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Original Article

Prolonged complete response to adjuvant tepotinib in a patient with newly diagnosed disseminated glioblastoma harboring mesenchymal-epithelial transition fusion

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Abstract

The prognosis of patients with glioblastoma (GBM) remains poor despite current treatments. Targeted therapy in GBM has been the subject of intense investigation but has not been successful in clinical trials. The reasons for the failure of targeted therapy in GBM are multifold and include a lack of patient selection in trials, the failure to identify driver mutations, and poor blood-brain barrier penetration of investigational drugs. Here, we describe a case of a durable complete response in a newly diagnosed patient with GBM with leptomeningeal dissemination and *PTPRZ1-MET* fusion who was treated with tepotinib, a brain-penetrant MET inhibitor. This case of successful targeted therapy in a patient with GBM demonstrates that early molecular testing, identification of driver molecular alterations, and treatment with brain-penetrant small molecule inhibitors have the potential to change the outcome in select patients with GBM.

Key words: glioblastoma; targeted therapy; tepotinib; molecular alteration; outcomes.

Implications for practice

The authors report a unique case of a complete and prolonged response to tepotinib, brain penetrant MET inhibitor, in a patient with glioblastoma with MET amplification. Upon the addition of tepotinib, the response was immediate and persisted for 35 months, furthering the potential of this monotherapy's ability to change the outcome in select glioblastoma patients.

Introduction

Mesenchymal-epithelial transition (*MET*) oncogene encodes for hepatocyte growth factor, a receptor-tyrosine kinase, and regulates cell development and growth. Pathologic fusion, copy number amplification, and point mutations of *MET* are well-characterized oncologic drivers in many solid tumor types.[1] The incidence of *MET* alterations in glioblastoma (GBM) is between 2% and 5%, and *MET* activation is associated with a poorer prognosis in gliomas, specifically with shorter progression-free survival, overall survival, and higher WHO grade.[2-4]

In many cancers, including glioblastoma, reconstruction of genes through fusion can lead to the amplification of oncogenes.[5] Fusion of protein tyrosine phosphatase receptor type zeta 1 (*PTPRZ1*) and *MET*, which was first described in 2014,[6] results from translocation events between the introns of *PTPRZ*, which is normally highly expressed in central nervous system tissue, and the *MET* proto-oncogene.[7] *PTPRZ1-MET* fusion leads to ligand-independent activation of the MET kinase, enabled by the coiled-coil structural protein modification.[8] *PTPRZ1-MET* fusion induces increased expression and phosphorylation of the MET oncoprotein, leading to higher expression of MET-PIK3CA-AKT1 regulators, STAT3 pathway.[7,9] Preclinical evidence suggests that aberrant *MET* fusion is a driver for MET activation, leading to tumor cells with hepatocyte growth factor independent self-activation.[10,11] *PTPRZ1-MET* fusion was reported in 15% of high-grade astrocytomas arising from lower-grade

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tumors in one study and was associated with significantly worse survival (median OS in patients with fusion was 127 days vs 248 days in those without).[6] Preclinical evidence also demonstrate sensitivity to MET-tyrosine kinase inhibitors (TKI) in tumors with MET fusions, suggesting that *PTPRZ1-MET* fusion is a potential target in the treatment of gliomas harboring this alteration.[6,10,11]

The first-generation *MET* inhibitor, cabozantinib, has had limited efficacy in recurrent GBM.[12,13] This is possibly due to poor blood-brain barrier penetration, lack of kinase selectivity, and importantly lack of patient selection with confirmed MET alterations prior to treatment.[12-15] More recently, the phase Ib GEINO 1402 trial looking at crizotinib in addition to standard radiation and temozolomide, followed by maintenance crizotinib showed that the regimen was safely tolerated and warrants further investigation.[15] Tepotinib hydrochloride hydrate, an oral MET tyrosine kinase inhibitor, selectively binds to *MET* and inhibits its phosphorylation. In 2021, the FDA granted accelerated approval of tepotinib for the treatment of metastatic non-small cell lung cancer harboring *MET* exon 14-skipping alterations on the basis of improved overall response rates in a non-randomized, open-label study.[16] There are several ongoing studies to determine the efficacy of tepotinib in advanced solid tumors, including gliomas.[17] However, its use in GBM has not been established.

Here, we describe a case in which adjuvant tepotinib monotherapy was effective in disseminated GBM, *IDH* wild type with *PTPRZ1-MET* fusion, resulting in a complete and durable response for 35 months. The success of tepotinib monotherapy makes it a valuable alternative treatment to traditional alkylating therapy in patients with GBM with *MET* alterations.

Case Study

In April 2020, a male in his late 20s presented with episodes of mild lightheadedness and an intermittent burning odor sensation for 3 years, and new-onset headaches. A brain MRI revealed a right lateral ventricle mass with parenchymal invasion and cerebellar contrast-enhancing nodules (Figure 1a). In May 2020, he underwent subtotal resection, with post-operative imaging showing residual nodular enhancement in the mid-posterior body of the right lateral ventricle and unchanged nodular-enhancing foci in the cerebellum (Figure 1b). An outside hospital pathologic examination revealed GBM, WHO grade 4, *IDH* wild-type, *MGMT*-unmethylated. A next-generation sequencing panel was performed and was positive for *PTPRZ1-MET* fusion and *MET* amplification at 7q31.2. The next-generation sequencing panel included somatic mutations in the coding sequence of 134 genes and selected copy number variations (amplifications) in 47 genes (overlap: 146 genes total).

Because of the intraventricular tumor location, an MRI of the spine was obtained that showed multifocal enhancement in the cervicothoracic spinal cord and cauda equina that was concerning for leptomeningeal spread (Figure 2a). His initial examination was significant for a left homonymous hemianopsia and left hemisensory loss; the Karnofsky Performance Score was 90.

A repeat MRI of the neuro-axis was obtained 4 weeks later for radiation treatment planning and showed rapid tumor progression, with multiple new contrast-enhancing nodules in the ventricles and extraventricular cerebrospinal fluid spaces (Figure 1c). He underwent proton craniospinal irradiation at 3600 cGy, followed by a tumor volume boost with IMRT at 2400 cGy. He did not receive concurrent temozolomide (TMZ) because of the large radiation field and concern for neurotoxicity. He experienced craniospinal irradiation–induced grade 2 neutropenia and grade 3 lymphopenia during concurrent chemoradiation therapy but did not require intervention. Postcraniospinal irradiation imaging revealed continuing disease progression; thus, adjuvant TMZ was initiated 4 weeks following concurrent chemoradiation therapy. The clinical team's intention was to add tepotinib to adjuvant TMZ, pending its approval as a single-patient compassionate-use investigational new drug. However, upon completion of 2 cycles of adjuvant TMZ, he developed prolonged grade 2 neutropenia and was not cleared to begin cycle 3 of adjuvant TMZ. Instead, he began 1000 mg of tepotinib hydrochloride hydrate monotherapy daily as a compassionate-use investigational new drug.

Following 1 cycle of tepotinib monotherapy, a brain and spine MRI showed complete resolution of contrast-enhancing lesions (Figures 1d and 2b). After 2 cycles of 1000 mg of tepotinib, the dose was reduced to 500 mg daily because of grade 1 creatinine elevation and grade 1 abdominal discomfort. After 9 cycles, he was transitioned from the compassionate use formulation to the commercially available drug at the equivalent dose of 450 mg of tepotinib-free base. Thirty-five months after the initiation of tepotinib, he presented with progressive headaches and was found to have disease progression in the cerebellum.

Discussion

Trials of targeted therapies in molecularly unselected patients with GBM have been largely unsuccessful, likely because of lack of patient selection, the failure to identify driver mutations, and poor blood-brain barrier penetration of investigational drugs.[18] Patient selection is more nuanced now than in previous years because of routine use of next generation sequencing for most patients with glioblastoma treated at major cancer centers. This expansion of molecular testing panels and their widespread use in glioma has resulted in a renewed interest in targeted therapy trials in select patient with GBM populations.[15] *PTPRZ1-MET* fusion and *MET* amplification were the sole molecular alterations in our patient's next-generation sequencing panel; therefore, we suspected that it was the driver alteration in his tumor. *PTPRZ1-MET* fusion has been described as a driver of glioma progression and an indicator of *MET*-inhibition sensitivity.[19] Finally, beyond patient selection and targeting relevant driver mutations, the ability of therapeutic drugs to penetrate the blood-brain barrier is imperative to their success in clinical trials in the central nervous system. In the case of tepotinib, a dramatic intracranial response was observed in a patient with non-small cell lung cancer with brain metastasis; this promising result encouraged us to use tepotinib in our patient with GBM.[20]

Our case demonstrates the promise of using tepotinib to target *MET* in GBM. We observed both immediate and durable responses in controlling GBM growth in our patient. Early targeted therapy in the adjuvant setting (after radiation therapy) in select patient populations, in lieu of or in addition to TMZ, can be an effective therapeutic strategy in GBM. As

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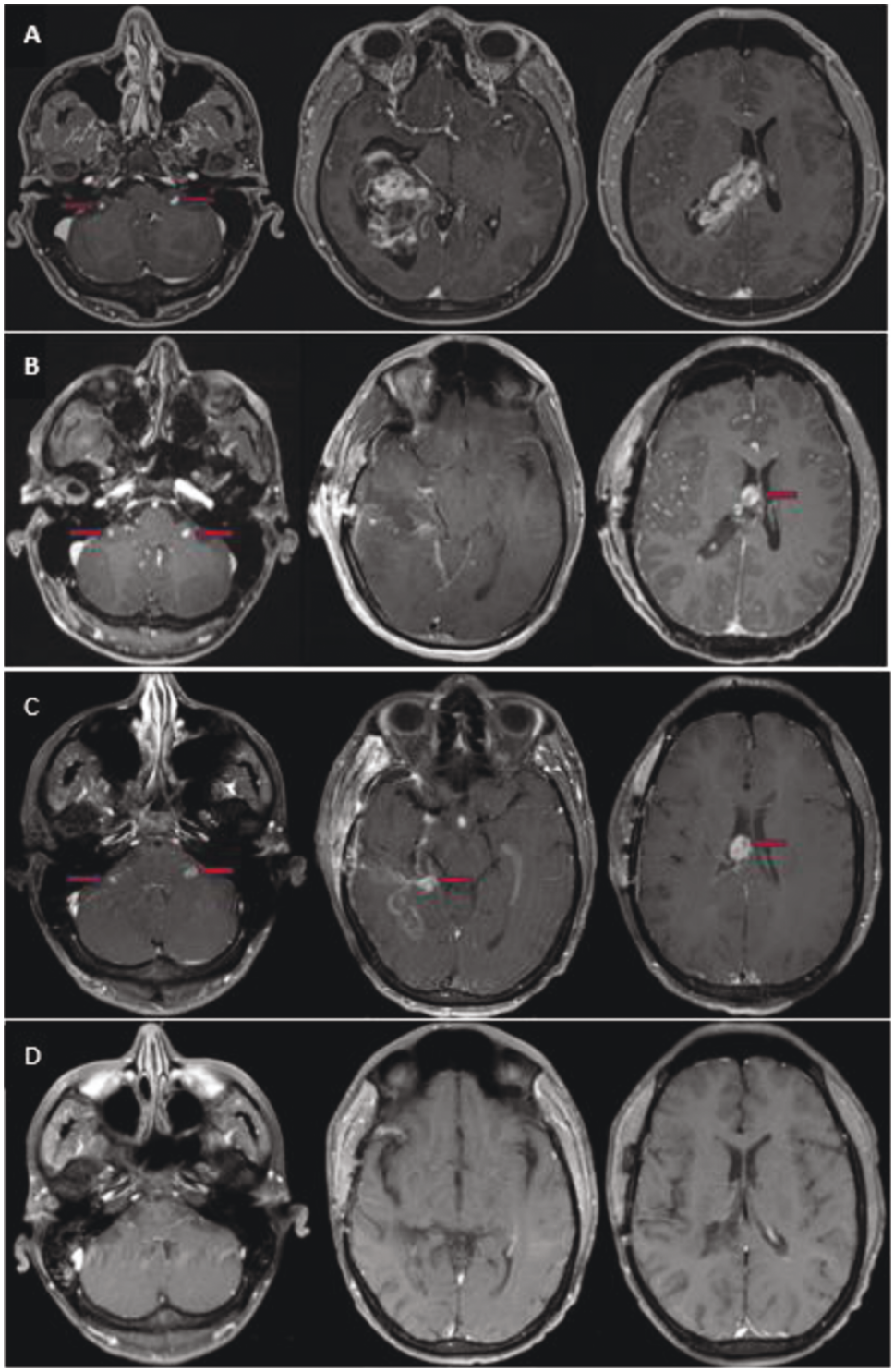

Figure 1. (A) Pre-operative T1-weighted post-contrast MRI sequence of the brain demonstrates contrast-enhancing lesions in the cerebellum and right lateral ventricle. (B) Post-operative T1-weighted post-contrast MRI of the brain demonstrates subtotal resection of the right lateral ventricle lesion and persistent enhancing nodules in the cerebellum. (C) Initial MRI of the brain 4 weeks after initial resection demonstrates disease progression, with new right frontal lesion (not pictured) and increased contrast enhancement in cerebellar lesions, an intraventricular lesion, and the surrounding resection cavity. (D) MRI of the brain with and without contrast, following cycle 1 of tepotinib showing near complete resolution of contrast-enhancing disease throughout the brain parenchyma, ventricle, and leptomeningeal space. This response has persisted for 35 months at last follow-up.

patients with GBM with *MET* alternations tend to have a poorer prognosis, an alternative to standard of care is imperative. Future clinical trials will further clarify the role of tepotinib in molecularly selected brain tumor patients.

Author contributions

Lily C. Pham (Conceptualization, Data curation, Writing—original draft, Writing—review & editing), Lauryn Weller (Project administration, Writing—review & editing), Claudia

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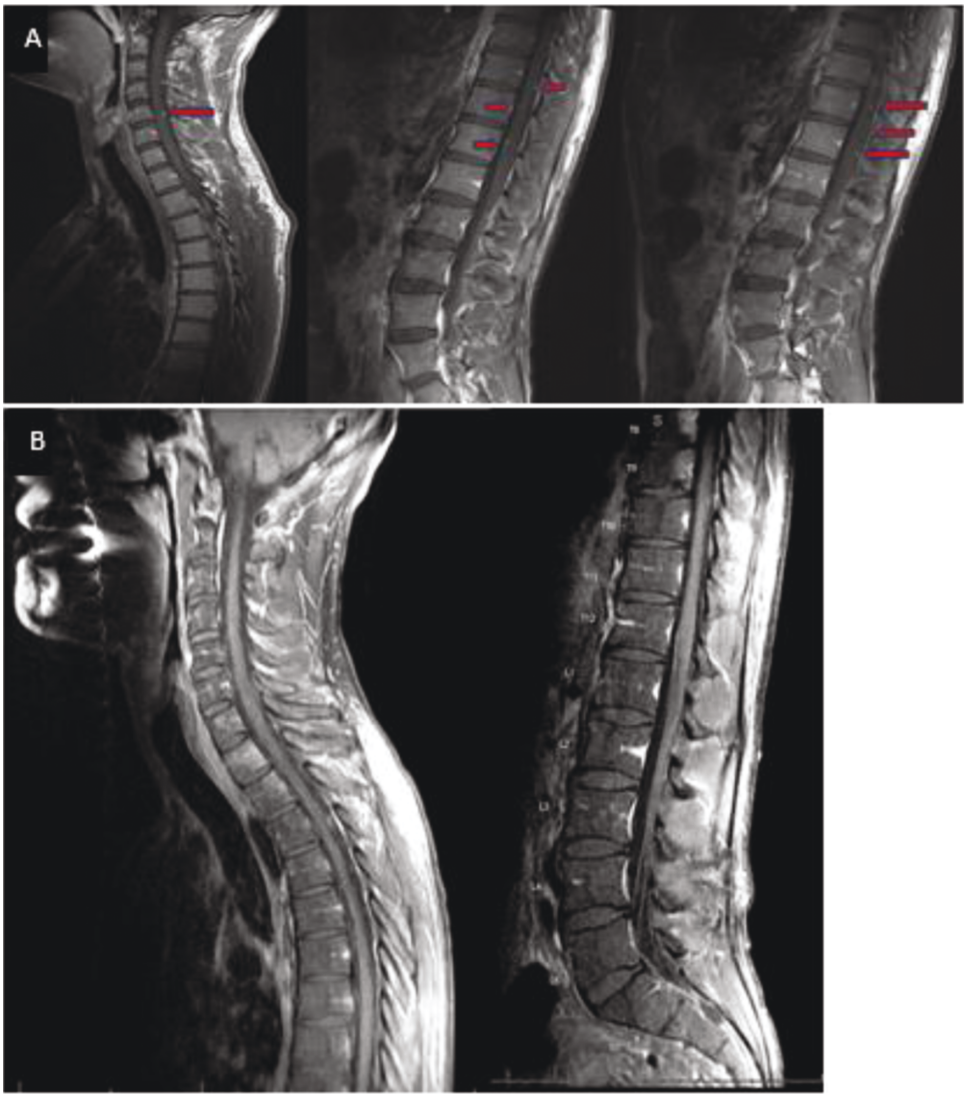

Figure 2. MRI of the spinal cord with and without contrast (A), initial MRI of the spine, shows punctate contrast-enhancing lesions throughout the thoracic and lumbar spine concerning for leptomeningeal spread. (B) following cycle 1 of tepotinib showing near complete resolution of contrast-enhancing disease throughout the spine's leptomeningeal space. This response has persisted for 35 months at last follow-up.

N. Gann (Conceptualization, Investigation, Writing—original draft, Writing—review & editing), Karl Maria Schumacher (Conceptualization, Writing—review & editing), Soetkin Vlassak (Conceptualization, Investigation, Methodology, Writing—review & editing), Todd Swanson (Conceptualization, Methodology, Writing—review & editing), Kaitlin Highsmith (Conceptualization, Project administration, Resources, Writing—review & editing), Barbara J. O'Brien (Conceptualization, Writing—review & editing), Sebnem Nash (Project administration, Resources, Writing—review & editing), Ashley Aaroe (Conceptualization, Resources, Writing—original draft, Writing—review & editing), John F. de Groot (Conceptualization, Supervision), Nazanin K. Majd (Conceptualization, Data curation, Validation, Writing—original draft, Writing—review & editing). First co-authors: Lily C. Pham and Lauryn Weller contributed equally to this work.

Conflicts of interest

Claudia N. Gann was at the time employed by Merck KGaA, which is the responsible pharmaceutical company. Barbara J. O'Brien reported research funding with EMD Serono (study now closed). John F. de Groot reported consulting advisory board member for Kintara Pharmaceuticals, Kazia, MundiPharma, Insightec, Monteris, Carthera, Samus, Sapience, DSP Pharma, Telix, Servier, Alpha Pharmaceuticals, and CapitalOne, and DSMB for Chimerix Consulting: MundiPharma, Insightec, Carthera, Kintara, Deciphera, and Kazia. The other authors indicated no financial relationships.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Kong DS, Song S-Y, Kim D-H, et al. *Prognostic significance of c-Met expression in glioblastomas*. *Cancer*. 2009;115(1):140-148. https://doi.org/10.1002/cncr.23972
2. Tasaki T, Fujita M, Okuda T, et al. *MET expressed in glioma stem cells is a potent therapeutic target for glioblastoma multiforme*. *Anticancer Res*. 2016;36(7):3571-3577.

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3. Pierscianek D, Kim Y-H, Motomura K, et al. *MET gain in diffuse astrocytomas is associated with poorer outcome*. *Brain Pathol*. 2013;23(1):13-18. https://doi.org/10.1111/j.1750-3639.2012.00609.x
4. Petterson SA, Dahlrot RH, Hermansen SK, et al. *High levels of c-Met is associated with poor prognosis in glioblastoma*. *J Neurooncol*. 2015;122(3):517-527. https://doi.org/10.1007/s11060-015-1723-3
5. Ah-Pine F, Casas D, Menei P, et al. *RNA-sequencing of IDH-wild-type glioblastoma with chromothripsis identifies novel gene fusions with potential oncogenic properties*. *Transl Oncol*. 2021;14(1):100884. https://doi.org/10.1016/j.tranon.2020.100884
6. Bao ZS, Chen H-M, Yang M-Y, et al. *RNA-seq of 272 gliomas revealed a novel, recurrent PTPRZ1-MET fusion transcript in secondary glioblastomas*. *Genome Res*. 2014;24(11):1765-1773. https://doi.org/10.1101/gr.165126.113
7. Chen HM, Yu K, Tang X-yan, et al. *Enhanced expression and phosphorylation of the MET oncoprotein by glioma-specific PTPRZ1-MET fusions*. *FEBS Lett*. 2015;589(13):1437-1443. https://doi.org/10.1016/j.febslet.2015.04.032
8. Huang R, Liu Y, Wang K, et al. *High-sensitive clinical diagnostic method for PTPRZ1-MET and the characteristic protein structure contributing to ligand-independent MET activation*. *CNS Neurosci Ther*. 2021;27(5):617-628. https://doi.org/10.1111/cns.13627
9. Altintas DM, Comoglio PM. *An observatory for the MET oncogene: a guide for targeted therapies*. *Cancers (Basel)* 2023;15(18):4672. https://doi.org/10.3390/cancers15184672
10. International Cancer Genome Consortium PedBrain Tumor, P. *Recurrent MET fusion genes represent a drug target in pediatric glioblastoma*. *Nat Med*. 2016;22(11):1314-1320.
11. Gow CH, Liu Y-N, Li H-Y, et al. *Oncogenic function of a KIF5B-MET fusion variant in non-small cell lung cancer*. *Neoplasia* 2018;20(8):838-847. https://doi.org/10.1016/j.neo.2018.06.007
12. Cloughesy TF, Drappatz J, de Groot J, et al. *Phase II study of cabozantinib in patients with progressive glioblastoma: subset analysis of patients with prior antiangiogenic therapy*. *Neuro Oncol* 2018;20(2):259-267. https://doi.org/10.1093/neuonc/nox151
13. Wen PY, Drappatz J, de Groot J, et al. *Phase II study of cabozantinib in patients with progressive glioblastoma: subset analysis of patients naive to antiangiogenic therapy*. *Neuro Oncol* 2018;20(2):249-258. https://doi.org/10.1093/neuonc/nox154
14. Oliveres H, Pineda E, Maurel J. *MET inhibitors in cancer: pitfalls and challenges*. *Expert Opin Investig Drugs*. 2020;29(1):73-85. https://doi.org/10.1080/13543784.2020.1699532
15. Martinez-Garcia M, et al. *Safety and efficacy of crizotinib in combination with temozolomide and radiotherapy in patients with newly diagnosed glioblastoma: phase Ib GEINO 1402 trial*. *Cancers (Basel)* 2022;14(10):2393-2407.
16. Paik PK, Felip E, Veillon R, et al. *Tepotinib in non–small-cell lung cancer with MET exon 14 skipping mutations*. *N Engl J Med*. 2020;383(10):931-943. https://doi.org/10.1056/nejmoa2004407
17. Markham A. *Tepotinib: first approval*. *Drugs*. 2020;80(8):829-833. https://doi.org/10.1007/s40265-020-01317-9
18. Ou A, Yung WKA, Majd N. *Molecular mechanisms of treatment resistance in glioblastoma*. *Int J Mol Sci* . 2020;22(1):351. https://doi.org/10.3390/ijms22010351
19. Hu H, Mu Q, Bao Z, et al. *Mutational landscape of secondary glioblastoma guides MET-targeted trial in brain tumor*. *Cell*. 2018;175(6):1665-1678.e18. https://doi.org/10.1016/j.cell.2018.09.038
20. Takamori S, Matsubara T, Fujishita T, et al. *Dramatic intracranial response to tepotinib in a patient with lung adenocarcinoma harboring MET exon 14 skipping mutation*. *Thorac Cancer* 2021;12(6):978-980. https://doi.org/10.1111/1759-7714.13871

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