Response to MET Inhibitors in Patients with Stage IV Lung Adenocarcinomas Harboring MET Mutations Causing Exon 14 Skipping

Paul K. Paik1,2, Alexander Drilon1,2, Pang-Dian Fan3, Helena Yu1,2, Natasha Rekhtman3, Michelle S. Ginsberg4, Laetitia Borsu3, Nikolaus Schultz5,6, Michael F. Berger2,3,5, Charles M. Rudin1,2, and Marc Ladanyi3,5

ABSTRACT

Mutations in the MET exon 14 RNA splice acceptor and donor sites, which lead to exon skipping, deletion of the juxtamembrane domain containing the CBL E3-ubiquitin ligase-binding site, and decreased turnover of the resultant aberrant MET protein, were previously reported to be oncogenic in preclinical models. We now report responses to the MET inhibitors crizotinib and cabozantinib in four patients with stage IV lung adenocarcinomas harboring mutations leading to MET exon 14 skipping, highlighting a new therapeutic strategy for the 4% of lung adenocarcinoma patients whose tumors harbor this previously underappreciated genetic alteration.

SIGNIFICANCE: Oncogenic mutations in the MET exon 14 splice sites that cause exon 14 skipping occur in 4% of lung adenocarcinomas. We report responses to the MET inhibitors crizotinib and cabozantinib in patients with lung adenocarcinomas harboring MET exon 14 splice site mutations, identifying a new potential therapeutic target in this disease. Cancer Discov; 5(8); 1–8. ©2015 AACR.

INTRODUCTION

Lung cancer is the leading cause of cancer-related death in both men and women (1). Great therapeutic strides have been made for those with the most common subtype of lung cancer, lung adenocarcinoma, in which an oncogenic driver and target for therapy can now be identified in the majority of patients (2). The MET proto-oncogene has been the focus of therapeutic studies in lung cancer for a number of years. MET, along with its ligand hepatocyte growth factor (HGF), plays a role in cell proliferation, apoptosis, and motility/invasion (3, 4). Gain-of-function alterations in MET are varied and include gene amplification, protein overexpression, and mutations in the juxtamembrane and semaphorin domains (5). The overall incidence of MET mutations varies, occurring in 3% of squamous cell lung cancers (6) and 8% of...
lung adenocarcinomas (7). MET gene amplification occurs in about 4% of lung adenocarcinomas and 1% of squamous cell lung cancers (6, 7). Clinical trials of MET-directed therapies have taken two approaches: monoclonal antibody therapy directed against the receptor or HGF ligand; and tyrosine kinase inhibition. In a recent phase III trial of stage IV nonsmall cell lung cancer (NSCLC) patients whose tumors demonstrated high MET protein expression by IHC, patients were randomized to receive second-line erlotinib with or without onartuzumab, an inhibitory anti-MET monoclonal antibody. This study showed no benefit to the addition of onartuzumab to erlotinib over erlotinib alone (8). In contrast, early reports do suggest that the tyrosine kinase inhibitor crizotinib has activity in patients with MET-amplified NSCLCs (9).

In 2003 and 2005, Ma and colleagues (10, 11) reported a series of novel MET exon 14 splicing variants, two in small cell lung cancer tumors involving a 2-bp insertion in a splice acceptor site 5′ of exon 14 and one in an NSCLC tumor involving an in-frame skip of exon 14. In 2006, Kong-Beltran and colleagues (12) identified another series of somatic intronic mutations in lung cancer cell lines and patient samples immediately flanking exon 14, which encodes the juxtamembrane domain and Y1003 residue that serves as the binding site for CBL, the E3 ubiquitin ligase that controls MET turnover. RT-PCR confirmed exon 14 skipping in each case. Coprecipitation of CBL and MET was lost in the presence of these variants. MET exon 14 skipping also led to a decrease in MET ubiquitination and delayed receptor downregulation after stimulation with HGF. Downstream ligand-dependent signaling through MAPK was also prolonged in cells transfected with a MET exon 14 splice variant. A xenograft model of Rat1A fibroblasts stably transfected with a MET exon 14 splice variant developed tumors whose growth rates were significantly higher than those with wild-type MET. Finally, HS96 lung adenocarcinoma cells, which harbor a MET exon 14 splice variant, exhibited MET signaling downregulation and a decrease in cell viability following treatment with onartuzumab. The scope of MET exon 14 splice variants in lung adenocarcinomas has since been defined by a number of other groups, including The Cancer Genome Atlas (TCGA; refs. 7, 13, 14).

On the basis of these data, we prospectively identified a series of 8 patients with MET exon 14 splice site alterations and treated 4 of them with one of the small-molecule MET inhibitors, crizotinib or cabozantinib.

**RESULTS**

Table 1 summarizes the clinicopathologic data for the 8 patients with MET exon 14 splice site alterations. There were no ROS1, RET, or ALK fusion events detected by Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT). The mutations we detected flanking MET exon 14 or deleting Y1003 are shown pictorially in Fig. 1. NanoString confirmed MET exon 14 skipping in all 5 patients who had leftover tumor material for this analysis (Supplementary Figs. S1 and S2). The specific case reports for 4 patients treated with a MET inhibitor follow below.

**Patient 2**

Patient 2 is an 80-year-old woman and a never-smoker who was diagnosed with a pT1aN0M0 stage IA lung adenocarcinoma in 2008. In 2010, the patient developed recurrence in a precarinal lymph node and received weekly docetaxel for 2 months. This was poorly tolerated. Her therapy was changed to pemetrexed, which she received from September 2011 until February 2012. Following disease progression, she underwent radiotherapy to the mediastinum totaling 66 Gy. She did well for just over 2 years, after which she developed a liver metastasis in June 2014. Her liver tumor was biopsied and sequenced, revealing lung adenocarcinoma positive for a MET c.3028G>C exon14 splice site mutation and MET amplification. MET IHC showed high MET expression, with an H-score of 300. The patient provided written informed consent for participation in a phase II clinical trial of cabozantinib, a tyrosine kinase inhibitor with activity against MET [Institutional Review Board (IRB) #12-097; NCT01639508]. She began treatment with cabozantinib at a dose of 60 mg orally daily in September 2014. Baseline PET imaging showed a 5-cm liver metastasis with SUVmax of 10.4. Follow-up imaging 4 weeks later showed complete resolution of 2[18F]fluoro-2-deoxy-d-glucose uptake in the liver lesion, meeting the definition of a PERCIST complete response (Fig. 2A). The patient remains on therapy with a dose reduction, having experienced grade 2 fatigue as her most severe adverse event to date.

**Patient 4**

Patient 4 was a 78-year-old man and a former smoker diagnosed with stage IV lung adenocarcinoma in December 2014. His NSCLC was diagnosed with a pT1aN0M0 stage IA lung adenocarcinoma in 2008. In 2010, the patient developed recurrence in a precarinal lymph node and received weekly docetaxel for 2 months. This was poorly tolerated. Her therapy was changed to pemetrexed, which she received from September 2011 until February 2012. Following disease progression, she underwent radiotherapy to the mediastinum totaling 66 Gy. She did well for just over 2 years, after which she developed a liver metastasis in June 2014. Her liver tumor was biopsied and sequenced, revealing lung adenocarcinoma positive for a MET c.3028G>C exon14 splice site mutation and MET amplification. MET IHC showed high MET expression, with an H-score of 300. The patient provided written informed consent for participation in a phase II clinical trial of cabozantinib, a tyrosine kinase inhibitor with activity against MET [Institutional Review Board (IRB) #12-097; NCT01639508]. She began treatment with cabozantinib at a dose of 60 mg orally daily in September 2014. Baseline PET imaging showed a 5-cm liver metastasis with SUVmax of 10.4. Follow-up imaging 4 weeks later showed complete resolution of 2[18F]fluoro-2-deoxy-d-glucose uptake in the liver lesion, meeting the definition of a PERCIST complete response (Fig. 2A). The patient remains on therapy with a dose reduction, having experienced grade 2 fatigue as her most severe adverse event to date.

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Table 1. Clinical, pathologic, and molecular characteristics of patients with stage IV lung adenocarcinomas harboring MET exon 14 splice site mutations (Continued)

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age</th>
<th>Sex</th>
<th>Smoking status (pack years)</th>
<th>MET exon 14 variant (mutant allele frequency)</th>
<th>Histology</th>
<th>Prior therapies</th>
<th>RECIST response</th>
<th>PFS, mo</th>
<th>OS, mo</th>
<th>Somatic mutations</th>
<th>Copy-number alterations</th>
<th>MET fold change</th>
<th>MET IHC (H-score)</th>
<th>MET mRNA exon 14 skip (NanoString)</th>
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<tr>
<td>1</td>
<td>73</td>
<td>F</td>
<td>F (6)</td>
<td>MET c.2888-19&gt;2888-2delCTTTCTCTCTTT TAA exon 14 splicing variant (0.51)</td>
<td>Poorly differentiated adenocarcinoma</td>
<td>MPOL328OA</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>9.2+</td>
<td>TP53 C135F, ASXL1 V1332F, ATRX E1159X, FAT1 M4205L, MET S204fs</td>
<td>MYC amp, RPS6KA4 amp, MEN1 amp, RPS6KB2 amp</td>
<td>Not amplified</td>
<td>300</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>F</td>
<td>N</td>
<td>MET c.3028G&gt;C exon 14 splicing variant (0.94)</td>
<td>Moderately differentiated adenocarcinoma</td>
<td>Docetaxel, pemetrexed</td>
<td>Cabozantinib (3rd line)</td>
<td>SD (0%), CR (PERCIST response)</td>
<td>5.1+</td>
<td>55.1+</td>
<td>Rb1 intragenic deletion, DICER1 Q1776X, EPHAS1 R853Q, KL4 M11, MLL I1929M, MTR D37N, TERT G225E</td>
<td>FUBP1 amp, GSK3B amp, SDHA amp, TERT amp, MET amp, KDM5A amp, RAD52 amp, MDM2 amp, BCL2L1 amp, NXX3-1 del, ETV6 del</td>
<td>6</td>
<td>300</td>
</tr>
<tr>
<td>3</td>
<td>79</td>
<td>F</td>
<td>N</td>
<td>MET c.3028+1G&gt;A exon 14 splicing variant (0.16)</td>
<td>Adenocarcinoma with squamous and spindle cell components</td>
<td>Unknown</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>5.3</td>
<td>NF1 L2755fs</td>
<td>None</td>
<td>Not amplified</td>
<td>300</td>
</tr>
<tr>
<td>4a (primary lung tumor)</td>
<td>80</td>
<td>M</td>
<td>F (20)</td>
<td>MET c.3024_3028del AGAAGGATATT exon 14 splicing variant (0.38)</td>
<td>Adenocarcinoma</td>
<td>Carboplatin + pemetrexed + bevacizumab; abraxane</td>
<td>Crizotinib (3rd line)</td>
<td>PR (-30%)</td>
<td>3.6</td>
<td>22.2</td>
<td>TP53 exon8 splice variant, FAT1 R782fs, FBXW7 G539V, MLL E1678K, NFI E572fs, NTRK2 I191T</td>
<td>YES1 amp</td>
<td>Not amplified</td>
<td>300</td>
</tr>
</tbody>
</table>
### Table 1. Clinical, pathologic, and molecular characteristics of patients with stage IV lung adenocarcinomas harboring MET exon 14 splice site mutations (Continued)

<table>
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<tr>
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<th>MET exon 14 variant (mutant allele frequency)</th>
<th>Histology</th>
<th>Prior therapies</th>
<th>MET therapy</th>
<th>RECIST response</th>
<th>PFS, mo</th>
<th>OS, mo</th>
<th>Somatic mutations</th>
<th>Copy-number alterations</th>
<th>MET fold change</th>
<th>MET IHC (H-score)</th>
<th>MET exon 14 skip (NanoString)</th>
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<tr>
<td>4b (liver metastasis)</td>
<td>80</td>
<td>M</td>
<td>F(20)</td>
<td>MET c.3024_3028delAGAA GGTATATT exon 14 splicing variant (0.57)</td>
<td>Adenocarcinoma</td>
<td>Carboplatin + pemetrexed + bevacizumab; abraxane</td>
<td>Crizotinib (3rd line)</td>
<td>PD (+133%)</td>
<td>0</td>
<td>22.2</td>
<td>TP53 exon 8 splice variant, FAT1 R782fs, FBXW7G539V, MLL E1678K, NF1 E572fs, TERT G674S</td>
<td>CDKN2B del, CDKN2A del</td>
<td>Not amplified</td>
<td>300</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>M</td>
<td>C(20)</td>
<td>MET p.V1001_F1007 del(c.3001_3021delGTA GACTCCAGCTACTTTT) (0.44) Poorly differentiated adenocarcinoma</td>
<td>Cisplatin + pemetrexed + bevacizumab</td>
<td>Crizotinib (3rd line)</td>
<td>PR (-31%)</td>
<td>4.6+</td>
<td>17.9+</td>
<td>TP53 R248P, R81 intragenic deletion, BRCA1 E648Q, MYC E1370, NF1 exon 56 splice variant, NDS1 E1902K, PDGFRB R397W</td>
<td>TERT gain, MET amp, MYC amp, NXX2-I amp</td>
<td>3.8</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>M</td>
<td>F(20)</td>
<td>MET c.3028+1G&gt;T exon 14 splicing variant (0.67) Adenocarcinoma</td>
<td>Cisplatin + pemetrexed</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>15.8+</td>
<td>PK3CA R108L, TET2 I871fs</td>
<td>None</td>
<td>Not amplified</td>
<td>NA</td>
<td>NA</td>
<td></td>
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<tr>
<td>7</td>
<td>90</td>
<td>F</td>
<td>N</td>
<td>MET c.3028G&gt;T exon 14 splicing variant Adenocarcinoma</td>
<td>Pemetrexed, gemcitabine</td>
<td>Crizotinib (3rd line)</td>
<td>PR (-47%)</td>
<td>3.1+</td>
<td>73.3+</td>
<td>None</td>
<td>CDK4 amp, MDM2 amp</td>
<td>Not amplified</td>
<td>300</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>86</td>
<td>M</td>
<td>N</td>
<td>MET c.3017_3028delCTT TCCAGAGGTA exon 14 splicing variant Adenocarcinoma</td>
<td>Pemetrexed, gemcitabine</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>12.0+</td>
<td>None</td>
<td>None</td>
<td>Not amplified</td>
<td>NA</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PFS, progression-free survival; OS, overall survival.
2012. Imaging showed metastases to the right pleura, mediastinal lymph nodes, and bone. Initial genotyping of his lung tumor by a mass spectrometry–based multiplex PCR assay (Sequenom MassARRAY) for common lung cancer oncogene point mutations (15), sizing assays (16) for EGFR and ERBB2 indels, and an ALK fluorescence in situ hybridization test was negative. He received treatment with carboplatin plus pemetrexed plus bevacizumab followed by maintenance pemetrexed plus bevacizumab from January 2013 to February 2014, with a partial response. CT imaging in March 2014 showed disease progression, with a new 3-cm right lung tumor and growth of an existing right lower lobe lung tumor. A biopsy of his new lung tumor was performed to obtain additional material for sequencing, revealing a MET c.3024-3028delAGAAGGTATATT exon 14 splice site mutation. MET IHC showed strong MET expression (H-score = 300). Second-line albumin-bound
pemetrexed was given every other week in the interim, with imaging after two cycles showing disease progression in his lung tumors as well as new liver metastases. The patient began treatment with crizotinib 250 mg orally twice daily in June 2014, provided off-label with insurance approval. Imaging after 4 and 8 weeks of therapy showed a response in his lung tumors, meeting RECIST partial response criteria (−30%; Fig. 2B). Unfortunately, his liver metastases grew despite efficacy in the lung. Because of a history of resected early-stage sarcomas, a biopsy of a liver metastasis was performed to confirm histology. This showed a poorly differentiated adenocarcinoma morphologically similar to his lung primary. The tumor contained the same MET exon 14 splice site mutation and showed strong MET expression (H-score 300). Additional changes were present, however, including CDKN2A deletion (fold change, −2.3) and CDKN2B deletion (fold change, −2.3).

The patient signed written informed consent to participate in a clinical trial of the MET inhibitor cabozantinib (IRB #12-097, NCT01639508) and ceased taking crizotinib as part of the washout period for the study. Unfortunately, before starting the clinical trial, he developed multilobar pneumonia and died despite treatment with broad-spectrum antibiotics.

### Patient 5

Patient 5 is a 65-year-old man and a former smoker who was diagnosed with stage IV lung adenocarcinoma in July 2013 following work-up for an episode of chest pain. Imaging showed widespread metastatic disease in the liver and bones, including the skull, sternum, spine, and bilateral hips. Outside molecular studies showed no evidence of alterations in EGFR and ALK. He was treated with first-line cisplatin plus pemetrexed plus bevacizumab followed by maintenance pemetrexed plus bevacizumab from September 2013 to July 2014, with a partial response. CT imaging in July 2014 showed increase in his lung tumor and a new liver metastasis, prompting a biopsy of his lung tumor for more comprehensive genotyping. This demonstrated adenocarcinoma morphologically similar to his initial biopsy and a MET c.3028+1G>T exon 14 splice site mutation. He was treated with second-line gemcitabine for 2 months, with CT imaging showing further disease progression in keeping with his worsening dyspnea and bone pain. He began crizotinib 250 mg orally twice daily in September 2014, provided off-label with insurance approval. Two weeks after starting treatment, the patient noted substantial improvement in his dyspnea and bone pain. CT imaging 6 weeks after initiation of crizotinib demonstrated a partial response to therapy (−31%; Fig. 2C and D). The patient remains on treatment without side effects.

### Patient 7

Patient 7 is a 90-year-old woman and a never-smoker who was diagnosed with recurrent metastatic lung adenocarcinoma to lymph node and lung in February 2009. She was treated with single-agent pemetrexed from April 2009 until June 2010 and single-agent gemcitabine from July 2010 until January 2014. A CT scan in January 2014 showed evidence of slight progression in multiple lung nodules in the setting of cumulative fatigue from chemotherapy. A treatment holiday was instituted and the patient observed with serial imaging. CT scan from July and September 2014 showed further progression.

On the basis of this, the patient underwent a new biopsy of her lung tumor in September 2014 for sequencing. MSK-IMPACT showed a single somatic mutation, a MET c.3028G>T exon 14 splicing variant, and two copy-number alterations—CDK4 and MDM2 amplification. Treatment with off-label crizotinib at a dose of 250 mg orally twice daily was instituted in November 2014 with subsequent imaging in January 2015 showing a partial response to therapy (−47%; Fig. 2E). The patient remains on treatment without side effects.

### Discussion

These data are, to our knowledge, the first to show that patients with lung adenocarcinomas harboring MET exon 14 splice site mutations can respond to MET-directed targeted therapy. More broadly, they underscore the potential clinical importance of looking beyond the exome for cancer-specific mutations that affect RNA processing and differential exon use. Although MET exon 14 splice site mutations occur with highest frequency in lung adenocarcinomas, they have also been identified in small cell lung cancer (10), glioblastoma multiforme (1%; ref. 17), and squamous cell head and neck cancers (1%; ref. 18). In addition to specific splice site mutations, larger-scale changes in pre-mRNA processing caused by recurrent mutations in U2AF1, which encodes an auxiliary factor that is required for U2 small nuclear ribonucleoprotein identification of 3′ splice sites, have recently been characterized and can lead to significantly different splicing programs involving numerous gene products (19). Mutations in U2AF1 occur with appreciable frequency in leukemias, lung adenocarcinomas (7), pancreatic cancers, and endometrial cancers (18). We believe this report may represent the first clinical validation of a new class of actionable driver events with potential relevance to patients across cancer types. Unlike most splice site mutations that result in loss of the reading frame and protein truncation, these splice site mutations induce MET exon 14 skipping and are activating and targetable.

Although somatic splice site mutations in MET have been previously reported, the absence of broadly applied comprehensive clinical sequencing platforms has limited our ability to routinely detect these mutations. Somatic splice site mutations flanking exon 14 occur in 4% of lung adenocarcinomas, based on recently published TCGA data and our own series (7). This frequency is comparable to that of ALK rearrangements, for which crizotinib is an FDA-approved therapy, and encompasses about 7,000 new patients per year in the United States alone. It is important to note that Ma and colleagues (10) also identified exon 14 splice site mutations in small cell lung cancer tumors, highlighting another thoracic malignancy in which patients may derive benefit from MET inhibitors.

Cabozantinib and crizotinib have low nanomolar specificity for a number of tyrosine kinases. The in vitro kinase inhibition profile for cabozantinib includes VEGFR2 (IC50, 0.035 nmol/L), MET (IC50, 1.3 nmol/L), RET (IC50, 5.2 nmol/L), TIE2 (IC50, 14.3 nmol/L), AXL (IC50, 7 nmol/L), FLT3 (IC50, 11.3 nmol/L), ROS1 (IC50, 10.9 nmol/L), and KIT (IC50, 4.6 nmol/L; refs. 20, 21). The kinase inhibition profile for crizotinib includes MET (IC50, 11 nmol/L), ALK (IC50, 24 nmol/L), and ROS1 (IC50, 2.1 nmol/L; refs. 21, 22). Mutational profiling of the tumors from patients 4 and 7 did not
reveal any other clear-cut somatic alterations that might contribute to the response to crizotinib. In contrast, the tumors from patients 2 and 5 demonstrated both MET exon 14 splice site mutations and MET amplification. Given data showing in vitro responses to the MET inhibitor SU11274 in a MET-amplified NSCLC cell line (11) and responses to crizotinib in lung adenocarcinoma patients whose tumors bear high degrees of MET amplification (9), the co-occurrence of both events may reflect the degree to which patient 2’s and patient 5’s tumors are dependent on MET signaling, and both may have contributed to drug sensitivity. An alternative explanation is that some or all of the responses to crizotinib seen in those patients with high MET-amplified tumors reported by Camidge and colleagues (9) were driven by undiagnosed MET exon 14 alterations. Indeed, lack of stratification for MET exon 14 alterations may also explain the discrepant survival outcomes reported in the phase II and phase III trials of erlotinib with or without onartuzumab in NSCLC patients (8, 23). Finally, it is possible that the tumors are dependent on other receptor tyrosine kinases in ways not captured by DNA sequencing, although this has not been the case for most other validated targets in NSCLC. As a whole, our data, in which 4 of 4 patients had radiographic responses to MET inhibitors and 2 of 4 patients had tumors that did not harbor concomitant MET amplification, suggest that the responses seen in these patients are in fact driven by MET exon 14 skipping events.

As for the significance of the three alterations that differed between the primary lung tumor and liver metastasis from patient 4, two—the NTRK2 and TERT mutations—fall in domains that do not currently have attributed functions. CDKN2A/B deletion leading to loss of the G1–S checkpoint in the liver metastasis could very well have caused primary deletion leading to loss of the G1–S checkpoint in domains that do not currently have attributed functions.

In conclusion, our data support prospective identification of MET exon 14 splice site mutations in patients with lung adenocarcinomas. Patients with these splice site mutations should ideally be treated in the context of a clinical trial of a MET inhibitor. For those patients who do not have access to a clinical trial and for whom standard therapy does not exist, use of off-label crizotinib should be considered.

**METHODS**

Patients at Memorial Sloan Kettering Cancer Center (MSKCC; New York, NY) with stage IV lung adenocarcinomas harboring MET exon 14 splice site mutations (N = 7) or a mutation deleting Y1003 (N = 1) were identified through a clinical assay based on hybrid capture and next-generation sequencing of 341 oncogenes and tumor suppressors termed MSK-IMPACT (24). Prospective testing began in February 2014 with data cutoff for this study in December 2014. A total of 178 lung adenocarcinoma patients were screened (MET exon 14 mutation frequency = 4%). Somatic mutations were called using matched germline DNA. This study was performed in accordance with the Declaration of Helsinki and was approved by the MSKCC IRB/Privacy Board through a Waiver of Authorization for the study of existing data.

MET IHC was performed on archival formalin-fixed, paraffin-embedded tissue using a rabbit monoclonal antibody (Ventana clone SP44) in a Clinical Laboratory Improvement Amendments (CLIA) laboratory. Membranous reactivity for MET was assessed using an H-score according to the following formula: H-score = % cells staining (0%–100%) × intensity (range from 1 to 3), where an H-score of 0 corresponded to no staining and a score of 300 to maximum staining intensity in the entire tumor (Supplementary Fig. S3).

Confirmation of MET exon 14 skipping was performed using the nCounter Analysis System (NanoString Technologies), a fluorescence-based platform for multiplexed digital mRNA profiling without amplification or generation of cDNA (25). A custom code set measuring the expression of 13 cancer-related genes, including MET, 16 different combinations of fusion genes, and eight housekeeping genes was used in our experiment. Detailed sequence information for the MET gene target regions is provided in Supplementary Table S1. There was sufficient archived tumor tissue from 5 of 8 patients for mRNA confirmation of exon 14 skipping. NCI-H596 cells (ATCC HTB-178) were tested as a positive control and 24 MET wild-type patient cases were tested as negative controls. H596 cells were obtained in December 2014, passed for fewer than 6 months, and were not reauthentificated.

Radiographic response to MET inhibition was performed by a single radiologist (M.S. Ginsberg) using RECIST 1.1 and PERCIST criteria.

**Disclosure of Potential Conflicts of Interest**

A. Drilon is a consultant/advisory board member for Exelixis. C.M. Rudin reports receiving a commercial research grant from BioMarin and is a consultant/advisory board member for AbbVie, Aveo, Boehringer-Ingehielm, GlaxoSmithKline, and Merck. No potential conflicts of interest were disclosed by the other authors.

**Authors’ Contributions**

Conception and design: P.K. Paik, A. Drilon, P.-D. Fan, M. Ladanyi
 Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): P.K. Paik, A. Drilon, P.-D. Fan, H. Yu, N. Rekhtman, M.S. Ginsberg, L. Borsu, M. Ladanyi
 Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): P.K. Paik, A. Drilon, P.-D. Fan, H. Yu, N. Schulz, M.F. Berger, M. Ladanyi
 Writing, review, and/or revision of the manuscript: P.K. Paik, A. Drilon, H. Yu, N. Rekhtman, M.S. Ginsberg, L. Borsu, C.M. Rudin, M. Ladanyi
 Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): P.K. Paik, M.F. Berger
 Study supervision: P.K. Paik, A. Drilon, M. Ladanyi

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**REFERENCES**

MET Inhibitors in MET Exon 14 Splice-Variant Lung Cancer


Correction: Response to MET Inhibitors in Patients with Stage IV Lung Adenocarcinomas Harboring MET Mutations Causing Exon 14 Skipping

In this article (Cancer Discovery 2015;5:842–9), which was published in the August 2015 issue of Cancer Discovery (1), a mutation is cited erroneously in the Results section under the “Patient 5” subheading. Specifically, the authors incorrectly refer to a MET c.3028+1G>T exon 14 splice site mutation rather than the correct MET p.V1001_F1007del mutation. The affected sentence should instead read, “This demonstrated adenocarcinoma morphologically similar to his initial biopsy and a MET p.V1001_F1007del mutation.” The online version of the article has been corrected and therefore no longer matches the print version. The authors regret this error.

REFERENCE

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