Novel MET Exon 14 Skipping Treatment-Naïve Lung Adenocarcinoma Presented Primary Resistance to Crizotinib

To the editor:

Lung cancer remains the leading cause of cancer-related death worldwide.[1] Remarkable treatment advances have been made with improvements in molecular testing for patients with NSCLC whose tumors harbor targetable somatic mutations. MNNG HOS Transforming gene (MET) exon 14 has been described around all the point and deletion mutations with other known oncogenic mutations in NSCLC suggesting its role as a targetable phenotype.[2] Almost all of the MET exon 14 mutations described to date cause skipping of MET exon 14 during pre-mRNA splicing, generating an in-frame, 47–amino acid deletion of the MET juxta-membrane domain with loss of the Y1003 c-Cbl binding site.[3] Several studies have proven that all of the MET exon 14 mutations are rare but particularly important forms of NSCLC with available effective therapies including crizotinib.[4] However, here we report a pulmonary adenocarcinoma patient harboring a novel MET exon 14 "deleting and inserting" mutation (c.3019_3028+29delinsACCTA, p.Phe1007fs) which also leads to MET exon 14 skipping; however, it has presented primary resistance to crizotinib.

A 63-year-old non-smoking male who came to the hospital had been coughing and had a headache for 1 month. A computed tomographic (CT) scan of his lung showed a primary tumor located at the lower lobe of the right lung with lymph node metastases in the right hilar and mediastinum (Fig. 1*B*, primary lesions and lung metastases). A CT of the brain showed multiple metastases with a huge edematous zone located in the parietal and frontal lobes (Fig. 1*B*, brain metastases I and II). The patient was initiated with whole brain radiotherapy (40 Gy/F). Tissue biopsy using endobronchial ultrasonography guided transbronchial needle aspiration was performed on primary lesions for lung adenocarcinoma. A novel phenotype named MET exon 14 c.3019_3028+29delinsACCTA(p.Phe1007fs) was detected with next-generation sequencing (NGS) (Fig. 1*B*, upper row) using a large panel including 108 lung cancer–related somatic gene mutations (Supplementary Material; Fig. 1*A*). The patient then received treatment with crizotinib 250 mg orally twice for 1 day. After 8 weeks, the patient was found to have increasing supraclavicular lymph node involvement and increasing of brain metastases by CT. Cytology of magnanimous pleural effusion was still lung adenocarcinoma. He was diagnosed with progressive disease. Tissue sample of supraclavicular lymph node and cytology of pleural effusion were also obtained to perform the NGS (Fig. 1*B*, lower row). Genotype of tissue and cytology were still MET exon 14 c.3019_3028+29delinsACCTA (p.Phe1007fs). However, comparing with the baseline, the tumor mutation burden of novel MET exon 14 skipping for post-crizotinib was increased (Fig. 1*C*). There was no other gene mutation (Fig. 1*B*, lower row). The structures of wild-type and novel MET exon 14 skipping were analyzed by SWISSMODEL and are shown in Figures 1*D* and 1*E*, respectively. After frameshift of c.3019_3028+29delinsACCTA (p.Phe1007fs), the core binding site of crizotinib was destroyed. The patient's medications were changed to a combination of cisplatin and pemetrexed. Follow-up data showed he died from brain progression 2 months later.

Although MET exon 14 mutations have been recognized for a long time and occurred at a frequency of approximately 3% in NSCLC,[5] screening for MET genomic alterations has not become standard in clinical practice. Unlike other MET exon 14 splicing alterations, 39 bases are deleted and 5 bases were inserted constantly for this novel skipping. This kind of skipping mutation cannot be detected by other common methods such as reverse transcriptase polymerase chain reaction (RT-PCR) and immunohistochemistry. So, improved sequencing techniques coupled with a heightened appreciation of the clinical significance of MET exon 14 skipping should enable and encourage more widespread testing for these mutations. Multiple reports have shown that lung cancers harboring MET exon 14 mutations can respond dramatically to small-molecule MET inhibitors such as crizotinib and cabozantinib.[4] However, there is no conforming data to show any MET exon skipping's primary resistance to MET inhibitors. We believe this report may be the first to present the clinical validation of a novel actionable driver mutation

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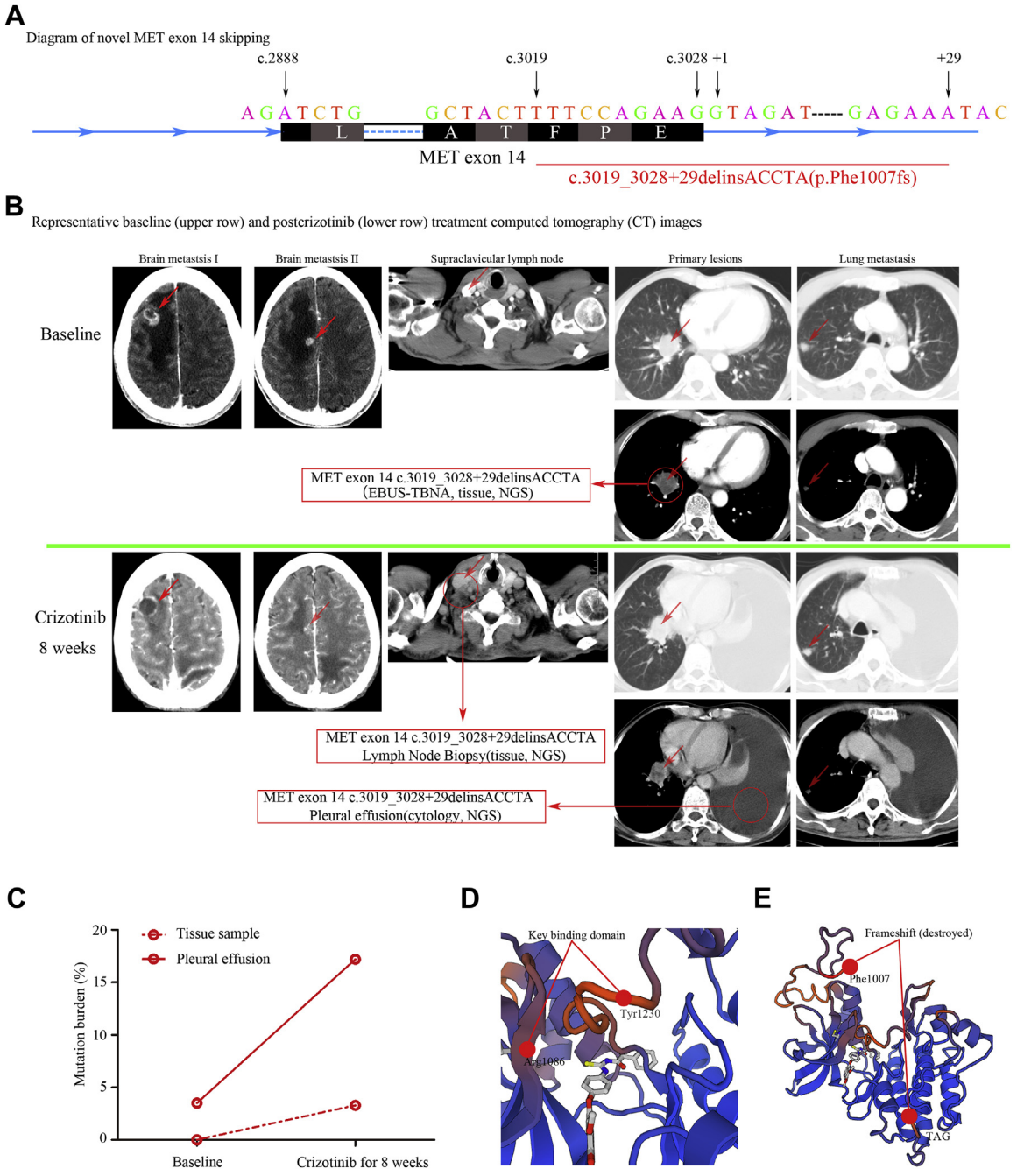

Figure 1. A novel MET exon 14 skipping presented resistance to Crizotinib. (*A*) Diagram of novel MET exon 14 alterations in relation to the 5' and 3' splice sites. The novel genotype is c.3019_3028+29delinsACCTA (p.Phe1007fs) which indicates in *red color* and *red line*. All the bases and positions are drafted in the *upper line*. The bases from c.3019 to c.3028 additional 29 base of intron 15 are deleted and amino acid sequences are frameshift with Phe1007fs. (*B*) Representative baseline (*upper row*) and post-Crizotinib (*lower row*) treatment CT images for a 64 year-old patient. The first and second columns show the brain metastasis I and II. The third column shows the undetectable supraclavicular lymph node (*upper row*) and new occurring supraclavicular lymph node (*lower row*). The fourth and last columns show the primary lesions and the lung metastasis. *Small red arrows* show the evaluable metastasis. *Red circles* and *large red arrows* indicate the location of biopsy (mass of pulmonary hilar, supraclavicular lymph node and cytology of pleural effusion). *Red frames* show the results of diver gene mutation detection including 108 genes associated lung cancer by NGS. (*C*) The tumor mutation burden of primary lesions and pleural effusion for novel MET exon 14 skipping in baseline and post-Crizotinib for 8 weeks, respectively. (*D,E*) The 3-dimensional model structure of MET wild-type and novel MET exon 14 skipping mutation analyzed by SWISSMODEL (https://swissmodel.expasy.org/). (*D*) The key binding domain of crizotinib was between Arg1086 to Try1230. (*E*) The entire amino acid from Ph1007 to the end are almost destroyed after new mutation occurring. The core binding sites of Crizotinib is lost. CT, computed tomography; NGS, next-generation sequencing; EBUS-TBNA, endobronchial ultrasonographic transbronchial needle aspiration.

showing primary resistance to crizotinib. Prospective basic and clinical studies are needed to develop novel MET inhibitors to evaluate accurate MET exon 14 splicing alterations for appropriate patients with NSCLC. Therefore, MET detection should be enrolled in the testing panel, and more targetable MET inhibitors should be monitored to provide precision management strategies for NSCLC.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2018.02.030.

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Spontaneous Transformation from *EGFR* and *ALK* Wild-Type Lung Adenocarcinoma to Neuroendocrine Carcinoma

To the Editor:

A 74-year-old man with a 50-pack-year smoking history was referred for abnormal lung nodules. He had an operation and postoperative interferon treatment for right renal clear cell cancer 9 years previously and annual computed tomography follow-up. The most recent computed tomography scan revealed two nodules in the upper lobe of the left lung. The left upper lobe was resected. One nodule was acinar adenocarcinoma with tumor cells diffusely positive for thyroid transcription factor 1, p53, and napsin and focally positive for synaptophysin and CD56 (Fig. 1A). The other nodule was a lymph node metastasis, as residual lymph node structure was present in the periphery. The lymph node metastasis was a combined small cell carcinoma and large cell neuroendocrine carcinoma, and it was diffusely positive for thyroid transcription factor 1, p53, and CD56 and focally positive for synaptophysin (Fig. 1B). No neuroendocrine morphologic features were observed in the primary tumor and no adenocarcinoma component was seen in the metastatic lymph node. The pathological stage was determined as pT1bN1M0, stage IIB. Polymerase chain reaction for *EGFR* mutation and immunohistochemistry for ALK receptor tyrosine kinase were both negative. We performed targeted next-generation sequencing to confirm the pathological results. After informed consent had been obtained, genomic DNA was extracted from each formalin-fixed, paraffin-embedded tumor tissue and from peripheral blood lymphocytes and subjected to the enrichment of target fragments with the use of a SureSelectXT Custom kit (Agilent Technologies, Santa Clara, CA). Custom-made probes for our Todai OncoPanel were designed to hybridize and capture the exons of 467 cancer-related genes. Massively parallel sequencing of the isolated fragments was performed with the NextSeq 500 platform (Illumina, San Diego, CA). We detected somatic single-nucleotide mutations, insertions/deletions, and copy number variations by comparison of tumor and normal reads.

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