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Tepotinib Efficacy in a Patient with Non-Small Cell Lung Cancer with Brain Metastasis Harboring an *HLA-DRB1-MET* Gene Fusion

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Abstract

Alterations in c-MET, a tyrosine kinase receptor encoded by the *MET* gene, have been reported in approximately 3% of non-small cell lung cancer (NSCLC) cases and carry important treatment implications. The best studied genetic alterations are exon 14 skipping and gene amplification; however, gene rearrangement has also been described, and multiple fusion partners have been reported. Recently, in *MET*ex14-mutated NSCLC, multitarget tyrosine kinase inhibitors (TKIs), such as crizotinib and cabozantinib, as well as MET-selective TKIs, such as tepotinib and capmatinib, have demonstrated durable responses. In this study, we present the case of a 41-year-old woman with advanced NSCLC harboring an *HLA-DRB1-MET* gene fusion. The patient was offered successively two different MET multikinase inhibitors, crizotinib and cabozantinib, and the selective inhibitor tepotinib. Each time, including under tepotinib, the patient experienced rapid and complete responses associated with a tremendous improvement in her physical function. ***The Oncologist*** 2020;25:916–920

Key Points

- To our knowledge, this is the first report of a patient with non-small cell lung cancer harboring an *HLA-DRB1-MET* gene fusion demonstrating a clinical response to multiple MET inhibitors, including tepotinib.
- This finding illustrates the efficacy and rationale to targeting MET regardless of fusion partner and gives insight to pooling of patients with different MET fusion products in trials assessing safety and efficacy of novel molecules.

Patient Story

The patient is a 43-year-old woman (never-smoker) with no significant medical history except that one of her children has retinoblastoma (negative for germline *RB1* mutations). She was diagnosed in September 2016 with locally advanced lung adenocarcinoma (stage IIIA: T2 N2 M0; Fig. 1A). The tumor was negative for programmed death ligand 1 expression (0%), *EGFR* mutations, and *ALK* and *ROS1* gene rearrangements. The patient was treated with concomitant chemotherapy (cisplatin and vinblastine) and radiotherapy between December 2016 and January 2017 and achieved partial radiologic response. However, during the radiotherapy, she developed severe postradiation dermatitis and grade 3 pneumonitis.

As the patient was young and a nonsmoker, a large-scale genetic sequencing panel was used to explore other rare genetic drivers, which included an anchored multiplex polymerase chain reaction–based targeted fusion assay using next-generation sequencing [1].

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The fusion assay revealed an in-frame transcript involving *HLA-DRB1* exon 4 (ENST00000360004) and *MET*

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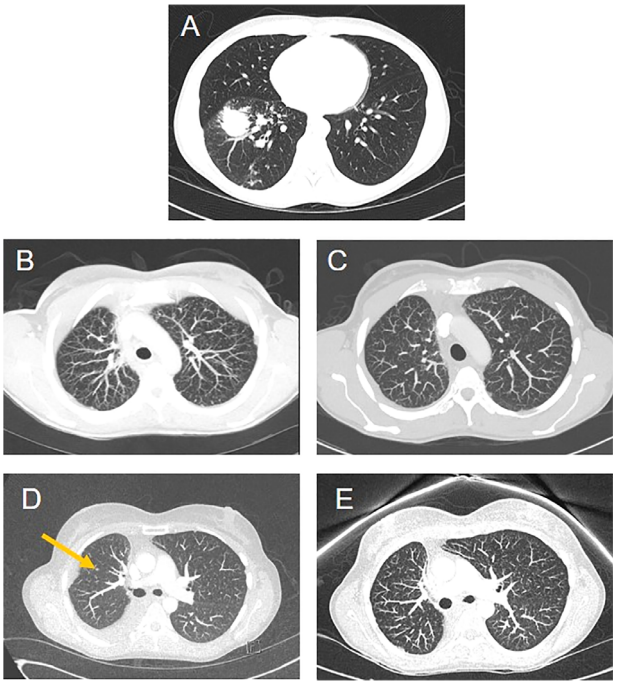

Figure 1. Thoracic computed tomography scans. **(A):** December 2016: diagnosis of locally advanced (stage IIIA) NSCLC. **(B):** September 2017: multiple millimeter-sized lung metastases. **(C):** November 2017: complete resolution of the lung lesions. **(D):** May 2019: new secondary lesion in right lung (yellow arrow). **(E):** August 2019: complete disappearance of the lung metastases.

exon 15 (ENST00000318493; Fig. 2A). *MET* rearrangement was confirmed by a *MET* break-apart fluorescence in situ hybridization assay ([2]B). The *HLA-DRB1-MET* gene fusion, which retains the immunoglobulin-like domain of HLA-DRB1 and the kinase domain of MET (Fig. 2C), is presumed to lead to oncogenic activation of MET. The *HLA-DRB1-MET* fusion gene that we identified in our patient has been reported only once before in a case of a 74-year-old woman who developed recurrent metastatic non-small cell lung cancer (NSCLC) [2]. This patient was treated with crizotinib and experienced a rapid and complete response, and her disease had remained stable for 8 months at the time of publication. In contrast, although our patient initially responded well to crizotinib, her disease progressed to symptomatic cerebral metastases within 6 months of initiating treatment. The presence of this fusion in our patient's tumor suggested that it may be sensitive to treatment with MET inhibitors.

Although still considered an emerging biomarker in NSCLC, alterations in *MET* are becoming established not only as important oncogenic drivers but as acquired resistance mechanisms to EGFR-targeted tyrosine kinase inhibitors (TKIs) in patients with *EGFR* mutations [3]. The best studied genetic alterations in *MET* in NSCLC are exon 14 skipping (*MET*ex14; 3%–4% of cases) and gene amplification (1%–5% of cases) [4]. Compared with gene amplification and *MET*ex14 mutations, reports of *MET* fusions are relatively rare [5]. Lack of expression of exon 14 leads to absence of the juxtamembrane region, which contains multiple sites for negative regulation [3]. Multiple *MET* fusion partners have been identified in NSCLC, including *KIF5B* [6, 7], *STARD3NL* [7], *HLA-DRB1* [2], *UBE2H* [8], and *ATXN7L1* [9]. It is thought that *MET* fusions that include the 3' *MET* kinase domain by fusing at exon 15 (e.g., fusions with 5' partners *KIF5B*, *STARD3NL*, *HLA-DRB1*) may become activated because of constitutive dimerization of MET [10]. It has also been suggested that *MET* kinase domain fusions may recapitulate the mechanism of *MET*ex14 mutants owing to loss of negative regulation in the juxtamembrane region [8].

Recently, case studies and early-phase trials in *MET*ex14-mutated NSCLC have demonstrated durable responses to multitarget TKIs, such as crizotinib and cabozantinib [11–13], as well as MET-selective TKIs, such as tepotinib and capmatinib [14–16]. MET TKIs may also improve overall survival in patients with *MET*ex14 mutations [17]. Although several therapies targeting MET are under development for selected cancers, only cabozantinib and crizotinib are approved in the U.S., Europe, and Canada.

The choice of MET kinase inhibitor may be important to consider when treating NSCLC with central nervous system (CNS) metastasis, given that these inhibitors vary in their ability to cross the blood-brain barrier. Despite producing objective responses in the primary tumor, crizotinib has limited activity in treating brain metastases as a result of poor CNS penetration [18]. In contrast, cabozantinib led to rapid intracranial responses in a case report of *MET*ex14-mutated NSCLC resistant to crizotinib [13]. Capmatinib also had activity in patients with brain metastases in a phase II trial in previously treated NSCLC with *MET*ex14 mutations [16, 19].

Patient Update

Seven months after completing first-line treatment with combination radiochemotherapy (August 2017), follow-up scans revealed that the patient had progressive disease. This was evidenced by an increase in the size of the primary tumor and the appearance of multiple subcentimetric bilateral lung and brain metastases (Figs. 1B, 3A), as well as centimetric lesions in the bone (2 lesions) and liver (1 lesion). The patient was started on crizotinib 250 mg twice daily in October 2017 and had an excellent clinical response after only a few weeks of treatment. Radiologic scans from November 2017 revealed complete resolution of the lung and brain lesions (Figs. 1C, 3B). Tolerance to crizotinib was excellent without any major adverse events, allowing the patient to return to work part time as a teacher.

The patient's disease recurred in May 2018, when she presented with symptomatic cerebral metastases (ataxia, dysphagia, fatigue, global psychomotor retardation, Eastern Cooperative Oncology Group [ECOG] performance status [PS] of 3; Fig. 3C), new infracentimetric lung lesions in the right parenchyma (8 mm and 6 mm), with right pleural effusion. At that time, the liver metastasis remained stable. The patient stopped work. Attempts to biopsy the lung lesions or obtain pleural fluid from the effusion failed to produce sufficient material to perform analyses to identify mechanisms of resistance and were further complicated by the presence of a grade 2 pneumothorax. There was no liquid biopsy performed either. The patient received whole brain radiation therapy (WBRT; 20 Gy in 5 fractions) with oral dexamethasone (4 mg four times daily) in June 2018. She experienced partial clinical improvement with respect to ataxia and

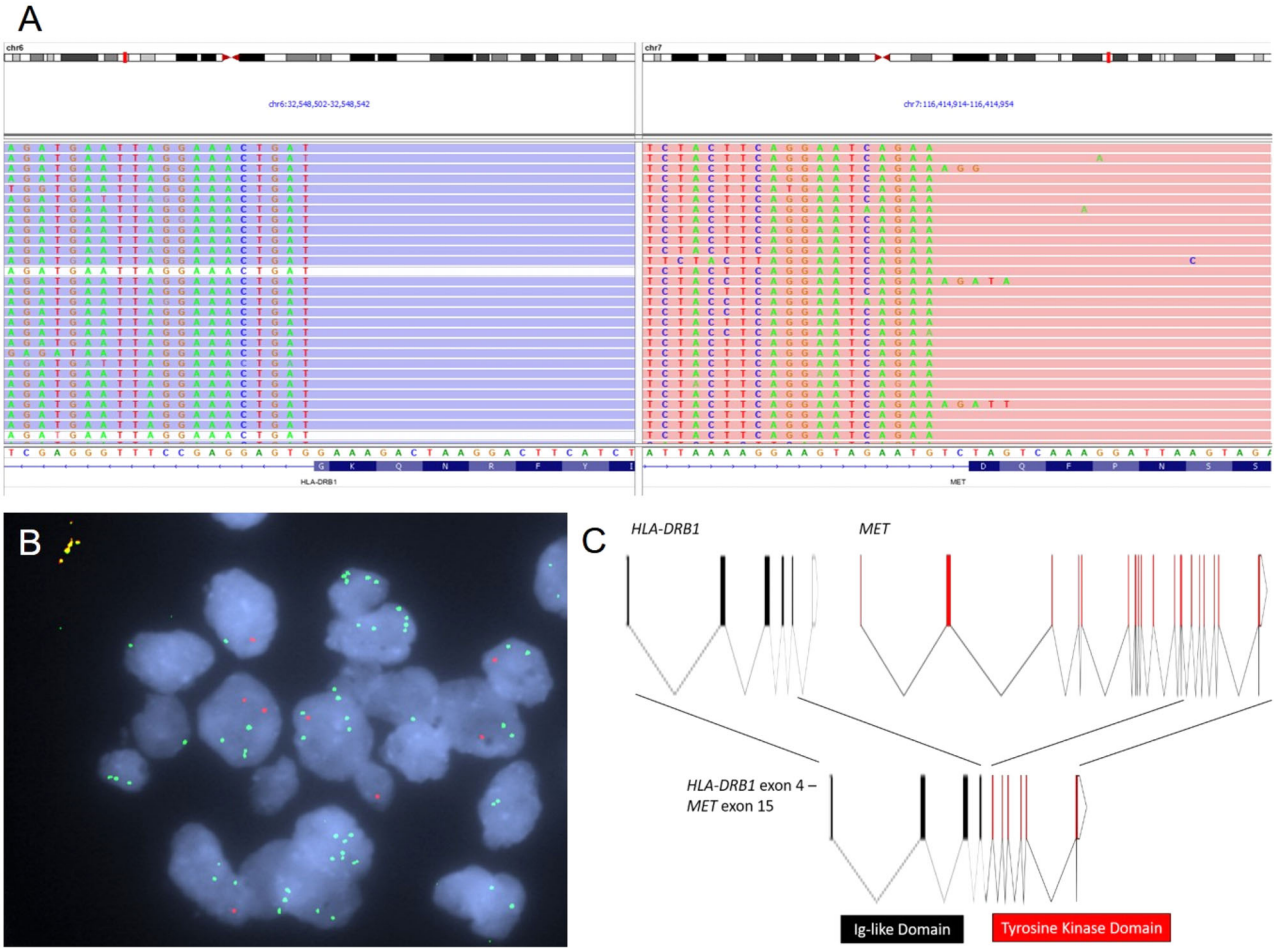

Figure 2. Molecular analysis of the tumor. **(A):** Screenshot of the Integrative Genomics Viewer from the next-generation sequencing fusion assay showing abundant supporting RNA reads with sequences starting from *HLA-DRB1* exon 4 and continuing to *MET* exon 15, indicating the presence of the *HLA-DRB1-MET* gene fusion. **(B):** Break-apart fluorescence in situ hybridization assay showing the separation of *MET* 5' green probes from 3' red probes, confirming *MET* translocation. **(C):** Schematic of intron-exon structures of the *HLA-DRB1* and *MET* genes and the *HLA-DRB1-MET* gene fusion.
Abbreviation: Ig, immunoglobulin.

dysphagia but still had neurological symptoms and required daily assistance for activities of daily living. She was then initiated on a second MET inhibitor, tepotinib, 500 mg once daily in July 2018 for 1 month (Special Access Program approval; supply from EMD Serono, a company of Merck KGaA). The dosage was then increased to 1,000 mg daily in August 2018. After 2 months on tepotinib, she showed significant improvement in her general and neurological status, and imaging showed a complete response in the brain (Fig. 3D), lung, and liver, without any adverse events. The patient was able to return to work part time.

The patient remained progression free for 9 months while on tepotinib until May 2019, when she developed new lung micronodules with pleural effusion (Fig. 1D) and a new liver lesion. There were no clinical or radiological signs of worsening cerebral involvement. She started treatment with cabozantinib 60 mg daily as third-line treatment in June 2019. The first radiological evaluation in August 2019 demonstrated complete resolution of the pleural effusion and the micronodules (Fig. 1E), whereas the liver lesion remained stable. Brain imaging was also free of recurrence. Cabozantinib was well tolerated, with the main adverse event being grade 1 xerostomia. At last follow-up in November 2019, the patient was asymptomatic, in good physical condition (ECOG PS of 1), and still on cabozantinib. The timeline of the patient's disease course and interventions is illustrated in Figure 4.

To our knowledge, this is the first report of tepotinib efficacy in a patient with NSCLC harboring an *HLA-DRB1-MET* gene fusion. This patient had an almost complete remission while on tepotinib, including in the brain, with a sustainable response of almost 9 months, although response in the brain is difficult to assess considering the sequential administration following WBRT. Tepotinib was very well tolerated by the patient even at 1,000 mg daily, and she did not have any related adverse events. Doses of up to 1,400 mg daily were previously shown to be well tolerated in phase I studies [20]. This efficacy is in line with interim data from the ongoing phase II VISION trial in patients with NSCLC with *MET*ex14 mutations, in which tepotinib 500 mg daily was shown to have durable clinical activity and a favorable safety profile, and patients with brain metastases at baseline benefitted equally from treatment [15]. The patient experienced a

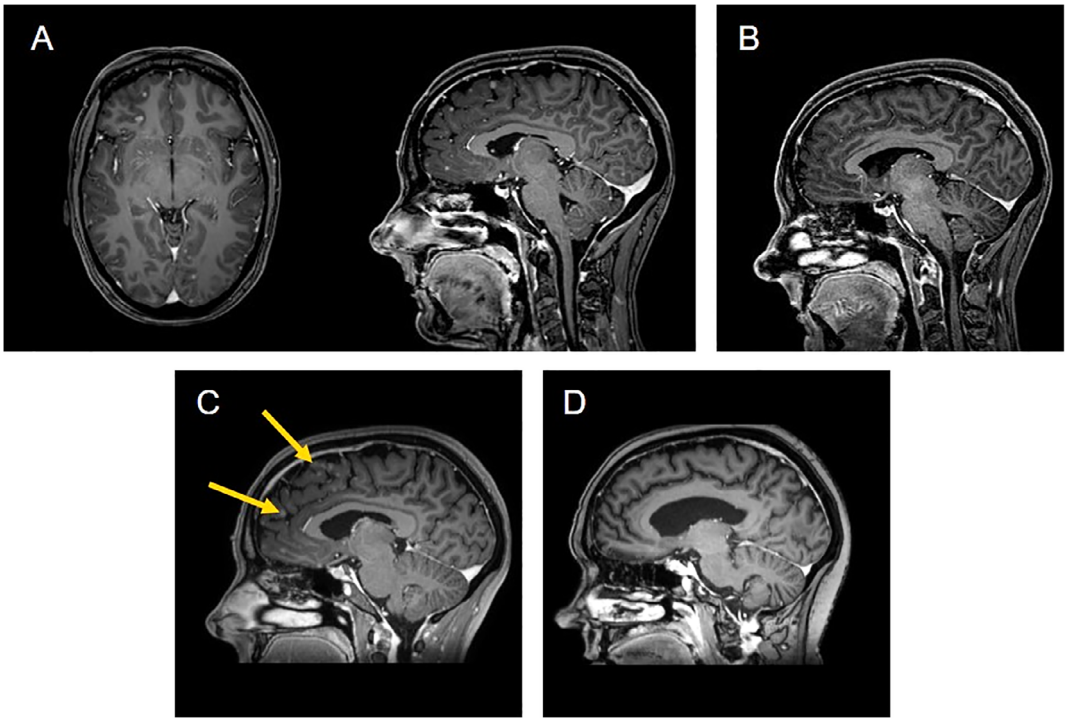

Figure 3. Brain magnetic resonance imaging scans. **(A):** August 2017: multiple disseminated brain metastases. **(B):** November 2017: complete resolution of the brain metastases. **(C):** May 2018: new secondary brain lesions (yellow arrow). **(D):** September 2018: complete resolution of the brain metastases.

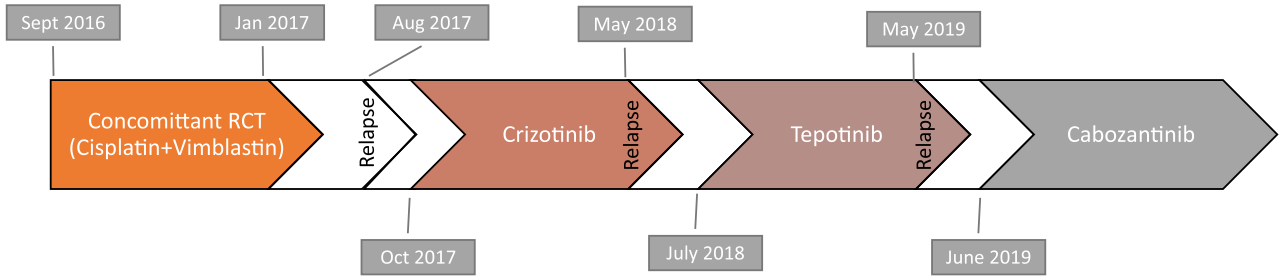

Figure 4. Timeline of the successive treatments. Note that the patient received whole brain radiation therapy with dexamethasone following relapse in May 2018 and prior to initiation of tepotinib in July 2018. The patient had not progressed on cabozantinib as of November 2019.
Abbreviation: RCT, radiochemotherapy.

tremendous improvement in her physical function and quality of life and even expressed the desire to return to work.

Glossary of Genomic Terms and Nomenclature

ALK: anaplastic lymphoma kinase
ATXN7L1: Ataxin 7 Like 1
EGFR: epidermal growth factor receptor
HLA-DRB1: major histocompatibility complex, class II, DR beta 1
KIF5B: Kinesin Family Member 5B
MET: mesenchymal-epithelial transition factor
ROS1: ROS proto-oncogene
STARD3NL: STARD3 N-Terminal Like
UBE2H: Ubiquitin Conjugating Enzyme E2H

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Disclosures

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