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Clinical Investigation

Multicenter, Phase 1, Dose Escalation Study of Hypofractionated Stereotactic Radiation Therapy With Bevacizumab for Recurrent Glioblastoma and Anaplastic Astrocytoma

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Summary

Contemporary RT techniques allow for highly accurate targeting of infiltrating tumor and more aggressive dosing regimens. Recent trials have explored

Purpose: To establish the maximum tolerated dose of a 3-fraction hypofractionated stereotactic reirradiation schedule when delivered with concomitant bevacizumab to treat recurrent high-grade gliomas.

Methods and Materials: Patients with recurrent high-grade glioma with Karnofsky performance status $\geq$60, history of standard fractionated initial radiation, tumor volume at recurrence $\leq$40 cm^3, and absence of brainstem or corpus callosum involvement were eligible. A standard 3+3 phase 1 dose escalation trial design was utilized, with dose-limiting toxicities defined as any grade 3 to 5 toxicities possibly, probably, or

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the safety and feasibility of hypofractionated stereotactic reirradiation for recurrent gliomas. Taking advantage of improved RT tolerance afforded by the combination with bevacizumab, we explored escalating doses of hypofractionated stereotactic reirradiation and found that doses up to 33 Gy delivered in 11 Gy × 3 fractions were reasonably safe and well-tolerated, with promising overall survival of 13 months.

definitely related to radiation. Bevacizumab was given at a dose of 10 mg/kg every 2 weeks. Hypofractionated stereotactic reirradiation was initiated after 2 bevacizumab doses, delivered in 3 fractions every other day, starting at 9 Gy per fraction.

Results: A total of 3 patients were enrolled at the 9 Gy × 3 dose level cohort, 5 in the 10 Gy × 3 cohort, and 7 in the 11 Gy × 3 cohort. One dose-limiting toxicity of grade 3 fatigue and cognitive deterioration possibly related to hypofractionated stereotactic reirradiation was observed in the 11 Gy × 3 cohort, and this dose was declared the maximum tolerated dose in combination with bevacizumab. Although no symptomatic radionecrosis was observed, substantial treatment-related effects and necrosis were observed in resected specimens. The intent-to-treat median overall survival was 13 months.

Conclusions: Reirradiation using a 3-fraction schedule with bevacizumab support is feasible and reasonably well tolerated. Dose-escalation was possible up to 11 Gy × 3, which achieves a near doubling in the delivered biological equivalent dose to normal brain, in comparison with our previous 6 Gy × 5 schedule. Promising overall survival warrants further investigation.

Introduction

Chemoradiotherapy with temozolomide is widely accepted as the standard initial treatment for newly diagnosed high-grade gliomas (HGGs) (1, 2). However, tumor progression or recurrence remains the norm, and salvage therapy options are limited, typically achieving median overall survival (OS) of 6 to 9 months (3-5). With the main pattern of failure remaining local recurrence (6), improved survival requires optimized local control. Historically, the use of salvage reirradiation has been limited by concerns of toxicity and potential injury to functional brain. More recently, advances in stereotactic radiation have significantly reduced the potential toxicity of reirradiation, because high precision targeting allows for better delineation of radiation margins and maximal sparing of normal brain tissue. A variety of regimens have been used, with total doses from 25 to 36 Gy, delivered in fraction sizes ranging from 3 to 9 Gy (7). Although prior studies all demonstrated the feasibility and safety of reirradiation in HGGs, in-depth clinical comparison of outcomes is difficult owing to differences in patient selection, previous pretreatment profiles, and variable use of concomitant chemotherapy, in addition to the variability in radiation treatment techniques, total dose, and dose per fraction. As such, the optimal total radiation dose and fractionation regimen remain unclear (8).

The premise for this phase 1 trial was based on a previous study investigating hypofractionated stereotactic reirradiation (HFSR) of 30 Gy delivered in 5 fractions in combination with bevacizumab for patients with HGG (9). The regimen was well-tolerated and demonstrated promising efficacy, with a median OS of 12.5 months. Within that trial the majority of patients still had local recurrence within the field of reirradiation (10). This raised the question of whether higher doses of radiation would be safe and, if so, more effective in preventing local tumor recurrence. Importantly, none of the patients in the previous trial had developed symptomatic radiation necrosis. Although the advantage of adding an anti−vascular endothelial growth factor (VEGF) drug such as bevacizumab to reirradiation has not been fully elucidated, there is mounting evidence supporting its role in mitigating the risk of symptomatic radiation necrosis and allowing for more-aggressive HFSR doses (9, 11-14). On the basis of the hypothesis that HFSR could be further escalated when used with bevacizumab, we designed this phase 1 trial with the primary objective of establishing the maximum tolerated dose of a 3-fraction HFSR schedule when delivered with concomitant bevacizumab to treat recurrent HGGs.

Methods and Materials

Patients

This investigator-initiated prospective study protocol was registered at clinicaltrials.gov (NCT01392209). The protocol and informed consent were approved by each participating institution's institutional review board. Written, informed consent was obtained from all patients. Roche provided bevacizumab and partial funding.

The inclusion criteria included histologically confirmed grade 3 or 4 glioma with imaging or pathologic evidence of recurrence, and tumor volume $\leq$40 cm^3. Patients must have received prior treatment of approximately 60 Gy of radiation therapy, and have Karnofsky performance status (KPS) $\geq$60, age $\geq$18 years, and adequate bone marrow and organ function. Exclusion criteria included multicentric disease, disease infiltrating the corpus callosum or the brainstem, prior use or contraindication to the use of bevacizumab, prior treatment with radiosurgery, and suspected or documented radionecrosis. Therapeutic anticoagulation (eg, for venous thromboembolism) was allowed.

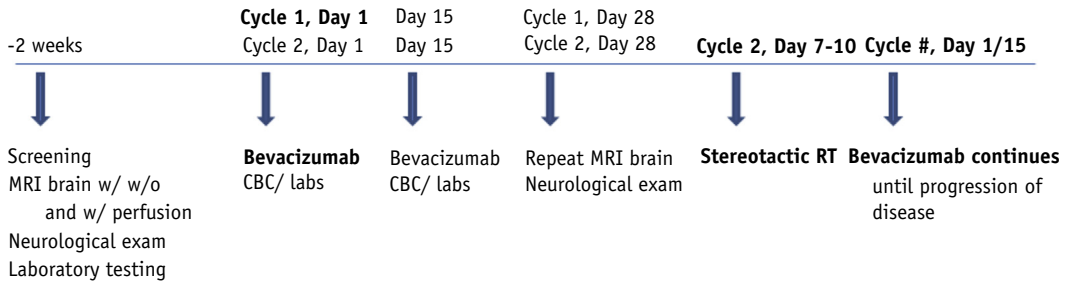

Fig. 1. Treatment schema. *Abbreviations:* CBC = complete blood count; RT = radiation therapy.

Treatment

The study treatment schema is shown in Figure 1. Patients received bevacizumab at a dose of 10 mg/kg intravenously once every 2 weeks on days 1 (±3 days) and 15 (±3 days) of each 28-day cycle. On day 28 (±4 days) the MRI was repeated for HFSR planning. If tumor size remained within study parameters, HFSR was started within days 7 to 10 of cycle 2, with a total of 3 treatments given on an every-other-day schedule (eg, Monday/Wednesday/Friday). Intensity modulated radiation therapy was utilized, with the initial reirradiation dose consisting of 9 Gy × 3 fractions, estimated to deliver a biologically equivalent dose only moderately higher in comparison with the 6 Gy × 5—fraction regimen given in the prior phase 2 study (9).

Magnetic resonance imaging scans were performed at baseline, then at the end of cycle 1 for radiation treatment planning, at the end of cycle 2, and then every second cycle thereafter until disease progression. T1 postcontrast and T2 fluid-attenuated inversion recovery images from postcycle 1 MRI were fused to the treatment planning CT scan to define the gross tumor volume (GTV), which encompassed T1 postcontrast enhancing disease; at the discretion of the treating radiation oncologist, mass-like T2/fluid-attenuated inversion recovery abnormality could be included in the GTV, provided other treatment parameters were followed. The planning treatment volume consisted of the GTV plus a 2- to 5-mm margin at the discretion of the treating radiation oncologist. The prescription dose covered a minimum of 95% of the planning treatment volume.

Blood pressure was monitored every other week. Complete blood count with differential was obtained every other week for the first 2 cycles and then once every cycle. Urine protein/creatinine ratio and chemistries including blood urea nitrogen, creatinine, sodium, potassium, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, total bilirubin, and total protein were measured every cycle until disease progression. Neurologic and physical examinations with KPS were performed after cycles 1 and 2, then after every 2 cycles.

Statistical design

A standard 3+3 statistical design was used. Dose-limiting toxicities (DLTs) were defined as any grade 3 to 5 radiation injury or any nonhematologic toxicity thought to be possibly, probably, or definitely related to radiation or the combination of radiation and bevacizumab, identified within the evaluation period of 3 months following the completion of radiation therapy. Patients were deemed evaluable for DLT assessment if they received at least 1 dose of reirradiation. Toxicities thought to be solely due to bevacizumab were not considered DLTs.

Because of the possibility of late toxicities developing after the 3-month DLT evaluation period, a safety stopping rule was also applied. If during the course of the trial more than 2 grade ≥3 late toxicities occurred at or below the highest radiation dose assigned at that point, accrual would be stopped, and the institutional Data and Safety Monitoring Committee would be consulted. Upon review of all toxicities, 1 or more of the following decisions would be made: (*1*) to proceed with the 3+3 design; (*2*) to discontinue accrual to the dose associated with the late toxicity or any dose above it; (*3*) to suspend the study and allow for a sufficiently long follow-up period to monitor late toxicities; and/or (*4*) to evaluate a lower dose.

Exploratory efficacy analyses consisted of response rate utilizing Neurologic Assessment in Neuro-Oncology criteria (15), as well as progression-free survival and OS, using Kaplan-Meier methodology.

Results

Patient characteristics

Table 1 illustrates the characteristics of the 15 patients with recurrent HGGs enrolled in the study. Eighty percent of the patients were men; median age was 63 years, median KPS was 90, and 67% had glioblastoma. Methylation status was known in 8 cases; 75% of these were unmethylated. Mean enhancing tumor size at largest diameter was 2.65 cm. Patients had received a median of 2 prior lines of treatment, with 60% having experienced 2 or more recurrences. Median time from initial diagnosis to study enrollment was

Table 1 Patient characteristics

Characteristics (n = 15)	Value
Sex	
Men	12 (80)
Women	3 (20)
Age (y)	
Median (range)	63 (50-73)
<60	5 (33)
≥60	10 (67)
Histology	
Glioblastoma	10 (67)
Anaplastic astrocytoma	5 (33)
KPS, median score (range)	90 (70-100)
MGMT methylation status	
Unknown	7 (47)
Unmethylated	6
Methylated	2
Prior salvage chemotherapies	
Median (range)	2 (1-3)
1 prior treatment, n	6
2 prior treatments, n	8
3 prior treatments, n	1
Mean (range) tumor size at largest diameter (cm)	2.65 (1.8-5.37)

Abbreviation: KPS = Karnofsky performance status.
Values are number (percentage) unless otherwise noted.

14.3 months. At the time of study enrollment, 5 patients were 7 to 12 months from initial diagnosis, 4 patients were 12.1 to 18 months from initial diagnosis, and 6 patients were >18 months from initial diagnosis. Though it was not feasible to collect detailed prior radiation treatment plans for review, the recurrences for all patients were local and would have been at least partially within the original high-dose field.

Treatment and toxicity

Three patients were enrolled into cohort 1 (9 Gy × 3), and all were evaluable, with no DLTs observed. A total of 5 patients were enrolled into cohort 2 (10 Gy × 3), 2 of whom were deemed nonevaluable for DLT at the end of cycle 1 owing to disease progression that exceeded the tumor volume limit of 40 cm^3, preventing the use of HFSR. For the 3 evaluable patients treated with HFSR, there were no DLTs. Four patients were enrolled in cohort 3 (11 Gy × 3); 1 patient came off study at the end of cycle 1, before initiating HFSR, owing to a grade 1 ischemic stroke observed on the MRI. Of the 3 patients evaluable for DLT, 1 patient had grade 3 fatigue and cognitive deterioration, which was deemed a DLT. As per the 3+3 design, that cohort was expanded with 3 additional patients, but no other DLTs were observed. Of note, 1 of the patients treated at this dose level developed a grade 2 ischemic stroke within the original radiation field but outside the reirradiation field. This grade 2 toxicity was thought to be potentially related to bevacizumab but not directly related to reirradiation and was not considered a DLT. However, from unanimous decision among investigators, further dose escalation was not attempted, and 11 Gy × 3 was deemed the MTD.

Table 2 Grades 3 and 4 toxicities deemed definitely, possibly, or likely related to study treatment (n = 15)

Toxicity	Grade 3	Grade 4
Fatigue	2	0
Hypertension	1	1
Central nervous system necrosis	1	0
Meningitis	1	0
Leukopenia	1	0
Lymphopenia	1	0
Neutropenia	1	0
Hyponatremia	1	0
Skin infection	1	0
Infections and other infestations	1	0
Muscle weakness	1	0

No grade 5 toxicities were observed.

For those patients who received HFSR on study, reasons for being removed from study included disease progression in 8 cases, toxicity in 2, 1 case of a prolonged treatment hold, and another patient who decided to withdraw for logistic reasons but who continued to receive bevacizumab as per protocol locally and was still followed for efficacy.

Toxicities associated with bevacizumab were in line with studies of single-agent bevacizumab. A summary of all grade 3 to 5 toxicities is shown in Table 2.

Exploratory efficacy analysis and patterns of recurrence

Given the small number of patients, analysis of efficacy is exploratory only; response assessment was performed using the Neurologic Assessment in Neuro-Oncology criteria (15). On the intent-to-treat basis (N = 15), the median OS (Fig. 2A) from time of treatment initiation was 13 months (95% confidence interval 10-15 months), and the median progression-free survival (Fig. 2B) was 7 months (95% confidence interval 4-9 months). Figure 3 shows response rate after initial bevacizumab treatment and best response after HFSR for the 12 evaluable patients for response. The objective response rate (complete response + partial response) was 21% before HFSRT (3 partial responses) and increased to a best response after HFSR of 50% (6 partial response and 1 complete response). Among the 12 patients who received reirradiation on study, 4 (33%) had distant recurrences, and 8 (67%) had local recurrences. Three patients underwent surgical resection for suspicion of tumor progression after HSFR. All patients had persistent tumor, although substantial treatment-related changes and necrosis were also present on histologic examination in all 3. In 1 of those patients, necrosis accounted for more than 90% of the sample, and this patient was deemed to have a treatment-

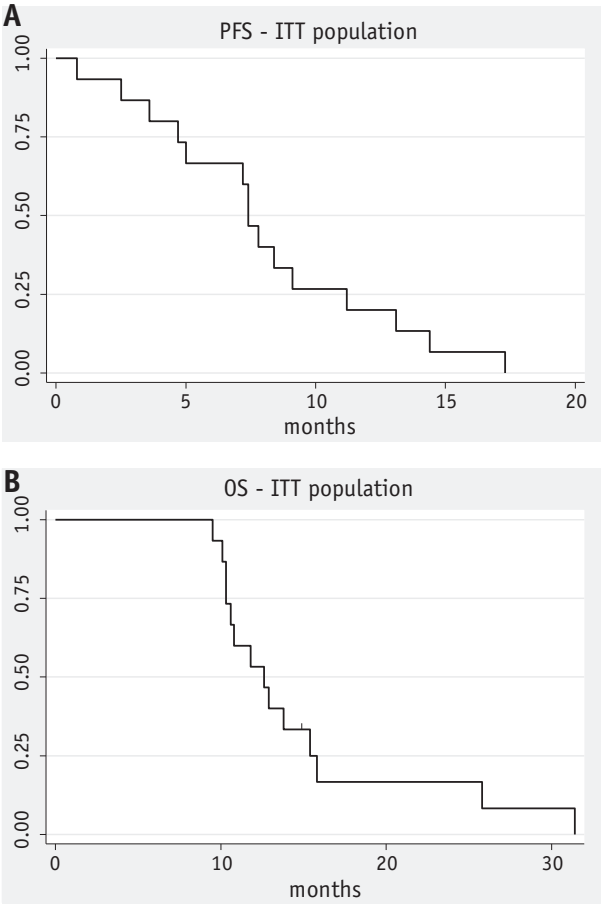

Fig. 2. (A) Progression-free survival (PFS, all patients, intent-to-treat [ITT] population, N = 15). (B) Overall survival (OS all patients, intent-to-treat population, N = 15).

related central nervous system necrosis, Common Terminology Criteria for Adverse Events grade 3.

Discussion

Recurrent HGGs carry a poor prognosis, and currently there are limited salvage treatment options. None of the frequently used therapies, including single-agent bevacizumab, nitrosoureas, or tumor treatment fields, have been shown to improve survival (3, 4). Although the efficacy of radiation therapy in gliomas remains undisputable, historical consensus has been against reirradiation for these patients because of associated risks of neurotoxicity (16) deriving from conventional external beam techniques. However, recent advances in radiation therapy techniques, particularly intensity modulated radiation therapy stereotactic technology, have allowed for more accurate spatial targeting and delivery of higher biologic doses to the infiltrating tumor, particularly in hypofractionated schedules. The widespread use of such techniques has revived interest in HFSR as an attractive treatment option for both newly diagnosed (14) and recurrent gliomas.

The rationale for hypofractionation is based on increased tumor cell kill as a direct result of higher radiation dose per fraction, reduction in tumor cell repopulation, and enhanced activity on glioma stem cells. Moreover, the convenience of a condensed treatment schedule is an important consideration, especially in patients with recurrent glioma, who often have poor performance status, limited mobility, and a short expected life span. Overall, data from studies using reirradiation at disease recurrence, alone (17-30) or in combination with temozolomide (31-37), nitrosourea (38), sorafenib (39), sunitinib (40), gefitinib (41), panobinostat (42), or bevacizumab (12, 13, 38, 43) support a therapeutic benefit with minimal toxicity. In particular, most of these studies have consistently reported a median OS in excess of 10 months, which compares favorably to available salvage chemotherapy or biologic therapies that typically achieve median OS of 7 to 9 months. However, it must be noted that with few exceptions (9, 40, 41), the vast majority of these studies are retrospective, therefore carrying inherent limitations and potential selection bias.

Maximizing the dose of HFSR at reirradiation must be weighed against the risk of injury to normal brain tissue, with substantial sequelae associated with resulting radiation necrosis. Here lies the potential role of adding an anti-VEGF drug, such as bevacizumab, with the intent of preventing symptomatic radiation necrosis and minimizing corticosteroid use. Bevacizumab, a monoclonal antibody against VEGF, was granted accelerated approval by the US Food and Drug Administration in May 2009 for the treatment of recurrent glioblastoma and is commonly used for recurrent disease (44, 45). It has been hypothesized that the addition of bevacizumab has the potential to produce an advantageous balance between normal brain protection from radiation injury through improvements in brain tolerance to radiation therapy and enhanced cytotoxicity of radiation on tumor cells and their neovasculature. It is theorized that the synergy of this combined therapy sensitizes the tumor endothelia to the delivered radiation, disrupts paradoxical angiogenesis, and induces apoptosis through the disinhibition of VEGF (9, 13). Antitumor effects on cancer stem cells and their perivascular niche have also been studied (11, 13). Recent phase 3 studies in newly diagnosed glioblastoma adding bevacizumab to standard radiation therapy (44, 46) have failed to improve survival, and therefore it remains unclear whether the synergistic effects observed in preclinical models exist in humans, or whether higher radiation therapy doses are required for triggering such effects. Perhaps more importantly, bevacizumab prevents symptomatic edema by decreasing vascular permeability, which seems to be the principal component of its radioprotective effects. When comparing hypofractionated reirradiation regimens that include bevacizumab with those that do not, bevacizumab seems to decrease rates of radiographically detectable radionecrosis (11, 13). It is, however, noteworthy that tissue analysis of some patients reoperated after HFSR in this and other

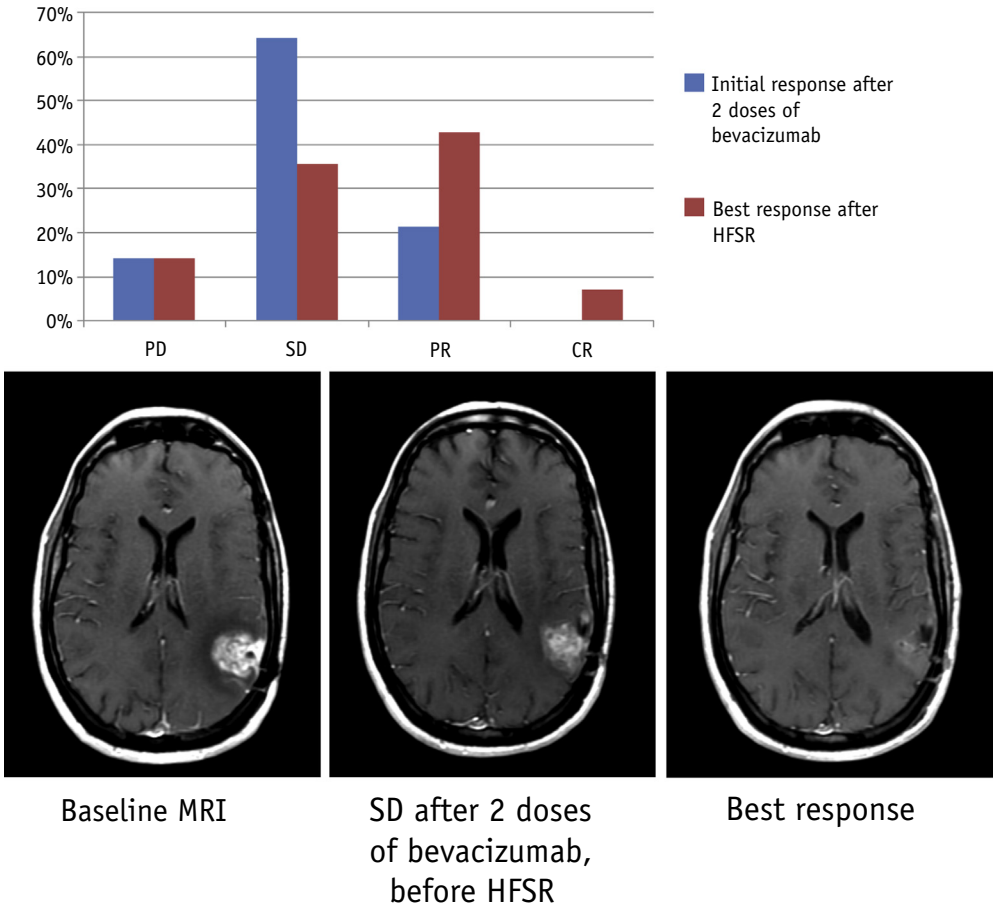

Fig. 3. Response rates after initial bevacizumab treatment and after hypofractionated stereotactic reirradiation (HFSR) (n = 12), and example of a patient with radiographic response seen on T1 postcontrast MRI after hypofractionated stereotactic reirradiation. *Abbreviations:* CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

studies has shown abundant tissue necrosis, which often develops without accompanying symptomatic edema or contrast enhancement on MRI. This suggests that radiation therapy–related tissue destruction seems to still occur, and although mostly asymptomatic, caution should be exerted when treating tumors located within eloquent areas of the brain; the use of functional MRI techniques to select patients for treatment may be of interest in such cases.

Challenges encountered during the study included the 3+3 trial design with a long DLT evaluation period, which is not an optimal means of conducting a trial in which late toxicities are expected. A continuous reassessment method may have been preferable, which would have expedited accrual and results. In addition, throughout treatment, and similar to daily neuro-oncology practice, it was difficult to differentiate tumor progression from radiation treatment effects, further exemplifying the need for novel neuroimaging tools. As with previous trials involving reirradiation, our patient population was restricted to those with a tumor volume <40 cm^3 and who were free of multifocal disease; this patient population may have an intrinsically better prognosis than unselected recurrent HGG populations (23). It remains unclear whether reirradiation of larger tumor volumes, inclusive of larger pools of patients, would be feasible with this aggressive fractionation regimen (47). Finally, this study did not formally evaluate quality of life or changes in neurocognitive function to fully assess the effect of our treatment regimen.

The study reported here demonstrates that for patients with recurrent HGGs, HFSR at doses up to 33 Gy delivered over 3 fractions in combination with bevacizumab is associated with an acceptable toxicity profile, and may achieve outcomes that are at least comparable to those with similar regimens delivered over 5 to 6 fractions. The resulting MTD represents a near doubling in the biologically equivalent dose to normal brain, as compared with our previous regimen of 30 Gy in 5 fractions. Further insight on the role of HFSR in recurrent glioblastoma will be provided by an ongoing randomized, phase 2 study (Radiation Therapy Oncology Group protocol 1205), which has a target accrual of 178 patients that are assigned to receive bevacizumab alone or in combination with reirradiation using 35 Gy in 10 fractions. Comparison of the toxicity profiles and outcome data will be of interest. Other planned or ongoing trials will investigate the combination with immune-checkpoint inhibitors, supported by preclinical studies showing synergistic effects between

hypofractionated radiation therapy and these agents. In the meantime, reirradiation strategies, particularly when combined with bevacizumab, remain a reasonable consideration for treatment of patients with recurrent HGG, who have few or no other therapeutic options.

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