**LETTER TO THE EDITOR**

**KIF5B-MET fusion variant in non-small cell lung cancer**

Dear Editor,

Lung cancer is the cancer type with the highest mortality rates worldwide. The treatment of lung adenocarcinoma (LADC) changed dramatically since the recognition of actionable oncogenic abnormalities. MET is a receptor tyrosine kinase activated by binding of its ligand hepatocyte growth factor, and a known oncogenic driver of lung cancer. Abnormal MET signaling can occur through a different number of mechanisms such as amplification, mutation and fusion. The most frequent oncogenic alteration of MET kinase involves MET exon 14 skipping mutations. MET fusions are rare in LADC. Kinases activated by gene fusions represent an important class of oncogenes being ALK, RET and ROS1 fusion, the most frequent in LADC.

Two reports suggest that MET signaling (through MET amplification) could also trigger resistance to ALK kinase inhibition in ALK rearranged tumors. Although the MET kinase fusions identified in two LADCs fulfill the criteria of primary oncogenic drivers, the MET Kinase domain (MET-KDD) rearrangement may be specifically associated with the ceritinib resistance phenotype in an ALK-rearranged background. Recently, a KIF5B-protein tyrosine kinase fusion transcript – KIF5B-MET – has been discovered in LADC patients, consisting of a chimeric fusion of exons 1–24 of KIF5B to either exons 14–21 or exons 15–21 of the MET proto-oncogene. This was denoted as K24/M14 or K24/M15 based on the last KIF5B and MET exons in the fusion, respectively. KIF5B-MET variant was demonstrated to have an oncogenic function in cancer cells. Furthermore, a novel fusion partner for MET was observed - STARD3NL.

The authors present the case of a 56-year-old Caucasian male, with stage IA lung adenocarcinoma - cT1bN0M0 (TNM classification, 8th edition), never-smoker. The patient started follow up due to image findings requested during a chest pain investigation. Clinically, denied constitutional symptoms, hemoptysis, dyspnea, cough or other relevant symptoms. Patient reported family history of premature coronary disease and mentioned past medical history of hypothyroidism, arterial hypertension, diabetes mellitus, dyslipidemia, and anxiety. There were no known respiratory disorders. Thorax CT revealed a nodule with ground glass texture and a central solid portion, measuring 14 mm and 5 mm, respectively, in the lateral segment of the lower left lobe, adjacent to the large fissure. Also, scattered throughout the pulmonary parenchyma, micronodular lesions were found; the largest, in the medial segment of the middle lobe, with 7 mm (assessed, after discussion in multidisciplinary meeting, as intrapulmonary lymph node – no biopsy was performed). Positron Emission Tomography (PET) showed the nodule in the lower lobe of the left lung does not have significant FDG uptake. CT-guided biopsy was performed, confirming the diagnosis of adenocarcinoma (TTF1, Napsin A and CK7 positive; CK20 – negative).

Immunohistochemical PD-L1 expression, using the 22C3 antibody concentrate (DAKO), showed low/intermediate positive results (1-49%). Next Generation Sequencing (NGS) was performed using the Oncomine Focus Assay on DNA and RNA obtained from tumor biopsy, that allows detection of SNVs and indels in genes AKT1, ALK, AR, BRAF, CDK4, CTNNB1, DDR2, EGFR, HER2, 3 e 4, ESR1, FGFR2 e 3, GNA11, GNAQ, HRAS, IDH1 and 2, JAK1, 2 and 3, KIT, KRAS, MAP2K1 and 2, MET, MTR, NRAS, PDGFR, PIM3, RAF1, RET, ROS1 and SMO; CNVs in genes AKT1, ALK, AR, BRAF, CCND1, CDK4, CDK6, EGFR, HER2, FGFR1, 2, 3 and 4, KIT, KRAS, MET, MYCN, PDGFR, PIK3CA; and gene fusions in genes BL1, AKT3, ALK, AXL, BRAF, EGFR, HER2, ERG, EV7, 4 and 5, FGFR1, 2 and 3, MET, NTRK1, 2 and 3, PDGFR, PPARG, RAF1, RET, ROS1. This NGS technique, validated locally, allows detection of nucleotide substitutions with allelic fraction >5% and rearrangements in 1% of the RNA, in samples with more than 20% of neoplastic cells, with a sensitivity >99%. Our fixed tissue sample was representative of the tumor and had approximately 10% neoplastic nuclei.

Mutation c.2917G>T (p.Asp973Tyr), in exon 22 of the NF1 gene and rearrangement of KIF5B (24)-Met (15) were found. Thus, a rare fusion variant involving the MET gene-KIF5B-MET (K24:M15) in a patient with LADC was identified, co-occurrent with a NF1 mutation of undetermined significance. The MET protooncogene is implicated in a variety of cancers, particularly in papillary renal cell carcinoma, where a number of somatic mutations have been described. In a mutation review, single MET fusions were found in four other cancers: low-grade glioma, hepatocellular carcinoma, thyroid cancer and lung adenocarcinoma, being KIF5B-MET fusion present in these last two cases. There are only two known types of KIF5B-MET gene fusion in LADC: K24:M15 and K24:M14. In the literature we found a total of five cases – three K24:M15 and two K24:M14. Our case is the 6th...

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reported case of KIF5B-MET gene fusion, the 4th reporting a K24:M15 fusion and the only one reporting a NFI1 commutation. The fusion gene between exon 24 of KIF5B and exon 14 of MET (K24:M14) was originally reported as 1 out of 513 LADC samples in a mutation review without mention to any treatment. Later on, an additional case with the variant was described, being the first documented case of a patient with a MET fusion-positive tumor (K24:M14) exhibiting a significant and sustained response to treatment with crizotinib in LADC.

The first patient identified with K24:M15 variant was a 33-year-old female with stage IV LADC treated with off-label crizotinib, having shown maintained clinical benefit, decrease in both tumor size and FDG uptake in PET/CT, and minimal side effects for at least 8 consecutive months. The other two cases were reported in a patient with a mixed-type LADC-sarcomatoid tumor, and in a patient with pulmonary sarcomatoid tumor. The patient with mixed type of LADC-sarcomatoid tumor had poor conventional chemotherapy (pemetrexed-cisplatin) response and the patient with pulmonary sarcomatoid tumor had supportive care; both had poor overall survival.

In our case, the patient was submitted to left uniportal video-assisted thoracoscopic surgery (VATS) with segmentectomy (S8) and exeresis of lymph node stations 5L, 8L 9L, N11 and N12. Pathologic examination of surgical piece revealed visceral pleural invasion (pT2N0), and adjuvant chemotherapy (alectinib) was started. Our case was radically treated, so no MET inhibitor was introduced; however, in case of future tumor progression, this might be an option.

Fusions beyond ALK, RET, and ROS1 have been documented in lung adenocarcinomas without associated oncogenic mutations. The authors present the 4th case in the world with a mutation of KIF5B-MET (K24:M15), but the single one describing a NFI1 commutation (the first being described with any MET fusion). The significance of this association remains unknown, especially regarding the role of a MET inhibitor in its treatment efficacy. The authors also highlight the importance of performing NGS in all patients with LADC, since recognition of oncogenic activation events represents targeted intervention opportunities, even if it is off label use in rare forms of presentation.

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References


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