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# How We Treat Recurrent Glioblastoma Today and Current Evidence

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## Abstract

**Purpose of Review** Recurrent glioblastoma (rGBM) has no standard treatment. Despite a better molecular knowledge, few therapies have brought changes in clinical practice so far. Here we will review the current data evaluating the re-radiation, re-resection, bevacizumab, and cytotoxic chemotherapy agents in this setting. We will also discuss the advances of immunotherapy and the possible benefit of this treatment for patients with rGBM.

**Recent Findings** Next-generation sequencing is increasingly utilized in the clinical practice of neuro-oncologists, bringing gene mutations as targets for therapies. As in other solid tumors, immunotherapy has been also extensively studied in rGBM, with interesting results in phase I and II trials. The most promising therapies in the horizon are combinations including immune checkpoint inhibitors, virotherapy, vaccines, and monoclonal antibodies.

**Summary** Although re-radiation, re-resection, bevacizumab, and chemotherapy are still the most widely used therapies for treating rGBM, the clinical benefit from these treatments is still not well established. Preliminary results of studies with immune checkpoint inhibitors were disappointing, but virotherapy emerges as more promising immunotherapy in rGBM, especially in combination with other strategies. In addition to the gain in overall survival, the improvement in the quality of life of these patients is also expected.

**Keywords** Recurrent glioblastoma · Re-irradiation · Immunotherapy in gliomas · Virotherapy

## Introduction

The treatment of recurrent glioblastoma multiforme (rGBM) is one of the biggest challenges in neuro-oncology. With a median overall survival (mOS) of 9 months (1•), patients with rGBM usually face rapid decline in performance status and quality of life, and neurocognitive adverse effect from treatments is an important concern.

In 2015, gliomas were better classified in molecular subgroups (2••), which has helped clinicians to identify more aggressive tumors and anticipate patterns of recurrence and possible targeted therapies, aiming for a more personalized treatment. However, despite the improved knowledge of the disease, rGBMs invariably recur and there is no effective standard treatment.

This article reviews current treatment options and developing therapies in rGBM, and discusses the scientific evidence for each treatment approach.

## Re-resection

Although surgery is not curative even for a newly diagnosed GBM, the benefit of upfront gross total resection (GTR) and impact in overall survival (OS) are well established in the initial treatment (3). The role of a surgical resection of rGBM, however, remains unclear, with conflicting data. The data regarding the relationship of OS with re-resection in relapsed disease are limited due to retrospective study design and lack of randomization (4, 5•).

Only approximately 20 to 30% of patients with rGBM are candidates for a second surgery (6). In addition to the morbidity of the procedure, it is also necessary to consider the extent of the lesion that can be safely resected, since the extent of

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surgery may have an impact on survival (4). Sastry et al. analyzed retrospectively 368 rGBM patients, of which 77 had resection at the time of first progression. GTR was achieved in 26 (33.8%), and STR was achieved in 51 (66.2%) patients. rGBM patients who underwent resection for first progression had increased median post-progression survival (12.8 months vs. 7.0 months) and median follow-up (21.6 vs. 16.0 months) when compared with patients who did not have resection.

One of the largest and newest systematic review and meta-analysis, which included 8 observational studies reporting prognostic hazard ratios (HR) in 10 cohorts (7••), also favored the surgical approach in rGBM patients. In this systematic review, 709 (37%) out of 1906 rGBM patients underwent repeat surgery at recurrence. Repeat surgery was shown to confer a statistically significant survival advantage compared with no surgery at recurrence in the pooled cohort (HR, 0.722; $p < 0.001$). Additional data also showed that newer studies trended toward a more superior prognostic advantage of repeat surgery compared with earlier studies.

There are definitely patients who benefit from a re-resection. Time to first progression, extension of the initial surgery, size and location of relapse, and performance status are likely factors with greatest impact on the survival benefit with surgery in rGBM (5•). With regard to molecular features, the impact of resection in relations to O6-methylguanine–DNA methyltransferase (MGMT) promoter methylation status has also been addressed. Pala et al. identified 127 cases treated for rGBM that were retrospectively analyzed (8). Patients treated non-surgically had inferior OS (14 vs. 31 months). The benefit of surgical treatment has also been demonstrated in the subgroup of cases with unmethylated MGMT promoter rGBM. Those who underwent GTR survived significantly longer than patients who underwent subtotal resection (OS 31 vs. 15 months, $p = 0.024$), suggesting that even unmethylated patients, who have a worse prognosis, benefit from a new surgical approach.

## Re-radiation Therapy

Despite standard of care approach, the rate of local failure is prevalent in high-grade glioma patients and most recurrences develop within the initial radiation field (9). Salvage re-irradiation (ReRT) is feasible and increasingly available due to technological and imaging advances. Most data evaluating ReRT come from retrospective analyses and small prospective trials, with a median overall survival (mOS) ranging from 9 to 13 months.

Two prospective studies evaluated ReRT for rGBM. Laing et al. treated 22 patients with 30–50 Gy in 6–10 fraction, with mOS of 9.8 months with good tolerability (10). In the other study, a phase I dose escalation trial, Hudes et al. reported data on 25 lesions in 20 patients with rGBM re-irradiated with 24 Gy in 3 Gy to 35 Gy in 3.5-Gy fractions with mOS of 10.5 months, and there was no grade 3 toxicity. Additionally, 45% of patients improved neurologically and 60% had decreased steroid requirements (11).

Combs et al. evaluated the efficacy of fractionated stereotactic radiotherapy (FSRT) in 172 patients. With a median dose of 36 Gy (15 to 62) in a fractionation of 5 × 2 Gy/week, OS and PFS were 8 months and 5 months, respectively, for rGBM (12). Hypofractionated stereotactic radiotherapy (HFSRT) has also been shown to be well tolerated and be an effective re-irradiation option in rGBM (13). Fogh et al. reported the largest series with 147 recurrent high-grade glioma patients treated with HFSRT in median dose of 35 Gy in 3.5-Gy fractions, with mOS of 11 months. In a multivariate analysis, younger age, smaller gross tumor volume, and shorter time between diagnosis and recurrence were correlated with benefit in survival (14).

Stereotactic radiosurgery (SRS) allows high dose of radiation in a single fraction, and can be considered for a salvage treatment mainly for small and well-defined lesion. Most studies evaluating SRS have shown PFS between 8 and 12 months similarly as FSRT approach (15•).

Combinations with chemotherapy, mostly temozolomide, or an anti-VEGF therapy, such as bevacizumab, have been retrospectively shown to be safe and effective. Franceschi et al. evaluated the repeat use of temozolomide with ReRT and showed a disease control rate of 43% (objective response or stable disease) (16). Another small study evaluated 36 recurrent glioma patients re-RT using FSRT with daily concurrent temozolomide 75 mg/m$^2$/day resulting in a PFS-6 of 42%, being only MGMT methylation statistically significant for OS benefit ($p = 0.03$) (17).

Recently, 118 rGBM patients treated with bevacizumab and FSRT were retrospectively analyzed to determine the optimal sequence of these two treatments in rGBM; however, the sequence of bevacizumab and FSRT administration at recurrence did not provide significant difference in OS (18).

Toxicity is an important concern for re-irradiation. Acute side effects may include headache, fatigue, permanent alopecia, and dermatitis (15•, 19). Late toxicity is often progressive and irreversible based on vascular changes, demyelination, and necrosis with neurocognitive and functional deficits frequently seen in long-term survivors. Radionecrosis is a major concern among late adverse events, and risks are increased when the primary radiation dose is 60 Gy or higher, in addition to a short interval between primary and ReRT (15•, 19).

Re-irradiation is reasonable in rGBM, as it has been shown to be active and well-tolerance based on small studies. A meaningful survival benefit with ReRT is yet to be defined since there is a lack of comparative trials. Local treatment for recurrence is better planned in an interdisciplinary team discussion considering factors such as histology, eloquent area,

age, tumor size, time to progression, prior therapies, and performance status.

## Alternating Electric Fields or Tumor-Treating Fields

The Optune system (Novocure, St. Helier, Jersey Isle, UK), initially called NovoTTF-100A, uses pre-set, low-intensity alternating electrical fields at an intermediate frequency of 200 kHz to create "tumor-treating fields" (TTF). The TTF penetrate cell walls to disrupt rapid cancer cell division and cause cell death (20).

A phase 3 study was conducted randomizing rGBM patients to TTF alone or physician's choice chemotherapy (21•). The study was designed to assess TTF arm superiority, and the primary endpoint was OS. The transducer arrays were placed on the patient's shaved scalp and connected to a portable battery or a power supply operated device. The TTF treatment needed to be administered continuously, for at least 20 h per day. After inclusion of 237 patients, mOS was 6.6 versus 6.0 months (HR 0.86; 95% CI 0.66–1.12), 1-year survival rate was 20% and 20%, and PFS rate at 6 months was 21.4% and 15.1% ($p = 0.13$), respectively in TTF and active control patients.

Although no demonstrated gain in OS was observed in this phase 3 trial, consensus-based guidelines published by the National Comprehensive Cancer Network (NCCN) include TTF therapy as a treatment option for patients with rGBM based on the trial data reviewed above as well as post-marketing analysis of > 450 patients treated commercially in the USA (22). However, rGBM patients often opt of out this treatment option, likely due to the discomfort of frequent need for shaving hair, and the need to keep the device on for prolonged hours each day, as these patients often desire to maximize quality of life.

## Cytotoxic Chemotherapy and Bevacizumab

Despite the lack of standard chemotherapy regimen in rGBM, cytotoxic chemotherapy is usually the preferred second-line treatment option for rGBM. Multiple meta-analyses have demonstrated the activity of alkylating agents in GBM, especially lomustine and carmustine. After the combination of radiotherapy and temozolomide became the standard treatment in newly diagnosed GBM (23), these alkylating agents have been extensively used in recurrent disease. However, the median PFS described in patients after relapse using these alkylating agents has been no longer than 2 months (1•, 24). The benefit is most pronounced for MGMT promoter–methylated patients (25•), and in those who undergo re-resection, where the use of lomustine after the surgery demonstrated a median PFS of 7 months (25•).

Temozolomide rechallenge can also be a reasonable option at recurrence. However, it is important to identify patients who are likely to benefit from this, such as patients with MGMT promoter–methylated tumors (26•) and treatment-free interval since last adjuvant temozolomide cycle longer than 5 months (27).

Bevacizumab, a recombinant humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF), binds to VEGF and inhibits VEGF receptor binding, thereby preventing the growth and maintenance of tumor blood vessels. After the significant response rate and clinical benefits in randomized phase II studies, the FDA approved bevacizumab for rGBM in 2009. Unfortunately, bevacizumab has not shown to extend OS in rGBM in phase 3 studies as a single agent nor combined with chemotherapy (1•). It is important to note that, in these studies, the crossover of patients was allowed and around 75–85% of the total patients included received the anti-VEGF monoclonal antibody.

A retrospective study using US population-based cancer registry data (SEER) compared OS of patients diagnosed with GBM before and after bevacizumab approval (2009) (28•), including over 12,800 patients. The results of this large population-based study suggested an improvement in OS among patients with a GBM diagnosis in 2010–2012 compared with 2006–2008. While the cause of this improvement cannot be proven in a retrospective analysis, the timing of the survival increase coincides with the approval of bevacizumab for the treatment of patients with progressive GBM, indicating a possible benefit of bevacizumab in this population. Probably a subgroup of tumors responds to bevacizumab (Fig. 1). However, there are currently no molecular markers that can identify them.

## Immunotherapy

### Immune Checkpoint Inhibitors

Macrophage and tumor cell populations upregulate cell surface receptors, particularly programmed cell death ligand 1 (PD-L1). PD-L1 bind to checkpoint receptors, such as programmed cell death (PD-1), on the surface of T cells, inhibiting T cells from attacking them through their recognition of tumor neoantigens as "foreign" (29). Immune checkpoint blockade utilizing antibodies directed against these inhibitory pathways has shown clinical efficacy in several solid tumors.

The rationale for using immune checkpoint inhibitors in the treatment of GBM has stemmed from several preclinical and clinical findings that revealed high PD-L1 expression in newly

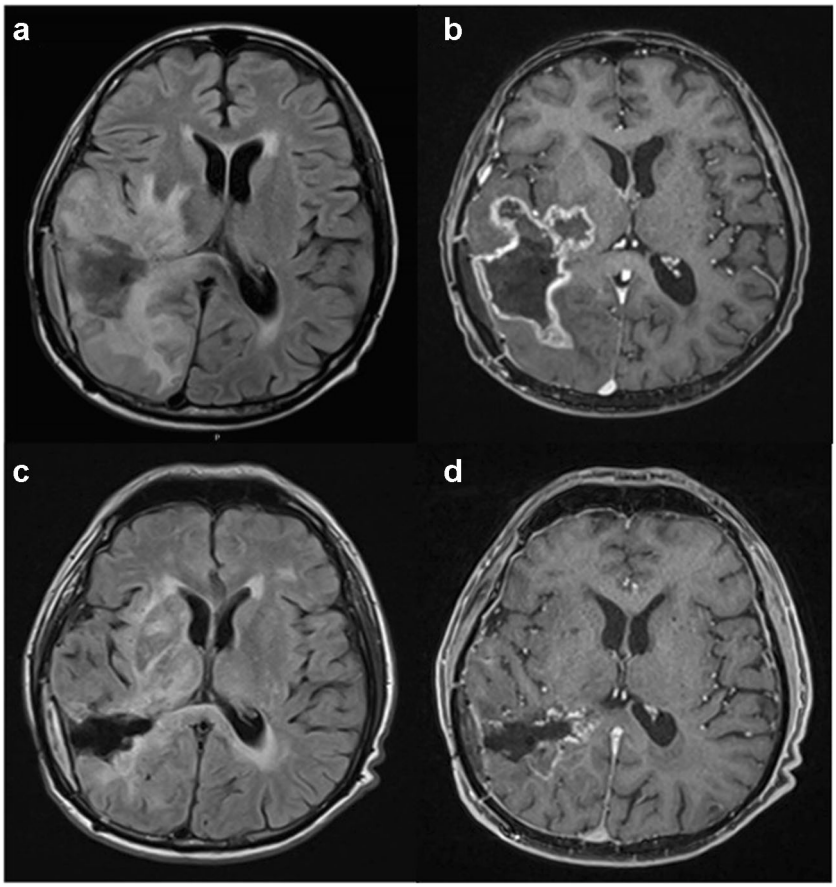


**Fig. 1** Unmethylated rGBM patient treated with bevacizumab after a biopsy-proven progression on temozolomide. T2 FLAIR (**a**) and T1 post contrast (**b**) are MRI images in October 2017 prior to starting bevacizumab. T2 FLAIR (**c**) and T1 post contrast (**d**) MRI images in October 2018 showed decrease in enhancing disease and surrounding edema, and sustained response

diagnosed as well as recurrent GBM, which correlated with worse clinical outcome (30).

Several ongoing clinical trials are evaluating the activity of immune checkpoint inhibitors in rGBM patients, including pembrolizumab, ipilimumab, and nivolumab. A recently completed phase III randomized trial involving patients with rGBM failed to demonstrate a survival benefit with nivolumab (31••). Published results from the phase I portion of the trial demonstrated a 40% 12-month OS in patients treated with nivolumab alone and no clinical benefit with increased toxicity with the addition of ipilimumab (32••).

A phase 2 study showed promising results in rGBM patients who were given pembrolizumab before re-resection (33). Thirty-five patients with recurrent, surgically resectable GBM were randomized to receive neoadjuvant and adjuvant pembrolizumab or just the adjuvant immune checkpoint inhibitor to evaluate the immune response and survival. Patients who received neoadjuvant pembrolizumab, with continued adjuvant therapy following surgery, had significantly extended OS compared with patients that received just the post-surgical PD-1 blockade alone (mOS 417 vs. 228 days; HR = 0.39, $p = 0.04$).

In a single-arm phase 2 trial, 15 patients with rGBM were treated with up to two doses of pembrolizumab prior to surgery and subsequently received pembrolizumab until disease progression or the development of unacceptable toxicities (34•). Median PFS was 7 months (95% CI 4–16), and mOS was not reached (95% CI 15 to not reached), with an estimated 1-year overall survival of 72% (52–99.6%). Analysis revealed that GBM tumors were markedly enriched with CD68+ macrophages but had a paucity of effector T cells. The high predominance of immunosuppressive CD68+ myeloid cells and a marked scarcity of T cells within the tumor microenvironment may be limiting the activity of PD-1 blockade.

Although immune checkpoint inhibitors have had dramatic success in the treatment of other advanced solid tumors, evidence to date demonstrates that novel approaches or combinations will likely be needed to achieve clinical benefits with these drugs in patients with rGBM.

## Vaccines

The rationale behind the development and use of cancer-associated vaccines is to stimulate the immune system to generate a humoral and immune response to tumor antigens, which can induce potent antitumor immunity, target tumor cells specifically, and provide surveillance against tumor recurrence through long-lasting immunologic memory.

One of the difficulties in the development of vaccines is the choice of tumor peptide, which ideally must have high

specificity and high incidence in the disease. Because of this, EGFRvIII was one of the first GBM-peptides used in the development of vaccines for GBM patients. In a phase II trial, the tolerance and activity seemed promising in patients with rGBM when a vaccine (rindopepimut) was combined with bevacizumab (35•), inducing potent EGFRvIII-specific immune response and tumor regression. However, the only randomized clinical phase 3 study using rindopepimut combined with standard treatment in newly diagnosed GBM failed to demonstrate overall survival gain (36••).

## Viral Therapy

Viral therapy can be divided into 2 groups: (1) replication-competent oncolytic viruses (OV) and (2) replication-deficient viral vectors used as a delivery mechanism for therapeutic genes (37). OV are designed to selectively target, infect, and replicate in tumor cells, while sparing the surrounding normal brain parenchyma (37). In the multiple OV being studied for gliomas, such HSV-1, the genes involved in oncolysis are distinct from the genes for neurovirulence, allowing for genetic manipulation that permits conditional replication and oncolysis of tumor cells (38).

Although intratumoral or resection bed inoculation is the most studied and simplest method of introducing viral vectors into high-grade gliomas, the mechanism of administration of OV remains non-standardized (37). Current approaches include simple injection versus attempts at convection-enhanced delivery, and systemic vascular delivery (intra-arterial and intravenous). The first method has the advantage of bypassing the blood–brain barrier and can introduce a high concentration of virus directly into the tumor. It has been shown that OV are neutralized through nonspecific attachment to serum proteins and circulating cells existing in the bloodstream (39).

Many preclinical studies have had encouraging results, but only a few modified OV have positive published data in phase 1 and 2 studies regarding safety, toxicity profile, and efficacy in rGBM patients. Preliminary data of phase 1 study with DNX2401 (formerly known as DELTA-24-RGD) oncolytic adenovirus was first presented in 2004, but results were published in 2018 (40••). This trial was a dose-escalation study in rGBM with two arms, A and B. Patients in group A received a single intratumoral injection of DNX-2401 into biopsy-confirmed recurrent tumor to evaluate safety and response across eight dose levels. In group B, patients underwent intratumoral injection followed 14 days later by en bloc resection to acquire post-treatment specimens. No dose-limiting toxicities were observed in the study; therefore, a maximum tolerated dose was not identified. In group A ($n = 25$), 20% of patients survived more than 3 years from treatment, and 3 patients had a $\geq 95\%$ reduction in the enhancing tumor (12%), with all three of these dramatic responses resulting in 3 years of PFS from the time of treatment. Analyses of post-treatment surgical specimens (group B, $n = 12$) showed that DNX-2401 replicates and spreads within the tumor, documenting direct virus-induced oncolysis in patients.

Recently, interim results of a phase 2 trial combining DNX-2401 with pembrolizumab were presented (41••). A single intratumoral dose of DNX-2401 was administered via cannula, followed 7 days later by 200 mg pembrolizumab every 3 weeks for up to 24 months or until confirmed progression or intolerable toxicity. From a total of 23 patients treated so far, preliminary efficacy includes two partial responses and 100% 9-month survival for the first 7 patients treated. Several cases of vasogenic edema have been managed with steroid tapers or low-dose bevacizumab.

Regarding nonlytic virus used as a delivery mechanism for therapeutic agents, Toca 511 (vocimagene amiretrorepvec) has been studied in a phase 1 trial for rGBM (42). Patients were submitted to a tumor resection and received Toca 511 under direct visualization by multiple injections into the walls of the resection cavity. Six weeks after the procedure, Toca FC (extended release 5-fluorocytosine) was administered for 7 days every 4 to 8 weeks in repeat cycles until radiological tumor progression. Toca 511 delivers a yeast cytosine deaminase gene to replicating cells. Cytosine deaminase expresses an enzyme that converts the prodrug Toca FC to 5-fluorouracil (5-FU), which usually is inefficient at crossing the blood–brain barrier. However, the combination of Toca 511 and Toca FC solves this problem because conversion to 5-FU occurs after 5-fluorocytosine has already crossed the blood–brain barrier into Toca 511–infected cells. The therapy combination treatment showed a favorable safety profile and better OS (13.6 months 95% CI 10.8 to 20.0) and was statistically improved relative to an external control using lomustine (HR 0.45; $p = 0.003$). An international phase 2/3 trial in patients with rGBM is underway.

There is an optimism regarding viral therapy for rGBM because there are encouraging results so far, with rGBM patients showing durable responses. Clinical phase 2/3 trials are ongoing, some of them in a combination with chemotherapy or immune checkpoint inhibitors (41••, 43), and results are being eagerly awaited.

## Next-generation Sequencing and Target Therapy

Genomic research of gliomas has revealed complex biology with potential for therapeutic impact (44). Despite the progress made in recent years, translating these advances in sequencing technologies into meaningful clinical information for patients with CNS malignancies remains challenging.

In rGBM, NGS emerges as a great opportunity for target therapy. However, although many NGS tests are

commercially available, the first step in the success of a personalized treatment is to understand the importance of a described pathway in the biology of the disease.

In a capture-based NGS genomic analysis assay of 236/315 cancer associated genes, Blumenthal et al. (44) identified a total of 241 alterations in 62 genes of 43 high-grade glioma patients, with a median of genomic alteration per patient of 4.5 (range 1–23). The most common genomic alteration detected was loss of CDKN2A/B gene (49%), followed by alterations in TP53 (44%), EGFR (40%), PIK3CA (28%), PTEN (28%), and IDH1 (19%). For a cohort of 25 GBMs, TERT promoter mutations were detected in eight cases (32%). EGFR, the epidermal growth factor receptor, was the most common therapeutically actionable mutated gene revealed in their cohort. They also reviewed clinical utility and response rates in correlation to NGS results. Thirteen of the patients in their series were treated with targeted agents according to their sequencing genotype results, representing a decision impact of 30%.

In light of increasing knowledge about incidence of mutations in GBM, multiple trials involving target therapy has been conducted. EGFR is the most studied mutation in rGBM, and multiple studies targeting EGFR have been conducted. Studies with tyrosine kinase inhibitors, like erlotinib and lapatinib, failed to demonstrate benefit in survival. However, update results of a phase II trial with depatuxizumab mafodotin, an EGFR monoclonal antibody conjugated to a tubulin inhibitor, showed clinical benefit (45). Depatuxizumab mafodotin plus temozolomide improved OS compared with lomustine or temozolomide alone in patients with EGFR-amplified rGBM, with 1-year OS 40 versus 28%, respectively.

Another promising target for therapy in gliomas is BRAF mutations such as V600E and fusion. The inhibition of the BRAF pathway has shown to be effective in the rGBM treatment. A basket trial conducted at Memorial Sloan Kettering Cancer Center showed activity of a BRAF inhibitor, vemurafenib, in recurrent gliomas with BRAF V600E mutation (46). Eleven BRAF V600E recurrent malignant glioma patients were included, and 6 had clinical benefit (stable disease or partial response), demonstrating the importance of this pathway in the progression of the disease.

## Conclusion

Despite aggressive surgery, radiation, and systemic chemotherapy, the prognosis for patients with GBM remains extremely poor. In recurrent disease, this is made worse by the absence of effective therapies. Re-radiation therapy and systemic treatment using combination with bevacizumab are still the most widely used therapies, although there is no robust scientific evidence demonstrating OS benefit.

Regarding immunotherapy, preliminary results from studies with immune checkpoint inhibitors have not shown desired results. However, increasing knowledge about the tumor microenvironment and better understanding of the CNS immune system, and good preliminary results of phase 1 trials with virotherapy suggest that combining multiple modalities of immunotherapy is still likely to be promising in treatment for rGBM.

There is a significant effort by the neuro-oncology community to include rGBM patients in clinical trials, aiming to establish more effective strategies against brain tumors. Furthermore, the NGS tests have become more accessible in the past decade, which has led to a better understanding of brain tumor biology and to better clinical trial design. It is important that these patients are cared for by a multidisciplinary team, including neuro-oncology, radiology, radiation oncology, and neurosurgery.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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