Response to Selpercatinib in a Patient With Recurrent Glioblastoma and *RET* Amplification

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ABSTRACT

Glioblastoma (GBM) is a malignant central nervous system neoplasm that remains largely incurable. Limited treatment options currently exist after disease progression on standard-of-care first-line therapy. However, repurposing the use of approved therapies in patients with potentially targetable genomic alterations continues to be an emerging area of interest. This report presents the first description of a patient with isocitrate dehydrogenase wild-type GBM with an underlying *RET* amplification who demonstrated a near-complete response while receiving therapy with the RET inhibitor selpercatinib. The case highlights the excellent blood-brain barrier penetration of selpercatinib, as well as its potential role in the management of *RET*-amplified GBM. Larger biomarker-enriched studies are needed to confirm the results of this case report. Given the rare incidence of *RET* alterations in GBM, findings from this report can help guide and support optimal treatment strategies for patients with *RET*-altered GBM.

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Background

Glioblastoma (GBM) is an aggressive central nervous system (CNS) neoplasm that remains largely incurable. Patients diagnosed with this disease have a poor prognosis, with survival rates of 14 to 15 months after diagnosis.[1] Surgery, if feasible, followed by radiation therapy in combination with temozolomide is the standard of care for most patients with newly diagnosed GBM.[2,3] Additionally, repurposing the use of approved targeted therapies in patients with specific genomic alterations or those with various genomic or metabolic abnormalities continues to be an emerging area of interest.[4] The selective RET inhibitor selpercatinib is poised to alter the treatment landscape for patients with *RET*-altered malignancies. Currently, selpercatinib has FDA-approved indications for the treatment of metastatic *RET* fusion–positive non–small cell lung cancer (NSCLC) and thyroid cancers, as well as *RET*-mutant medullary thyroid cancer (MTC) requiring systemic treatment.[5] Recent evidence has also demonstrated antitumor activity in additional *RET* fusion–driven advanced solid tumors.[6] However, the implications of genomic alterations outside of *RET* fusion–positive and *RET* mutation–positive disease have not been fully characterized. Thus, the safety and efficacy of selpercatinib has not been fully described in solid tumors with additional *RET* alterations, specifically those harboring *RET* amplification.

This report presents the first description of a patient with recurrent GBM and a concurrent *RET* amplification who demonstrated clinically significant disease response while receiving selpercatinib therapy. The patient's consent was obtained for publication of this manuscript.

Case Presentation

A 48-year-old man with no significant past medical history presented with sudden onset of severe right-sided headache and emesis. MRI revealed 2 rim-enhancing lesions in the right temporal lobe. The patient underwent a gross total resection of the lesions, with surgical pathology revealing a GBM. MGMT promoter was unmethylated, and no *IDH* mutations were detected. The tumor sample was clinically

profiled at a College of American Pathologists–accredited, CLIA-certified laboratory (Tempus Laboratories) using the Tempus xT laboratory developed test (LDT), similar to previously described methods.[7] Additional review of next-generation sequencing (NGS) revealed *ATM* exon 10 splice acceptor mutation, *CDK4* amplification, *MDM2* amplification, and *RET* amplification.

The patient underwent radiation therapy with concurrent temozolomide. The presence of an *ATM* mutation led to the initiation of olaparib with adjuvant temozolomide following completion of chemoradiotherapy. Additionally, he was treated with an externally applied, alternating tumor-treating field treatment (Optune, Novocure).[8] Four cycles of maintenance temozolomide + olaparib therapy were completed but were subsequently discontinued due to disease progression. Pseudoprogression was a consideration; however, the patient met RANO criteria given his MRI findings, proximity to completing chemoradiotherapy (>12 weeks), ongoing need for steroids, and worsening neurologic symptoms.[9] As mentioned previously, further evaluation of genomic sequencing demonstrated the presence of a *RET* amplification. These findings, in addition to the recently published efficacy data regarding the use of selpercatinib in patients with metastatic NSCLC to the brain with known *RET*-mutated disease, provided rationale for the use of selpercatinib upon disease progression.[10]

Selpercatinib was dosed at 160 mg twice daily as a continuous regimen. After 6 weeks of selpercatinib treatment, MRI results demonstrated near-complete resolution of gadolinium-enhanced disease on MRI, with a significant reduction in mass effect and vasogenic edema (Figure 1). Seizure activity had also resolved. Repeat MRI results after 12 weeks of therapy continued to show a positive response to therapy with no new areas of disease. After 12 weeks of treatment, selpercatinib was held due to treatment-related liver enzyme elevation. After liver enzyme normalization, selpercatinib was restarted and titrated back to full-dose therapy. During this period of drug titration, imaging revealed a partial response. However, after 8 months of selpercatinib treatment, repeat MRI revealed unequivocal disease progression. Selpercatinib was discontinued and the patient was initiated on the next line of therapy.

Discussion

Progression Versus Pseudoprogression

Although our patient met standard RANO criteria for disease progression, we thought pseudoprogression was possible given exposure to olaparib while on maintenance temozolomide. As reported by Baxter et al,[11] the rate of pseudoprogression approached 20% in a cohort of children exposed to the combination of veliparib and radiation, followed by maintenance temozolomide. However,

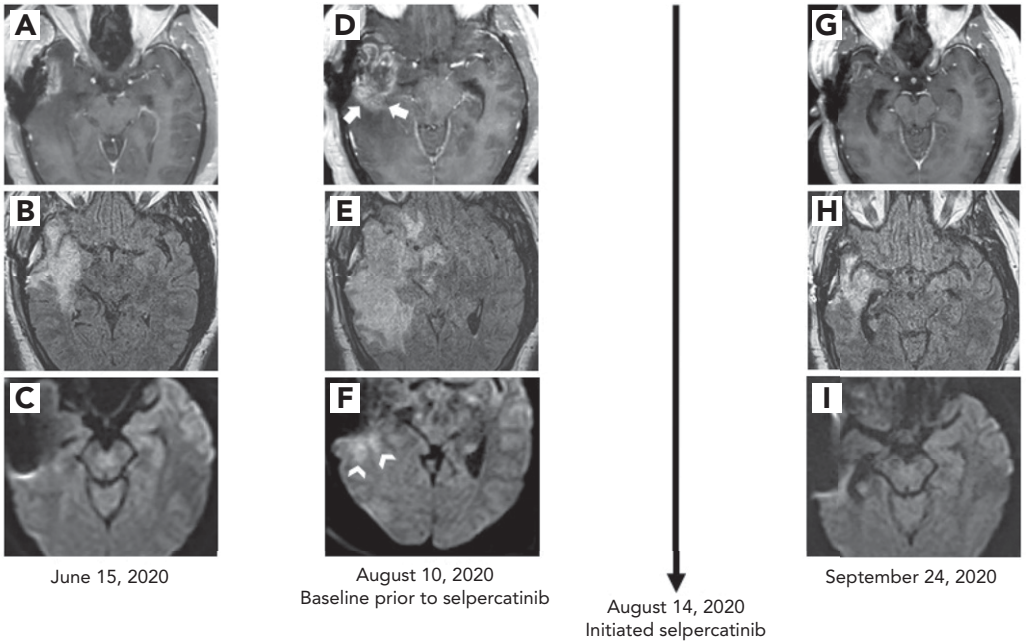

Figure 1. MRI examinations 8 weeks prior to progression **(A, B, C)**, at the time of progression **(D, E, F)**, and 6 weeks after initiation of selpercatinib **(G, H, I)**. Postcontrast T1 at the time of progression **(D)** shows a significant increase in heterogeneous enhancement in the right temporal lobe with a discrete nodule along the posterior aspect of the lesion (arrows). Corresponding FLAIR image **(E)** shows markedly increased edema and associated mass effect compared with 8 weeks prior **(B)**. Diffusion-weighted image **(F)** shows a new area of restricted diffusion posteriorly (arrowheads). MRI 6 weeks after initiating selpercatinib shows near complete resolution of contrast enhancement **(G)**, significant reduction in mass effect and edema **(H)**, and resolution of restricted diffusion **(I)**.

it is worth mentioning that a meta-analysis of 73 studies in high-grade glioma by Abbasi et al[12] reported a 36% incidence of pseudoprogression in patients treated with standard therapy. Therefore, we speculate that the presence of a PARP inhibitor did not appear to add to the risk of pseudoprogression, considering that the likelihood of pseudoprogression is seemingly higher with standard-of-care therapy. From a molecular standpoint, MGMT promotor unmethylated disease is more likely to progress early during treatment.[13] The possibility of pseudoprogression was further diminished given that the patient did not improve on increasing doses of steroids.

With our patient starting selpercatinib, followed by his rapid clinical and radiographic improvement, it was favored that this was true progression of disease. However, it is also plausible that selpercatinib, although being a highly specific RET inhibitor, could induce a response similar to bevacizumab given that *RET* signaling may be involved in crosstalk with the VEGF pathway.[14] This is further supported by selpercatinib having the known adverse effects of hypertension and impaired wound healing.[5]

RET-Altered Disease and Current Practices

Considered a proto-oncogene, the *RET* gene encodes a transmembrane receptor tyrosine kinase that is composed of a large extracellular domain, an intracellular kinase, and a transmembrane domain.[15] Alterations in *RET* are primarily activated through chromosomal rearrangements leading to gene fusions or through specific point mutations. Activation of oncogenicity through *RET*-fusion proteins leads to ligand-independent dimerization, constitutively active *RET*, and ultimately uncontrolled cellular proliferation.[10] Multikinase inhibitors (MKIs) with RET inhibitor activity, such as cabozantinib and vandetanib, have historically been used for the targeted treatment of *RET*-driven cancers.[16,17] However, both agents are associated with limited overall and duration of responses, as well as risk of a variety of off-target adverse effects.[16–19]

Advances in the field of *RET*-targeted therapies have led to the recent approval of selpercatinib. Selpercatinib is a novel, ATP-competitive, highly selective small-molecule RET kinase inhibitor with significant CNS penetration and low potential for drug interactions (Figure 2). This agent has demonstrated an improved efficacy and safety profile compared with previous agents used to target malignancies with known *RET*-fusion alterations. Currently, selpercatinib is approved for the treatment of adult patients with metastatic *RET* fusion–positive NSCLC and thyroid cancer, as well as adult and pediatric patients with *RET*-mutant MTC requiring systemic therapy.[5] Selpercatinib has demonstrated response rates of 64% to 85% in patients previously treated with a *RET* targeted therapy and

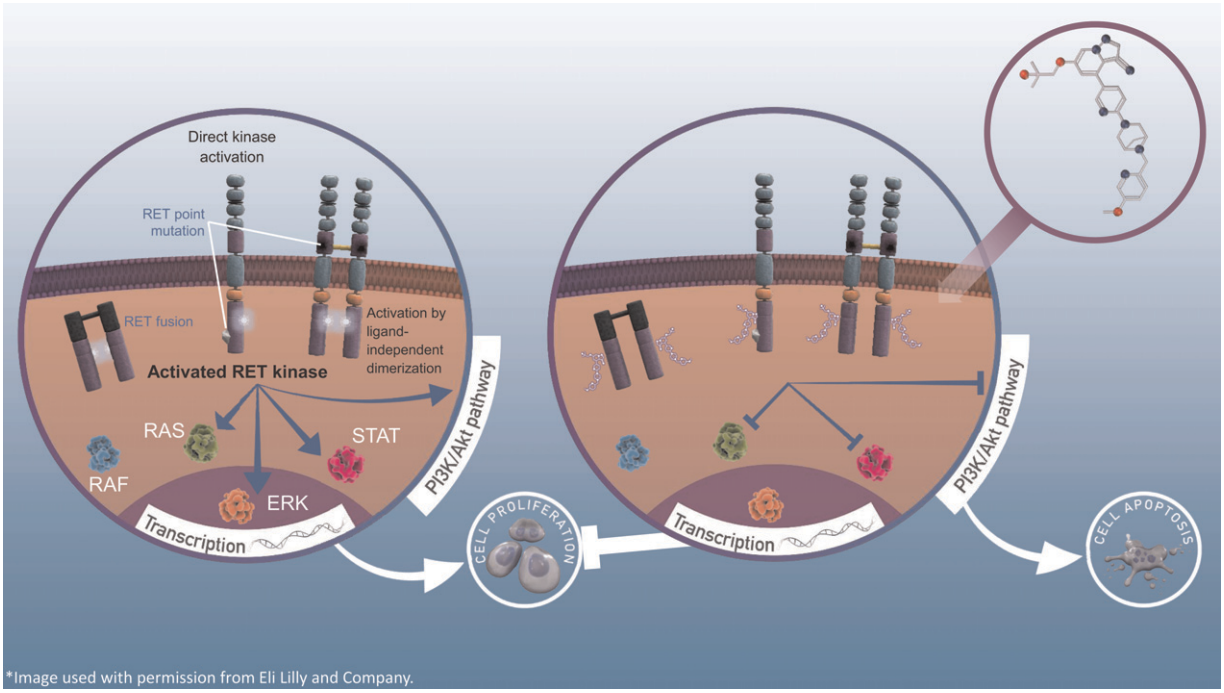

Figure 2. Selpercatinib is a highly selective, ATP-competitive, RET receptor tyrosine kinase inhibitor. Binding of selpercatinib to *RET*-fusion or point-mutated *RET* receptors results in inhibition of RET kinase activity and changes in intracellular signaling pathways which lead to decreased cellular proliferation and increased cellular apoptosis.
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those who are treatment-naïve.[10,20] Selpercatinib demonstrated lasting and durable clinical responses in those who respond to therapy yielding significant progression-free survival rates and durations of response. Additionally, selpercatinib has demonstrated clinical activity among patients with known CNS metastases. Of the 11 patients with NSCLC previously treated with chemotherapy who had measurable CNS disease, 91% had a clinical response (3 complete responses, 7 partial responses, and 1 stable disease), with a median CNS duration of response of 10.1 months.[10]

Pharmacokinetics and Pharmacodynamics of Selpercatinib and Blood–Brain Barrier Penetration

For drugs used in the treatment of CNS-related diseases, attaining the targetable concentrations needed for a clinical response is complicated by the presence of the blood–brain barrier (BBB). The BBB plays an essential role in maintaining homeostasis within the CNS environment and is equipped with a wide array of both influx and efflux transport proteins that regulate concentration ion gradients, the delivery of macromolecules to meet the energy needs of the brain, and prevents the entry of numerous, potentially harmful substances from entering the CNS environment.[21–23] Evaluation of currently available literature has demonstrated varying levels of CNS penetration of tyrosine kinase inhibitors (TKIs) with activity against *RET* (Table 1).[24–31] The CNS penetration of selpercatinib has been demonstrated in both in vitro and in vivo mouse tumor models and multiple patient case reports.[32,33] As described previously, the ability of selpercatinib to effectively cross the BBB has been further supported by the efficacy and responses demonstrated in patients with *RET*-altered NSCLC who had confirmed metastases to the brain.[10]

The dose–response relationship of selpercatinib has not been fully characterized. However, depending on the *RET* alteration, the IC_{50} for selpercatinib ranges from 0.92 to 67.8 nanomolar.[5] Given the high selectivity and potency of selpercatinib for multiple *RET* alterations, limited concentrations of active drug are needed to permeate the BBB to have an effect at the site of action if present within the CNS space. Although selpercatinib has the highest specificity for inhibition of *RET* alterations, achievement of higher concentrations leads to inhibition of additional tyrosine kinases, including various isoforms of VEGF and fibroblast growth factor receptor, both of which have isoforms that have been implicated in the growth and survival of various CNS malignancies.[5,15,34] These characteristics provide a better reasoning and rationale for the effective CNS penetration seen with selpercatinib and its potential use in patients with known *RET*-altered GBM.

Targeting *RET* Alterations and Potential Off-Target Activities

The complexity of genomic changes seen in *RET*-driven malignancies highlights the need for further investigation of this mutation. *RET* rearrangements are mutually exclusive with other driver mutations.[35] In NSCLC, at least 12 different gene partners have been described for *RET* mutations, including *KIF5B*, *CCDC6*, *MYO5C*, *TRIM33*, and *ERC1*.[35,36] Functional studies have shown that inhibitors of RET are capable of inhibiting a wide range of *RET* alterations, including gatekeeper mutations V804L and V804M, KIF5B-RE, CCDC6-*RET*, M918T, and C634W.[34] As their name suggests, MKIs target a spectrum of kinases outside of *RET*. Due to the similarities in homology between the kinase domain of RET and other TKIs, MKIs may have activity against *RET* mutations at higher concentrations. However, the off-

Table 1. Comparison of TKIs With Activity Against *RET*

RET Inhibitors	*RET* Selectivity[a]	BBB Penetration[b]	Evidence of CNS Response
Cabozantinib	++	Modest clinical evidence	Cloughesy et al[24] Wen et al[25]
Pralsetinib	+++	Modest clinical evidence	Gainor[26]
Vandetanib	++	Low clinical evidence	Kreisl et al[27]
Selpercatinib	+++	Modest clinical evidence	Drilon et al[10]
Sunitinib	+	Low clinical evidence	Grisanti et al[28]
Sorafenib	+	Low clinical evidence	Nabors et al[29]
Lenvatinib	+	No clinical evidence	N/A
Nintedanib	+	Negative clinical evidence	Norden et al[30] Muhic et al[31]
Agerafenib	+++	No clinical evidence	N/A

Abbreviations: BBB, blood–brain barrier; CNS, central nervous system; N/A, not applicable; TKI, tyrosine kinase inhibitor.
[a]+ = low selectivity; ++ = moderate selectivity; +++ = high selectivity.
[b]No clinical evidence = no preclinical or phase I–III trials reported; low clinical evidence = phase I trials reported supporting agent in CNS disease; modest clinical evidence = phase II trials reported supporting agent in CNS disease; negative clinical evidence = phase I–III trials supporting lack of efficacy in CNS disease.

target effects of MKIs can lead to inferior inhibition of *RET* and increased incidence of adverse events, leading to potential dose modifications or drug discontinuation. VEGFR2 inhibitors, such as cabozantinib and vandetanib, have different efficacies against various *RET* mutations and can effectively block the activity of *RET* M918T. However, they are unable to inhibit gatekeeper mutations, including *RET* V804M and *RET* V804L, and may lead to mechanisms of acquired resistance to various MKIs.[15,35]

According to the AACR Project GENIE Consortium, *RET* is altered in approximately 2.75% of malignant CNS neoplasms, with a total of 37 glioblastoma and 15 anaplastic astrocytoma cases reported.[37] A similar prevalence of *RET*-altered glioma cases have been reported in the cBioPortal for Cancer Genomics, with an incidence of 6.6%.[38,39] Overexpression of RET kinase has only been identified in 7 glioma tissue samples per the Catalogue of Somatic Mutations in Cancer (COSMIC) database.[40] Woo et al[41] conducted NGS in 356 diffuse gliomas and identified 2 patients harboring oncogenic *RET*-fusion mutations. With such a low prevalence, potential therapeutic targets for *RET*-mutated GBM have not been evaluated in either the preclinical or clinical stages of drug development.

Response to selpercatinib in the setting of *RET* amplification has not been previously reported. To better understand potential mechanisms surrounding the observed response in this case report, further analysis of the tumor sample was performed using whole-exome sequencing. A low-level ANKRD26-*RET* fusion was detected in the DNA, with 12 supporting reads. NGS analysis confirmed that this fusion was not detected in the RNA, even with low support. Additionally, the RET kinase domain was retained, signifying that this would be predicted to be oncogenic in nature. However, due to the ANKRD26-*RET* fusion low level of support in the DNA and absence within the RNA, it is difficult to determine whether this was a true *RET*-fusion or rather sequencing noise that may have arisen as a side effect of the *RET* amplification. Although limited, low-level fusion events in the setting of specific gene copy number amplifications have been previously described in patients with newly diagnosed GBM via the proposed breakage-fusion-bridge cycle model, specifically in the setting of *EGFR* copy number amplification.[42] Given the lack of fusion protein detected in the tumor RNA, it can be theorized that a fusion protein cannot be ultimately transcribed and would not be a factor in the process of tumorigenesis. This suggests that selpercatinib could have activity against the RET kinase domain and that *RET* amplification revealed in this case could be the primary driver of the observed response.

Conclusions

Some of the primary challenges associated with the treatment of GBM include the inability of many systemic therapies to effectively penetrate the BBB and the heterogeneity of oncogenic drivers at the molecular level. As described in this report, selpercatinib provided a complete and durable clinical response in this patient with *RET*-amplified GBM who, as we highly suspect, was experiencing true disease progression. Activity against *RET*-amplified disease has not been previously described with selpercatinib. However, this report provides clinical evidence that selpercatinib has high specificity and activity against RET tyrosine kinases that are overexpressed and acting as an underlying oncogenic driver. Additionally, this report further supports the ability of selpercatinib to effectively cross the BBB in concentrations high enough to produce a profound clinical response.

To our knowledge, this is the first case report that describes a patient with *RET*-amplified disease being treated with and responding to selpercatinib therapy. Given the rare occurrence of *RET* alterations in GBM, our experience with this case may help inform future biomarker-enriched studies within this population.

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