MET 14 Deletion in Sarcomatoid Non–Small-Cell Lung Cancer Detected by Next-Generation Sequencing and Successfully Treated with a MET Inhibitor

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The patient is a 61-year-old male never smoker who first presented with pain in his left hip and right-sided chest pain in 2014. Imaging revealed lytic bone lesions in the left iliac wing, right sixth rib, left eleventh rib, and T12. Core biopsy was performed on the left iliac wing, and it revealed CK7+, TTF1+, and vimentin+ sarcomatoid non–small-cell lung cancer. Comprehensive genomic profiling was performed through FoundationOne (Foundation Medicine, Inc., Cambridge, MA) on the pretreatment biopsy specimen, and the tumor harbored two *MET* alterations predicted to result in skipping of exon 14 (c.2888-5_2890TTAAGATC>A and c.3028+2T>G) and a known activating point mutation in *MET* (p.H1094Y, c.3280C>T).

The patient was treated with radiation to painful bony lesions followed by carboplatin, paclitaxel, and bevacizumab on the ECOG5508 trial (NCT01107626). Although there was some evidence for response after two cycles, he experienced clear progressive disease after four cycles and MET-directed therapy was considered.

Skipping of exon 14 deletes a region of the juxtamembrane domain causing a decreased rate of MET degradation. Mutations leading to *MET* exon 14 skipping have previously been reported including responses to MET inhibitors.[1–3] In light of the multiple *MET* alterations observed in the patient including an activating mutation, he was treated on a clinical trial of the MET inhibitor crizotinib (NCT00585195). He experienced a partial response by Response Evaluation Criteria in Solid Tumors 1.0 criteria, which was accompanied by the patient reporting symptomatic improvement in activity level and pain. Most notably, a dominant right-sided chest mass decreased from 8.2 to 6.1 cm, but there was no clear change in bony lesions (Fig. 1). This lasted for more than 5 months until he experienced progressive pain. Imaging confirmed progression both in the lung and in bony lesions. The patient is now on hospice care.

This case illustrates the potential of comprehensive genomic profiling to identify mutations that are actionable on clinical trials and the potential activity of crizotinib against *MET* exon 14 splice site mutations, a hypothesis being tested by ongoing studies (NCT00585195). Such findings will be applicable to a sizable group of patients—*MET* mutations have been estimated to occur in 3% of squamous cell cancers of the lung[4] and 3–8% of adenocarcinomas of the lung[1,5] as well as in other lung neoplasms, brain gliomas, and cancers of unknown primary.[1]

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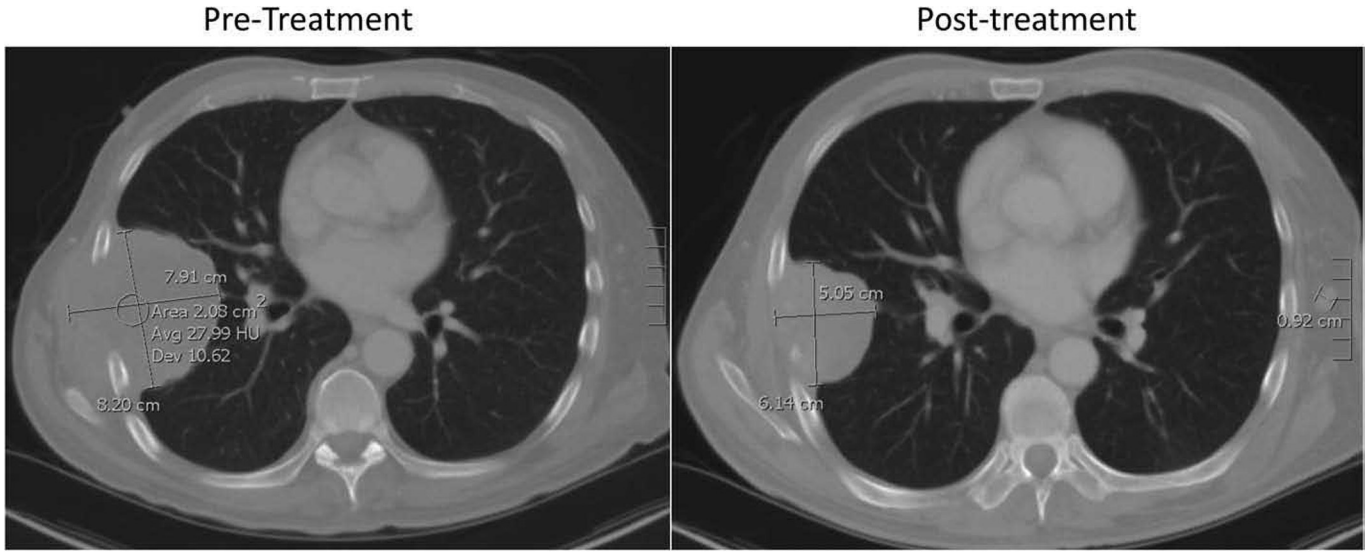

FIGURE 1. Pre- and post treatment CT scans.