* gene were diverse splice-site DNA mutations leading to RNA splicing-based skipping of *MET* exon 14, which corresponds to the juxta-membrane portion of the receptor. This results in activation of the MET kinase activity. These somatic mutations were first reported in primary lung cancer specimens and in lung cancer cell lines (4,5) and described to increase MET stability by decreasing the protein ubiquitination and therefore prolonged receptor signalling upon HGF stimulation. The *in vitro* studies conducted by Liu *et al*. showed that mutations at the splice sites of exon 14 were oncogenic in two cell lines (Hs746T and H596 cell lines). Indeed, inhibition of MET, by RNA interference or by crizotinib [anti-ALK and anti-MET tyrosine kinase inhibitor (TKI)] decreased cell viability and activation of PI3K/AKT/mTOR and MAPK pathways. A case-report supports these pre-clinical data, showing a major response under crizotinib for a patient with pulmonary SC with mutations at the splice sites of exon 14 of *MET* and refractory to chemotherapy. In all tumors, mutations were mutually exclusive of other alterations (EGFR, KRAS, BRAF, ALK). Another study presented at ASCO 2015 by Paik *et al*. also showed the effectiveness of crizotinib and cabozantinib (TKI anti-RET and anti-MET) in 7 patients with lung adenocarcinoma with mutations at the splice sites of exon 14 of *MET*, with 75% partial responses and 25% stabilizations (6). Similar cases were also reported by Frampton (7).

Several large series defining the genomic landscape of lung adenocarcinoma identified *MET* exon 14 skipping mutations to occur in approximately 3% of tumors (7-12) and 2% in other lung neoplasms (7). In smaller series of SC, different prevalences have been reported from 3% (1) to 22% in the series of Liu *et al*. (3). Demographical, ethnicity, clinical and histological characteristics of the SC could influence the prevalence like the proportion of SC

with an adenocarcinoma component or the high rate of *KRAS* mutated tumors in the Liu's cohort. Further studies are necessary to evaluate the frequency of these mutations in larger cohorts including Caucasian patients with SC and other histological subtypes. However, the main reason of variable prevalence may be the diagnosis testing of the *MET* exon 14 splice-site mutations. Indeed, dozens of distinct *MET* exon 14 sequence variants have been described. Moreover, they include base substitutions, deletions, insertions, or complex indels that can be located at splice acceptor or donor sites, even in the app. Totally 25 bp intronic non-coding region immediately adjacent to the splice acceptor site. There are also whole deletions of *MET* exon 14. Therefore, it is a true challenge to perform accurate screening for *MET* exon 14 splicing alterations, especially in the routine practice. For example, the whole exome sequencing used by Liu *et al.* can miss alterations in the intronic regions. The use of formalin-fixed paraffin-embedded tumors limits the easiest analysis of RNA sequences. Thus, the screening for *MET* mutations in the clinical setting is challenging and requires appropriate laboratory and analytical method to detect each of them with high sensitivity and specificity. Accurate sequencing, detection, variant annotation and reporting of the different class of *MET* alterations conferring probably different clinical sensitivity to MET inhibitors will be soon critically important for improving the care of patient with SC and other lung neoplasms.

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Footnote

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Conflicts of Interest: A Cortot is doing expertise for Novartis and Pfizer. The other authors have no conflicts of interest to declare.

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