Vabametkib Treatment in Refractory Glioblastoma: A Case Report

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ACCOMPANYING CONTENT

Protocol

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Introduction

Glioblastoma (GBM) is the most aggressive among the various forms of diffuse gliomas. The prognosis of patients with this disease remains poor despite implementation of multimodal treatment, highlighting the need for more effective therapies.[1]

MET, a receptor tyrosine kinase, plays a crucial role in tumor biology,[2] with studies indicating its significance in enhancing glioma cell proliferation and invasion.[3-5] *MET* alterations, including amplification, fusion genes, and exon 14 skipping mutations, have been identified in GBM.[6,7] The poor prognostic impact of *MET* alterations suggests potentials for targeted therapies.[8,9] However, trials with nonselective *MET* inhibitors have yielded unsatisfactory results.[10]

Vabametkib (ABN401) is a potent selective c-MET inhibitor that has shown promising antitumor effects in advanced solid cancers.[11-13] Herein, we present a case of a patient with progressive GBM, isocitrate dehydrogenase (IDH)-wildtype, WHO grade 4 who benefited from vabametkib treatment.

Case Report

A 25-year-old Asian female patient was diagnosed with brain tumor infiltrating the corpus callosum and cerebellum in July 2023. Her initial symptoms, including headache and confusion, indicated increased intracranial pressure. She underwent external ventricular drainage followed by near-total tumor resection surgery. The pathology confirmed GBM, IDH-wildtype, WHO grade 4, and negative for O^6-methylguanine DNA methyltransferase promoter methylation. She received radiotherapy with concurrent temozolomide chemotherapy postoperatively. However, before the start of adjuvant chemotherapy, she showed disease progression 4 weeks after completion of concurrent chemoradiation treatment. A second surgery was performed, but neurological symptoms (cognitive impairment and motor weakness) persisted. The surgical specimen was analyzed using a next-generation sequencing panel, whereupon *MET* exon 14 deletion, amplification, and *CTTNBP2-MET* fusion were identified. On the basis of these findings, oral vabametkib at a once-daily dose of 800 mg was administered from January 2024, under the Early Access Program. The dosage was determined based on the phase II dose from a phase I dose-escalation study (ClinicalTrials.gov identifier: NCT04052971). After 16 days of treatment, follow-up magnetic resonance imaging (MRI) revealed a partial response as defined by the Response Assessment in Neuro-Oncology criteria (Fig 1). Her clinical symptoms improved, with no notable toxicity from the drug. The patient continued treatment until March 2024, when follow-up MRI showed tumor growth. At the time of treatment cessation, her Karnofsky Performance Scale score of 20 at diagnosis had increased to 40. She passed away in May 2024 (progression-free survival, 2.4 months; overall survival [OS], 9.4 months).

Postmortem whole-genome sequencing (WGS), immunohistochemical (IHC), fluorescence in situ hybridization (FISH), and droplet digital polymerase chain reaction (ddPCR) analyses were performed to gain a comprehensive genomic landscape of the case. The WGS, IHC, and

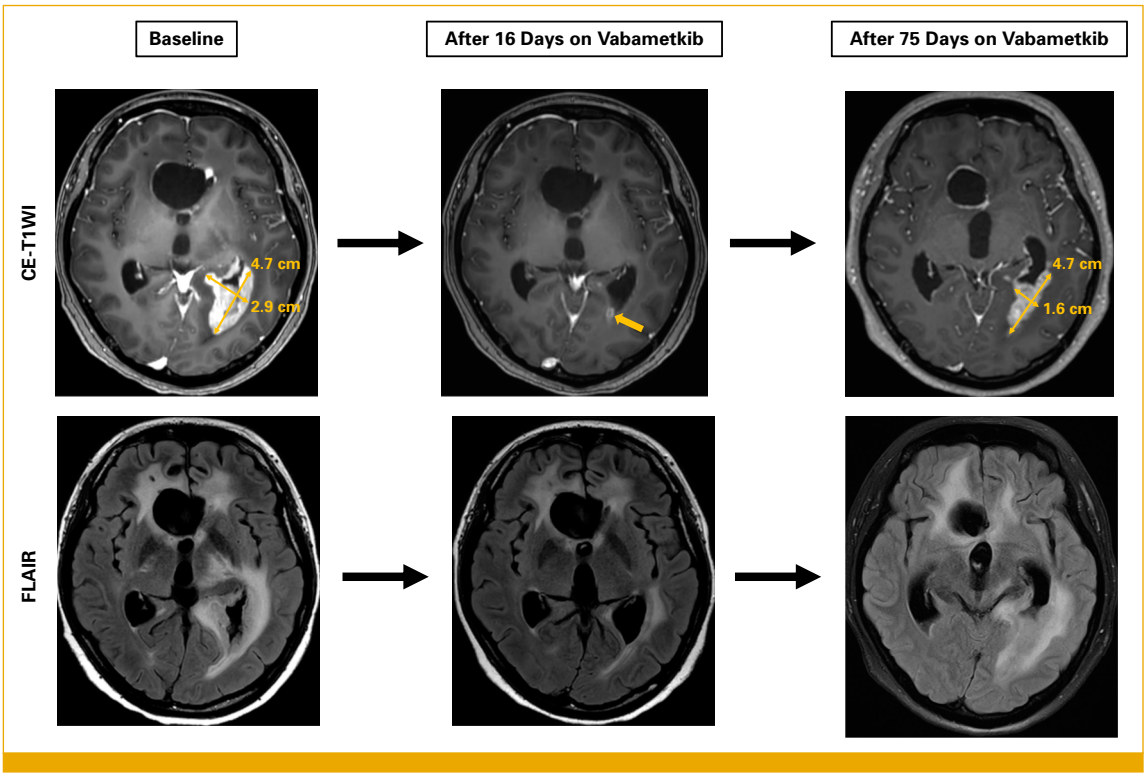

FIG 1. Tumor response according to RANO criteria. The MRIs show a partial response (as defined by RANO criteria) 16 days after vabametkib treatment and disease progression after 75 days. FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; RANO, response assessment in neuro-oncology.

FISH results reaffirmed a *CTTNBP2-MET* fusion leading to *MET* overexpression and excluded variants in *NF1*, *RAD51D*, *BRCA1*, *PDGFRA*, *NBN*, and *TP53* (Fig 2). The ddPCR confirmed the *MET* exon 14 skipping. The vabametkib treatment and genetic testing were approved by the institutional review board (IRB no.: 2023-1618), and biological samples were handled according to the Bioethics and Safety Act. Informed consent form was obtained from the patient by the investigators. The early access program is approved via a separate form instead of a protocol. Accordingly, the relevant documents required under local IRB regulations were submitted. Informed consent to publish information and images from the participant was also obtained by the investigators.

Discussion

To our knowledge, this first in-human experience and available evidence from in vivo studies suggest that *MET* alterations may be a potential therapeutic target in GBM. In this patient with progressive GBM, vabametkib treatment led to substantial tumor reduction within the corpus callosum, an area associated with a particularly grave prognosis. The median OS for patients with GBM with bilateral corpus callosum involvement is approximately 7 months.[14] The OS of our patient was 9.4 months, without observed drug toxicity, implying that the early introduction of vabametkib may improve survival in patients with GBM with *MET* alterations.

Recent single-cell transcriptomic analyses have revealed that GBM exhibits extensive intratumoral heterogeneity, characterized not only by the coexistence of distinct cellular states—such as neural progenitor-like, oligodendrocyte progenitor-like, astrocyte-like, and mesenchymal-like—but also by dynamic plasticity that allows transitions between these states.[15] This plasticity enables tumor cells to adapt under therapeutic pressure, contributing to disease progression despite initial clinical and radiographic responses. Moreover, genomic heterogeneity driven by extrachromosomal DNA carrying oncogene amplifications like *MET* further facilitates rapid clonal evolution and resistance.[16] Additional studies are warranted to elucidate the relationship between the dynamic cellular landscape of GBM and the therapeutic response to vabametkib, with the goal of achieving sustained clinical benefit.

This case highlights the importance of early genetic screening to identify candidates for precision medicine, which could transform the management of GBM by enabling the timely detection of actionable genomic signatures and introducing targeted therapies to significantly improve survival outcomes.

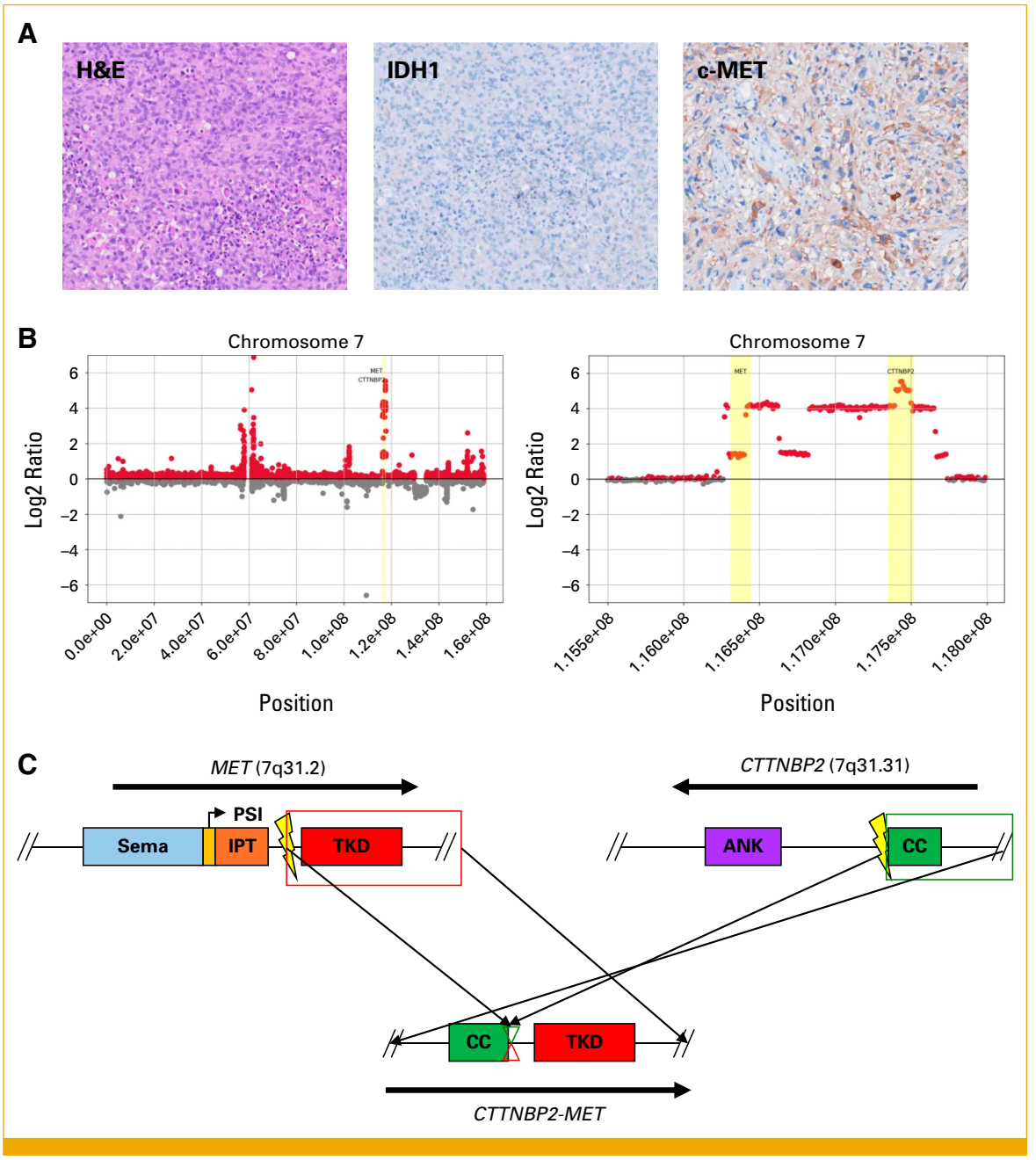

FIG 2. Molecular and histopathologic analysis of the patient with GBM. (A) Representative H&E staining and IHC analysis of IDH1 and c-MET staining in GBM patient tissue. (B) Somatic CN alterations in the patient with GBM. The left plot displays alterations on chromosome seven and right plot displays CN gains of between *MET* and *CTTNBP2*. (C) Schematic diagram of the *CTTNBP2-MET* gene fusion. CN, copy number; GBM, glioblastoma; H&E, hematoxylin and eosin; IDH, isocitrate dehydrogenase; IHC, immunohistochemical.

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DATA SHARING STATEMENT

All data generated or analyzed during this study are included in the article.

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Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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No other potential conflicts of interest were reported.

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