Response to Crizotinib in a Patient With Lung Adenocarcinoma Harboring a MET Splice Site Mutation

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Clinical Practice Points

- Lung adenocarcinoma has been increasingly subdivided based on the presence of certain driver oncogenes that confer susceptibility to targeted therapy.
- Similar to ALK and ROS1 rearranged lung adenocarcinomas, those that harbor MET amplification were recently found to respond to the multitargeted tyrosine kinase inhibitor crizotinib.
- We describe clinical activity of crizotinib in a patient with lung adenocarcinoma with a MET splice site mutation.
- Although these mutations occur at nearly twice the frequency of MET amplification, special attention is required to detect them on clinical next-generation sequencing platforms.
- Our findings suggest the need to expand efforts to identify these mutations and evaluate responsiveness to c-Met inhibition in genotype-directed clinical trials.

Introduction

MET (c-Met; mesenchymal–epithelial transition factor) is a receptor tyrosine kinase that was first characterized as a proto-oncogene in 1984 in a chemically transformed osteosarcoma cell line.1 Located on chromosome 7q21-31, the MET gene encodes a cell surface receptor tyrosine kinase composed of a 50 kDa α chain and a 140 kDa transmembrane β chain linked by a disulfide bond. The natural ligand for c-Met is hepatocyte growth factor (HGF), also known as scatter factor.2 After binding of HGF, the c-Met receptor undergoes dimerization and phosphorylation, which in turn promotes recruitment of downstream effector proteins, leading to activation of multiple signaling cascades, including the MAPK, PI3K/Akt, STAT and NF-κB pathways.3 Physiologic roles for HGF/MET signaling include embryogenesis, development, and wound healing.3–5

Aberrant activation of the c-Met receptor tyrosine kinase promotes oncogenicity in a subset of lung adenocarcinomas. A variety of mechanisms can result in constitutive c-Met signaling, including MET gene amplification, protein overexpression, activating point mutations, and induction of its ligand HGF.3,6,7 Crizotinib, a multitargeted tyrosine kinase inhibitor that is approved by the US Food and Drug Administration for the therapy of lung adenocarcinomas harboring ALK fusions and has activity in ROS1-rearranged lung adenocarcinoma (but is not yet FDA-approved for this indication),8–10 was also recently found to be clinically active in tumors with high level MET amplification.11 These findings have prompted the clinical development of more selective c-Met inhibitors for evaluation in this particular patient population.

MET splice site mutation has also been demonstrated to induce constitutive activity and confer sensitivity to c-Met inhibition in vitro.12,13 Indeed, frequent activating MET splice site mutations were recently described in whole exome sequencing discovery efforts in lung adenocarcinoma.14 However, the clinical activity of c-Met inhibition in this context remains unknown. We identified one such mutation using targeted next-generation sequencing (NGS) in a patient with lung adenocarcinoma and treated him with crizotinib.

Case Report

An 86-year-old never-smoking man presented with left lower extremity weakness and unsteadiness. A brain magnetic resonance imaging scan revealed 3 enhancing lesions measuring up to 1.4 cm
in the right frontal lobe and left cerebellar hemisphere, suggestive of metastatic disease. Chest and abdominopelvic computed tomographic (CT) scans revealed a 5.6 cm right lower lobe mass and mediastinal lymphadenopathy, as well as a right adrenal nodule. Positron emission tomography confirmed mild to moderate fluorodeoxyglucose avidity of the lung mass, subcarinal lymph node, and adrenal nodule. Core biopsy of the lung mass identified TTF-1-positive lung adenocarcinoma. Standard genotyping for alterations in EGFR, KRAS, ALK, ROS1, and RET was negative.

The patient underwent stereotactic radiotherapy (2000 cGy) to each brain lesion, followed by palliative radiation (3900 cGy) to the obstructing lung mass. A single cycle of pemetrexed was complicated by cellulitis and not pursued further. Biopsy of the right adrenal lesion was then performed for more comprehensive profiling. Targeted NGS identified a MET splice site mutation predicted to be activating based on comparison to similar mutations reported in the literature. Immunohistochemistry (IHC) revealed 2+ phosphorylated c-Met in 50% of cells, consistent with c-Met activation.

Given these findings and the clinical activity of crizotinib in MET-amplified lung adenocarcinoma, the patient initiated therapy with crizotinib. After 5 weeks, chest/abdominopelvic CT scans revealed significant improvement of the lung mass and a decrease in the size of the unirradiated adrenal lesion from 2.0 × 1.9 cm to 1.4 × 1.2 cm (Figure 2A and B). Unfortunately, associated pneumonitis necessitated crizotinib discontinuation. Disease progression occurred 8 weeks later, after which time palliative care was pursued.

Discussion

To our knowledge, this is the first report that associates clinical response to crizotinib with MET splice site mutation in lung adenocarcinoma. Because this elderly patient was unable to tolerate even single-agent pemetrexed, we empirically treated him with crizotinib because of the reported activity in MET-amplified non–small cell lung cancer and an acceptable toxicity profile. Although it is difficult to separate the response of his lung mass from the continued effects of palliative radiation, we observed a clear decrease in size of the unirradiated adrenal lesion from which the MET splice site mutation was identified. Because more selective c-Met inhibitors remain in clinical development, we were unable to transition him to alternative agents after the development of crizotinib toxicity, and thus we could not assess durability of activity.

Recent whole exome sequencing data in lung adenocarcinoma revealed MET exon 14 splice site mutations in 4.3% of patients, twice the frequency of MET amplification. This intronic deletion, c. 2887-18_2887-7del12, resides in the polypyrimidine tract just...
upstream of the exon 14 5’ splice acceptor site (Figure 1A). Mutations affecting this tract or the 3’ splice donor site cause in-frame skipping of exon 14.13 The resulting protein lacks a portion of the juxtamembrane domain, which eliminates binding of Cbl, an E3 ubiquitin ligase involved in c-Met down-regulation. Consequently, studies show that c-Met protein lacking exon 14 has enhanced activity, consistent with the IHC results in this case.

Importantly, clinical targeted NGS assays that include MET exon primers typically read sequence into splice sites (Figure 1A), highlighting the importance of examining these key intron/exon junctions from patient sequencing data. Without bioinformatics platforms that analyze and capture these additional reads, it is likely that such mutations are frequently overlooked. Their potential clinical relevance in lung adenocarcinoma suggests that heightened efforts should be made to identify and report these mutations in such patients.

### Conclusion

In conclusion, although clinical trials are necessary to confirm our findings, these results suggest a benefit of targeted therapy in a patient population greater than ROS1- and approaching the frequency of ALK-rearranged lung cancer. Indeed, additional efforts to identify MET splice site mutations in lung adenocarcinoma patients and enroll them in genotype-directed studies may expand the repertoire of genotype-directed therapy and further realize the goal of personalized cancer medicine.

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### Disclosure

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### References

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