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Case Report

Lessons from Exceptional Responders with High-Grade Brain Tumors Treated with Precision Targeted Therapies

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ABSTRACT

Background: High-grade gliomas are associated with dismal outcomes and have devastating neurologic sequelae. Standard-of-care surgery, radiation, and temozolomide yield a median survival of 14–16 months in patients with glioblastoma (GBM). **Methods:** We report four patients with high-grade glioma (two with GBM; one initially diagnosed with GBM, now classified as World Health Organization grade 4 *IDH1*-mutant astrocytoma; and one with oligosarcoma [grade 4]). Tumor next-generation sequencing (NGS) was performed for all four patients, and they were treated based on their biomarkers. **Results:** NGS yielded actionable alterations targeted after conventional surgery/chemoradiation therapy: imatinib (for *KIT* and *PDGRA* amplification) and bevacizumab (for *KDR* [*VEGFR2*] amplification); everolimus (mTOR inhibitor for *TSC2* and *PTEN* loss-of-function alterations); and ivosidenib (IDH1 inhibitor for *IDH1* mutations in two cases, including the oligosarcoma). Three patients remain in radiographic and clinical remission at 39+, 48, and 52+ months; the patient with oligosarcoma showed clinical and imaging response lasting 8 months. **Conclusions:** Our exceptional responders with high-grade gliomas suggest that biomarker-matched targeted therapy can benefit select patients with high-grade glioma and warrants prospective clinical trials.

Keywords: high-grade glioma, precision oncology, targeted therapy, exceptional responders

BACKGROUND

Exceptional responders are patients who achieve a remarkable response to cancer therapy, despite having a cancer type that is generally considered difficult to treat. Occasionally, reports of even single exceptional responders have launched a new treatment paradigm for specific lethal cancers. For instance, a case report of an exceptional response in a patient with an advanced gastrointestinal stromal tumor (GIST) (characterized by *KIT* mutations) treated with the KIT kinase inhibitor imatinib transformed the outlook for these cancers, which previously had response rates approaching zero after traditional therapy.[1] Currently, the vast majority of patients with GIST respond to matched gene-targeted therapy such as imatinib and other kinase inhibitors.[2] With the emergence of precision medicine and advances in genomics, there is significant interest in identifying the molecular characteristics of exceptional responders to improve patient outcomes. For example, the National Cancer Institute's Exceptional Responders Initiative, initiated in 2014, aims to identify individuals who have experienced exceptional responses to cancer therapy and analyze their tumors to gain insights into the underlying mechanisms of exceptional response.[3]

High-grade gliomas, particularly glioblastoma (GBM), are difficult-to-treat malignant brain tumors with debilitating neurologic consequences.[4] GBM is the most common primary malignant brain tumor and is often resistant to conventional therapies. Debulking surgery, concomitant radiation, and temozolomide followed by six cycles of adjuvant temozolomide has been the standard of care. However, this regimen is associated with a median survival of approximately 14.6 months, and less than 5% of patients survive 3 years; the 2-year survival rate is approximately 27%, and median progression-free survival (PFS) is approximately 6.9 months.[5–7]

The main prognostic factors for high-grade brain tumors include: age, Karnofsky performance status (KPS), baseline neurologic function, number of presenting symptoms, comorbidities, *IDH1/2* mutation, methylguanine-DNA methyltransferase (MGMT) promoter methylation, ATRX loss, 1p/19q codeletion, *TERT* promoter mutation, *EGFR* amplification, chromosome 7 gain/10 loss, *TP53* mutation, *CDKN2A/B* deletion, tumor location, tumor volume, contrast enhancement, peritumoral edema, multifocality or midline crossing, extent of resection, postoperative performance status, timing of chemoradiotherapy, and response to temozolomide. However, most patients do poorly, with few long-term progression-free survivors. Patients with *IDH* mutations and/or MGMT methylation have a better prognosis than those without these changes.

Although significant headway has been made with the use of precision medicine and matching targeted therapy to tumor markers in other complex cancers, such advances in high-grade gliomas have lagged.

This case series report describes the molecular landscape and treatment outcomes, as well as lessons learned, for four patients with high-grade glioma who attained remarkable responses when treated with matched targeted therapy.

PATIENTS

The patients included in this case series were selected for having undergone next-generation sequencing (NGS) testing of tumor tissue, receiving matched therapy, and having an exceptional response in the setting of a high-grade brain tumor. All patients had exhausted most standard treatment options, and matched gene- or immune-targeted therapies were selected based on NGS results and tumor PD-L1 immunohistochemistry (IHC) expression. Before treatment, the molecular findings along with clinical data may have been discussed at local molecular tumor boards. Pathology was reviewed by certified pathologists/neuropathologists with expertise in brain tumors. The patients consented to sharing of their medical information and images.

Case 1

A 67-year-old woman was admitted to the emergency room at a tertiary care hospital in May 2021 with sudden onset of left hemiplegia and dysarthria. Magnetic resonance imaging (MRI) revealed a large, necrotic, vascular tumor in the right temporofrontal region, measuring approximately 6.5 × 5.5 × 5 cm. The tumor had significant perilesional edema and was causing a midline shift, suggesting a high-grade brain tumor.

The patient underwent a right frontotemporal craniotomy with subtotal resection of the tumor. Pathology revealed an *IDH1* wild-type, GBM (Ki-67 = 30%). O^6-MGMT analysis showed hypermethylation by polymerase chain reaction (PCR). After surgery, the patient's neurological symptoms improved gradually over the 3 weeks. The patient then received standard daily radiotherapy with 30 fractions concurrent with daily temozolomide 75 mg/m^2 a day by mouth for approximately 6 weeks.

Comprehensive genomic profiling tumor analysis (Foundation One CDx, Foundation Medicine, Inc.) (NGS) was conducted. The results showed mutations and amplifications in *PDGFRA*, as well as amplifications in *KIT* and *KDR* (*VEGFR-2*) genes, with an *IDH1* wild-type result (Table 1) (*PDGRA*, *KIT*, and *KDR* genes reside on chromosome 4q12, which is a known amplicon in cancer).[8] Based on these findings and re-emergence of neurologic symptoms, the patient was started (July 2021) on a treatment regimen of bevacizumab (VEGF-A antibody that targets the VEGFR2 [KDR] ligand]) 10 mg/kg intravenously (IV) every 2 weeks and imatinib[9] (KIT and PDGFRA inhibitor) 400 mg/day orally. Follow-up MRI scans performed at approximately 2-month intervals showed significant ongoing regression of the tumor size and reduction

Table 1. Summary of cases

	Case 1	Case 2	Case 3	Case 4
Age and sex	67-year-old woman	40-year-old man	66-year-old man	28-year-old man
Prior therapy	Surgery followed by temozolomide and radiation	Surgery followed by temozolomide and radiation	Surgery, radiation, temozolomide, lomustine, pembrolizumab plus bevacizumab	Surgery, temozolomide and radiation; bevacizumab
Features	MGMT methylated; *IDH* wild type	MGMT methylated, *IDH1* mutant	1p19q co-deleted, MGMT methylated, *IDH1 R132* mutated	MGMT unmethylated, *IDH* wild type
Pathology	Grade 4 GBM	Grade 4 GBM (current classification would be WHO grade 4 Astrocytoma, *IDH1* mutant)	Oligodendroglioma transforming into oligosarcoma (grade 4) on recurrence	Grade 4 GBM
NGS	Foundation Medicine F1CDX	Tempus	CARIS Life Sciences	ACT-Onco/ACT Genomics
Genomic findings	*KIT* amplification (x26 copy number) *PDGFRA E1032D* and amplification (s26 copy number) *KDR* amplification (X26 copy number) (KDR = VEGFR2) *CDKN2A/B p16INK4a* loss and *p14ARF* loss exons 2-3 *TERT* promoter -146C>T, *TP53 T125A* TMB: 5 mutations/mb; MS stable	*ATM R3008C, IDH1 R132H, TP53 R280fs, TERT c.-124C>T, CDKN2A/B* loss TMB: 4.2 mutations/mb; MS stable	*IDH1 R132* and *TP53 R282* TMB: 2 mutations/mb; MS stable	*PTEN E7fs,* homozygous *TSC2* deletion *PALB2* and *BRCA2* heterozygous deletion TMB: 1 mutation/mb; MS stable
Other findings	None	PD-L1 IHC negative	PD-L1 score of 25% (SP142 IHC stain)	None
Matched therapy	Bevacizumab (*VEGF-A* antibody for *VEGFR-2/KDR* amplification and for *TP53* mutation, which elevates the *VEGF/VEGFR* axis) plus imatinib (*PDGFRA* (for *PDGFRA* mutation and amplification) and *KIT* inhibitor (for *KIT* amplification)	Ivosidenib (IDH inhibitor) for *IDH1 R132H* alteration	Pembrolizumab (for PD-L1 IHC positive) plus bevacizumab (for *TP53* mutation, which elevates the VEGF/VEGFR axis) plus ivosidenib (for *IDH1* mutation)	Everolimus (mTOR inhibitor) for *PTEN* and *TSC2* alterations, both of which activate the mTOR signal
Outcome	Complete remission ongoing at 39+ months of treatment	Progression free at 52+ months	Progression-free survival was 8 months	Complete remission for 48 mo of everolimus therapy

Abbreviations: GBM: glioblastoma; IHC: immunohistochemistry; MGMT: methylguanine-DNA methyltransferase; NGS: next-generation sequencing; TMB: tumor mutational burden; WHO: World Health Organization.

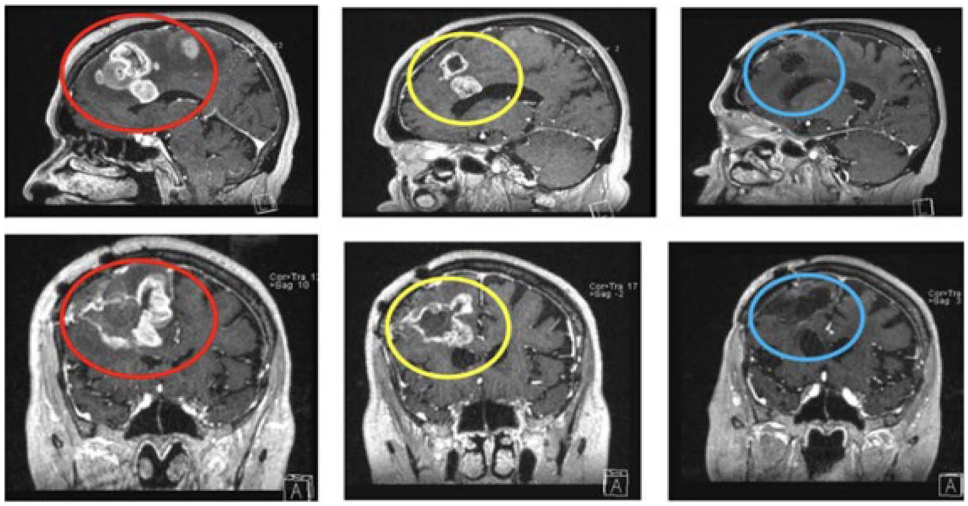

Figure 1. Serial magnetic resonance images of the brain for case 1 (T1 postcontrast images). *Left*: Postoperative multifocal mass in the right frontotemporal area (red circle) accompanied by surrounding edema. *Middle*: At 1 month follow-up after concurrent radiochemotherapy, the mass had partially reduced in size, while the edema persisted in the same area (yellow circle). During this period, treatment with imatinib and bevacizumab was initiated. *Right*: By the 28th month after the administration of bevacizumab and imatinib, there was no contrast-enhancing lesion observed in the area (green circle), consistent with complete radiological response. The patient was progression-free at 39+ months.

of the perilesional edema (Fig. 1). A follow-up neurological examination revealed complete resolution of the left hemiplegia and improvement of the dysarthria. The patient's KPS score improved from 70 before treatment to 90 after treatment. Both drugs were tolerated without significant adverse effects, and the patient remains progression-free (no evidence of contrast enhancement) at 39+ months.

Case 2

A 40-year-old man presented to the hospital for a seizure. MRI of the brain showed a right frontal lobe mass concerning for malignancy. The patient underwent surgical resection. Pathology was consistent with GBM and positive for MGMT promoter methylation. This tumor would now be classified as World Health Organization (WHO) grade 4 astrocytoma, *IDH1* mutant.[10] NGS showed several genomic alterations, including *ATM R3008C, IDH1 R132H, TP53 R280fs, TERT c.-124C>T,* and *CDKN2A/B* loss. Immune profiling was unremarkable (PD-L1 negative by IHC, microsatellite-stable, tumor mutational burden = 4.2 m/MB [low]) (Table 1).

After surgery, the patient started adjuvant chemoradiation therapy with temozolomide. Ivosidenib 500 mg orally every other day for *IDH1 R132H* alteration was added (dose reduced because it was given in conjunction with temozolomide). After completing a 6-month course of temozolomide, the patient continued on ivosidenib with standard dosing (500 mg orally daily). The patient has tolerated ivosidenib without significant side effects. Serial images with MRIs of the brain are without evidence of tumor progression and show only postsurgical changes (Fig. 2). He continues to work full-time at a job that requires high-level intellectual function. PFS at the time of last follow-up exceeded 52+ months.

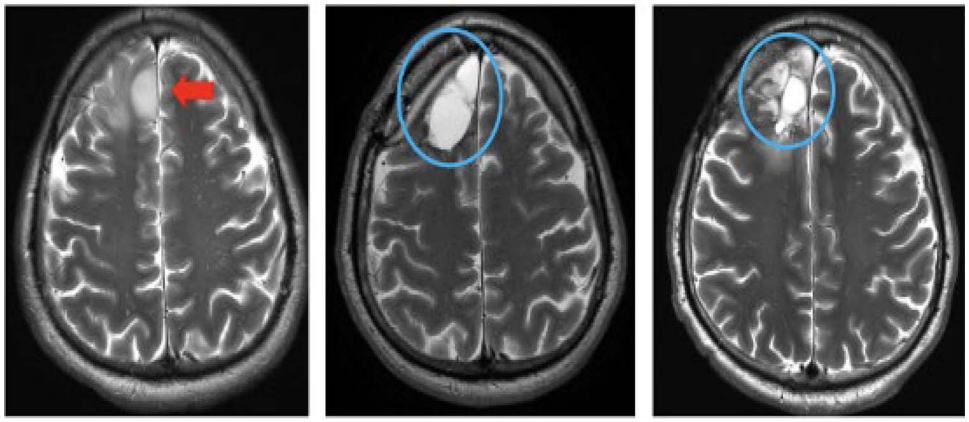

Figure 2. Serial magnetic resonance images of the brain for case 2 (T2 images). *Left*: Right frontal mass at the time of diagnosis (red arrow). *Middle* and *right*: MRI brain at 1 and 23 months after tumor resection, respectively (blue circle shows postsurgical change without disease recurrence). The patient was progression-free at 52+ months.

Case 3

A 66-year-old man with a history of WHO grade 2 oligodendroglioma (1p19q co-deleted, *IDH1 R132* mutated, MGMT methylated) initially presented with a seizure in February 2021 (Table 1). He underwent tumor resection followed by radiotherapy plus concomitant and adjuvant temozolomide until February 2022. Unfortunately, tumor recurrence in August 2022 required re-resection, and pathology was consistent with oligodendroglioma transforming into oligosarcoma (grade 4) (as read by neuropathologist, indicating aggressive appearance; classification not in WHO update).[10] The patient was treated with lomustine, but had radiographic progression of his tumor after 3 months. He subsequently started therapy with pembrolizumab and bevacizumab in December 2022 and, after a brief period of response, had further progression of the disease in February of 2023. He also had significant functional and clinical decline, with seizures and worsening neurological deficits, including difficulty walking, dysarthria, and left-sided weakness, leading to prolonged hospitalization. NGS testing (CARIS Life Sciences) of his tumor tissue showed *IDH1 R132* and *TP53 R282W* pathogenic mutations. He also had a high PD-L1 score of 25% (SP142 IHC stain, CARIS Life Sciences). Although hospice was considered and recommended based on the advanced neurologic deterioration and poor functional status, because of the above genomic findings, the patient was continued on bevacizumab (*TP53* mutation upregulates VEGFA, which can be targeted by anti–VEGF-based antibodies such as bevacizumab)[11–13] and pembrolizumab, but with the addition of ivosedinib at half dose (250 mg daily) to the treatment regimen to target *IDH1 R132* mutation.[14] The patient started treatment with this combination in February 2023 and had a clinical response with marked improvement in his neurological deficits. Follow-up MRI of the brain in April and August 2023 showed ongoing radiographic treatment responses. He was followed at home, and his pembrolizumab was stopped in July 2023 due to generalized body aches and joint pain; in September 2023, his bevacizumab was held because of a reduction in vasogenic edema. Unfortunately, in October 2023, the seizures recurred, and his neurologic condition deteriorated again; follow-up brain MRI showed worsening disease. PFS was approximately 8 months. The patient died in December 2023.

Case 4

A 28-year-old man presented to the emergency department in March 2019 with complaints of headache and balance loss. A mass and edema were identified in the right cerebral hemisphere on imaging. The patient underwent gross total resection in March 2019, with histopathological examination reported as GBM. MGMT was unmethylated, and *IDH* wild type. Postoperatively, standard adjuvant chemoradiotherapy that was followed by temozolomide was administered for six cycles.

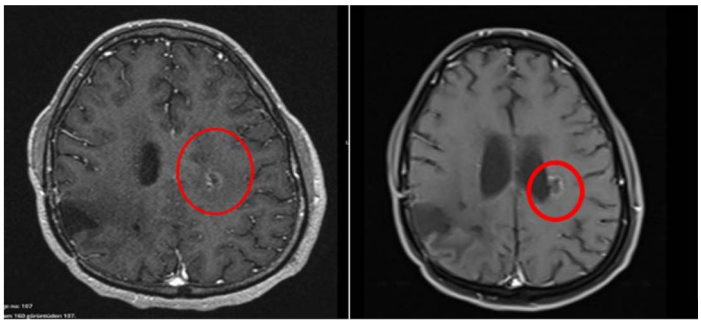

Figure 3. Serial magnetic resonance images of the brain for case 4 (T1 postcontrast images). *Left*: March 2021 images showing progression (accompanied by clinical worsening). Specifically, in the left cerebral hemisphere, a rim-shaped, 15-mm contrast-enhancing nodular lesion adjacent to the left lateral ventricle atrium in the parietal lobe with diffusion restriction (red circle) was observed. Compared with the prior exam (not shown), progression in the lesion size was noted, accompanied by edema. *Right*: December 2023 images show encephalomalacic changes without postoperative diffusion restriction adjacent to craniectomy. In the left cerebral hemisphere, a rim-shaped contrast-enhancing nodular lesion (11 mm) without diffusion restriction was seen. Compared with the March 2021 examination, regression was observed in lesion size, edema effect, and diffusion restriction The patient remained progression-free (complete remission) for 48 months on everolimus.

During follow-up, the patient experienced a headache in October 2020, and MRI revealed disease progression. Bevacizumab was initiated at a dose of 7.5 mg/kg IV every 2 weeks. The patient showed symptomatic improvement from the beginning of bevacizumab treatment. However, in February 2021, owing to radiological and clinical progression, temozolomide was reintroduced. Additionally, comprehensive genomic profiling (ACT-Onco/ACT Genomics; 440 gene panel) of the initial surgical specimen revealed *PTEN E7fs* and homozygous *TSC2* deletion (both of which activate mTOR signaling) with wild-type *IDH1/2* genes (Table 1). The patient had no stigmata consistent with tuberous sclerosis. As a result of the NGS findings, the patient was started oral everolimus (mTOR inhibitor) 10 mg daily in April 2021. The dose was reduced to 5 mg/day due to cough and suspected pulmonary toxicity. The tumor did not show progression for 48 months on everolimus (Fig. 3). The patient remains asymptomatic (no further toxicity), having a complete radiological response.

DISCUSSION

Herein, we present four patients diagnosed with pathology-confirmed high-grade gliomas who were treated with matched targeted therapy and had exceptional outcomes. Three of these patients presented with GBM (though in one case, because the tumor is *IDH1*-alteration positive, it would now be classified as WHO grade 4 astrocytoma, *IDH1* mutant[10]). In each case, the patient received a matched targeted drug or drugs individualized according to the patient's biomarkers. Two patients with GBM remain alive and in complete

remission for 39+ and 48 months. The patient with *IDH*-mutant grade 4 astrocytoma had PFS of 52+ months. The drugs used include imatinib and bevacizumab (case 1) to target *PDGFRA* and *KIT* amplification (imatinib) and *KDR* (*VEGFR2*) amplification. Bevacizumab is a VEGF-A antibody (VEGF-A activates both VEGFR1 and VEGFR2). Of interest, *PDGFRA*, *KIT*, and *KDR* reside on the same amplicon on the long arm of chromosome 4 (4q12), with amplification of this region found in 0.65% of 132,872 cancers, with GBM being enriched for 4q12 amplification (4.7% of cases).[8] For case 2, ivosidenib, an IDH1 inhibitor, was given for an *IDH1* mutation in a tumor initially diagnosed as a GBM (now called WHO grade 4 astrocytoma, *IDH1* mutant). Of note, for case 3 (patient with an oligodendroglioma transforming into grade 4 oligosarcoma on recurrence), the malignancy was also *IDH1* mutation-positive. This patient also had a PD-L1 IHC score of 25% and a *TP53* mutation (the latter was associated with elevation of VEGF/VEGFR signaling and correlated with a better response to the anti-VEGF antibody bevacizumab).[11–13] However, therapy with the anti-PD1 pembrolizumab together with bevacizumab failed to stop progression. When ivosidenib was added, the patient's clinical condition and imaging improved substantially, and this response lasted 8 months. Recently, vorasidenib, an *IDH1* and *IDH2* inhibitor, was shown to significantly prolong PFS when compared with placebo (27.7 vs 11.1 months) in patients with lower-grade (grade 2) *IDH*-mutant gliomas.[14,15] Our results suggest that targeting *IDH* in high-grade brain tumors with *IDH1* mutations may merit additional investigation.

Our fourth patient is also of significant interest. The tumor in this patient was a GBM, and he had recurrence after surgery, radiation, temozolomide, and bevacizumab. The tumor showed a *TSC2* pathogenic alteration and a *PTEN* alteration, both of which can activate mTOR signaling (patient had no stigmata of hereditary tuberous sclerosis). He was treated with the mTOR inhibitor everolimus and remained progression-free for 48 months. Tuberous sclerosis complex is a rare autosomal dominant disorder caused by mutations in either *TSC1* or *TSC2* genes; it presents with hamartomas in multiple organs, including the skin, central nervous system, kidney, and lung, as well as neuropsychiatric disorders. Brain lesions in tuberous sclerosis include cortical/subcortical glioneuronal tubers, subependymal glial nodules (SENs), and subependymal giant cell astrocytomas (SEGAs).[16] These tumor types were considered in the differential diagnosis, but no similarity with these tumors was detected in the histopathological analysis.

Alterations in *PTEN*, which activate the mTOR signal, occur in approximately 30–40% of GBM. *TSC1* and *TSC2* alterations also occur in GBM, albeit rarely, and similarly activate the mTOR signaling pathway. A teenager with GBM and a *TSC2* mutation with an excellent response to everolimus has been reported.[17] Notably, the Food and Drug Administration has approved the mTOR inhibitor nab-sirolimus for malignant perivascular epithelioid cell tumors (PEComas), which are characterized by alterations in *TSC1* and *TSC2* genes.[18]

In summary, these four patients with high-grade gliomas were treated with targeted treatments customized to their molecular alterations, and each patient attained exceptional responses. In three cases, the tumors showed no signs of progression after 3 years. The fourth patient had an aggressive tumor with sarcomatoid features.[19] Although causality cannot be inferred from case series, and these are not recognized salvage regimens, our observations suggest that individualized biomarker-based therapy merits additional prospective investigation in high-grade brain tumors, similar to that performed for other solid cancers.[20–22]

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