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MET mutation associated with responsiveness to crizotinib

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TO THE EDITOR

Activation of c-MET oncogene can be the result of amplification or activating mutations. In this letter we would like to share our experience of treating a patient with metastatic lung adenocarcinoma, whose tumor was found to harbor a *MET* mutation occurring at a splice site within the juxtamembrane domain.

A 71 year old Caucasian man with a 15 pack-year smoking history presented to our clinic with a biopsy-proven left lung adenocarcinoma with a 6.4 × 5 cm left pleural-based mass invading the fourth rib, left hilar lymphadenopathy and numerous bilateral sub-centimeter pulmonary nodules. He received palliative thoracic radiation to a total dose of 3000 cGy, followed by 2 cycles of chemotherapy with carboplatin AUC 5 and pemetrexed 500 mg/m^2 intravenously every 3 weeks. Follow-up CT scan of the chest and abdomen revealed improvement in the previously irradiated left lung mass, mediastinal and hilar adenopathy, but new and enlarging pulmonary nodules, bilateral supraclavicular adenopathy and new sclerotic bone lesions.

Targeted next-generation sequencing of 42 cancer-related genes (Comprehensive Cancer Gene Set version 2 assay, GPS@WUSTL, St. Louis, MO) was performed on DNA derived from the formalin-fixed paraffin-embedded tumor biopsy specimen.[1] A *MET* single nucleotide variant (SNV) was identified, chr7:g.116412043G>C, involving the terminal nucleotide of exon 14 (Figure 1). This variant could result in a p.D1028H missense mutation (NM_001127500:c.3082G>C), but is also predicted by in-silico modeling to affect the splice donor site (Figure 2). Fluorescence in-situ hybridization (FISH) analysis was performed using commercial probes (Abbott Molecular, Des Plaines, IL) for *MET/CEP7* (7q31.2/7p11.1-q11.1). Polysomy of chromosome 7 was noted (CEP7 and *MET* average copy numbers 2.31 and 2.23, respectively), although the *MET*/CEP7 ratio of 0.96 was negative for *MET* amplification. He was started on crizotinib 250 mg orally twice daily. Restaging CT scans after 6 weeks of therapy revealed decrease in size of the pulmonary lesions with continued response at 6 months (Figure 3).

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The *MET* receptor tyrosine kinase is a known oncogene, with a somatic mutation frequency of 8.3% in lung adenocarcinoma and 2% in lung squamous cell carcinoma, based on sequencing data from The Cancer Genome Atlas (TCGA).[2] *MET* mutations are seen typically in smokers, and may co-occur with *TP53* mutations.[3] Unlike activating *EGFR* mutations that occur primarily in the tyrosine kinase domain, *MET* mutations are distributed across all domains of the gene. While mutations in the semaphorin domain may affect ligand-binding affinity, juxtamembrane domain mutations impact CBL mediated ubiquitination and MET receptor degradation. Somatic splice site mutations involving *MET* exon 14, resulting in deletion of the juxtamembrane domain, have been described in lung cancer.[4,5] The juxtamembrane domain contains a binding site for CBL, which is required for ubiquitin-mediated MET degradation. The variant described here could result in over-activation of MET via skipping of exon 14 with loss of the CBL/ubiquitin-mediated degradation (Figure 2). To the best of our knowledge, this is the first report demonstrating successful targeting of this MET tyrosine kinase variant by crizotinib.

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REFERENCES

1. Sehn JK, Hagemann IS, Pfeifer JD, Cottrell CE, Lockwood CM. Diagnostic utility of targeted next-generation sequencing in problematic cases. The American journal of surgical pathology. 2014; 38:534–41. [PubMed: 24451277]
2. Gao J, Aksoy BA, Dogrusoz U, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Science signaling. 2013; 6:pl1. [PubMed: 23550210]
3. Krishnaswamy S, Kanteti R, Duke-Cohan JS, et al. Ethnic differences and functional analysis of MET mutations in lung cancer. Clinical cancer research : an official journal of the American Association for Cancer Research. 2009; 15:5714–23. [PubMed: 19723643]
4. Kong-Beltran M, Seshagiri S, Zha J, et al. Somatic mutations lead to an oncogenic deletion of met in lung cancer. Cancer research. 2006; 66:283–9. [PubMed: 16397241]
5. Asaoka Y, Tada M, Ikenoue T, et al. Gastric cancer cell line Hs746T harbors a splice site mutation of c-Met causing juxtamembrane domain deletion. Biochemical and biophysical research communications. 2010; 394:1042–6. [PubMed: 20331976]

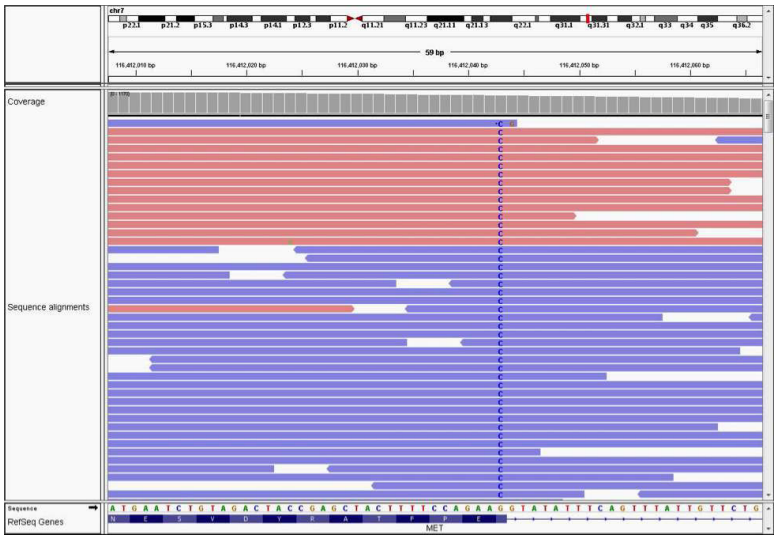

Figure 1.

MET chr7:g.116412043G>C alteration as viewed in the Integrative Genomics Viewer (Broad Institute, Cambridge, MA). The guanine to cytosine alteration is highlighted at the terminus of *MET* exon 14.

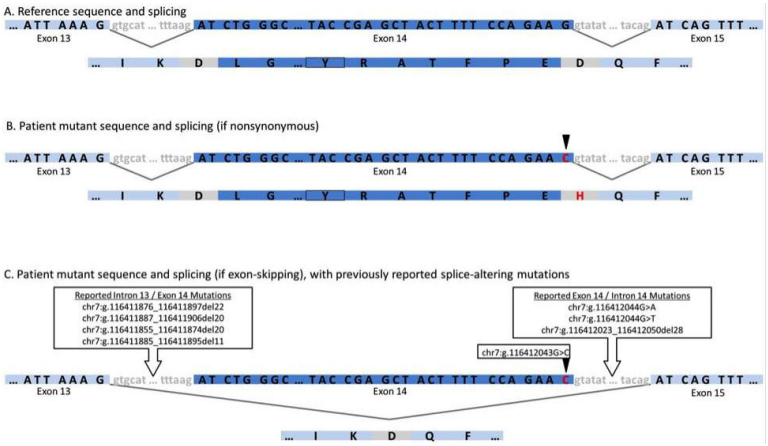

Figure 2.

MET alteration and predicted outcomes. Each panel shows *MET* exon 14 and flanking DNA sequence with splicing events indicated by black lines followed by the resulting protein sequence. A) Normal *MET* sequence and splicing. The c-Cbl binding site (Y1021) is marked with a box. B) Effect of chr7:g.116412043G>C alteration (red, arrow) if splicing is unimpaired resulting in a p.D1028H substitution without deletion of exon 14. C) Alternately, as predicted by splice site algorithms, the variant could result in altered splicing with deletion of exon 14, as has been described for other *MET* splice site variants in lung cancer.

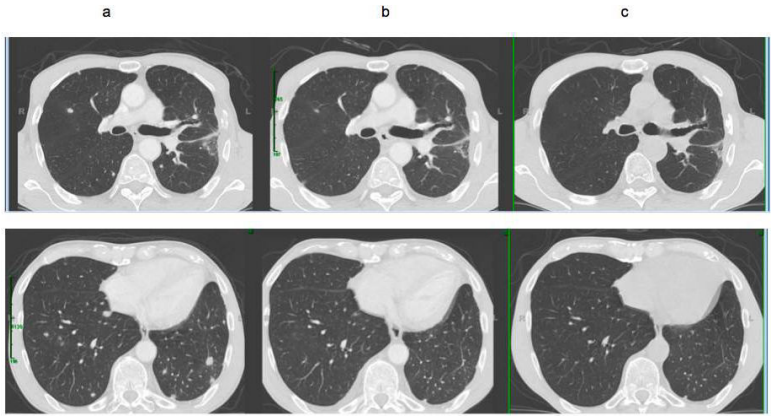

Figure 3.

Radiographic response to crizotinib. CT scans (a) at baseline (and (b) after 6 weeks and (c) 6 months of crizotinib.