A Phase II Study of Pulsed Reduced Dose-Rate Radiation Therapy with Bevacizumab for Recurrent High-Grade Gliomas

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CO11374: A Phase II Study of Pulsed Reduced Dose-Rate Radiation Therapy with Bevacizumab for Recurrent High-Grade Gliomas

CO-PRINCIPAL INVESTIGATOR:

Steven Howard, MD, PhD
Department of Human Oncology
Wisconsin School of Medicine and Public Health
Madison. WI 53792
howard@humonc.wisc.edu

CO-PRINCIPAL INVESTIGATOR:

Patrick Grogan, MD, PhD
Department of Medicine
Division of Hematology and Oncology
University of Wisconsin School of Medicine and Public Health
Madison, WI 53792
pgrogan@uwhealth.org

CO-INVESTIGATORS:

Shahriar Salamat, M.D.
Department of Pathology
University Wisconsin School of Medicine and Public Health
Madison. WI 53792
Shahriar Salamat ssalamat@wisc.edu

Jeffrey Helgager, M.D.
Department of Pathology
University Wisconsin School of Medicine and Public Health
Madison. WI 53792
jhelgager@wisc.edu

Christopher Platta, M.D.
Aspirus Regional Cancer Center
215 N. 28th Avenue
Wausau, WI 54401

STATISTICIAN:	Rick Chappell PhD Depts. of Statistics, Biostatistics and Medical Informatics University of Wisconsin School of Medicine and Public Health Madison. WI 53792 chappell@biostat.wisc.edu
RESEARCH PROGRAM MANAGER	Diana Trask BS Department of Human Oncology Wisconsin School of Medicine and Public Health Madison. WI 53792 trask@humonc.wisc.edu (608)263-9528
CONSULTANT	Minesh Mehta, MD University of Maryland

SYNOPSIS

Title	A Phase II Study of the Efficacy of Pulsed Reduced Dose-Rate (PRDR) Radiation Therapy with Bevacizumab for Recurrent High-Grade Gliomas
Short Title	Radiation Therapy with Bevacizumab for Recurrent Gliomas
Protocol Date	10/14/2020
Study Duration	Group2 (1 year); Group 1 (2.0 years); group 3&4 (4 years)
Study Center(s)	UW
Objectives	To determine the efficacy of PRDR retreatment radiation therapy (RT), and bevacizumab followed by adjuvant bevacizumab in the setting of recurrent high grade gliomas, as measured by overall survival. Secondary endpoints will include progression free survival, toxicities, and the impact of this regimen on neurological symptoms.
Number of Subjects	80
Diagnosis and Main Inclusion Criteria	All patients will be diagnosed with recurrent high grade gliomas (glioblastoma [group 1&2] or anaplastic glioma [group 3&4]) will be placed into groups 1-4 based on their histologic diagnosis and prior exposure to bevacizumab*.
Treatment Summary	Patients will be given radiation therapy in 27 fractions over 5.5 weeks using a PRDR technique. Concurrent bevacizumab will be given during radiation therapy. Post radiation, bevacizumab may be continued "off study" per SOC schedules and guidelines
Analysis Summary	Data will be analyzed using Kaplan-Meier curves for survival endpoints. Toxicity data will be summarized descriptively.

Note: prior bevacizumab = group 2 &4, no prior bevacizumab = group 1 & 3

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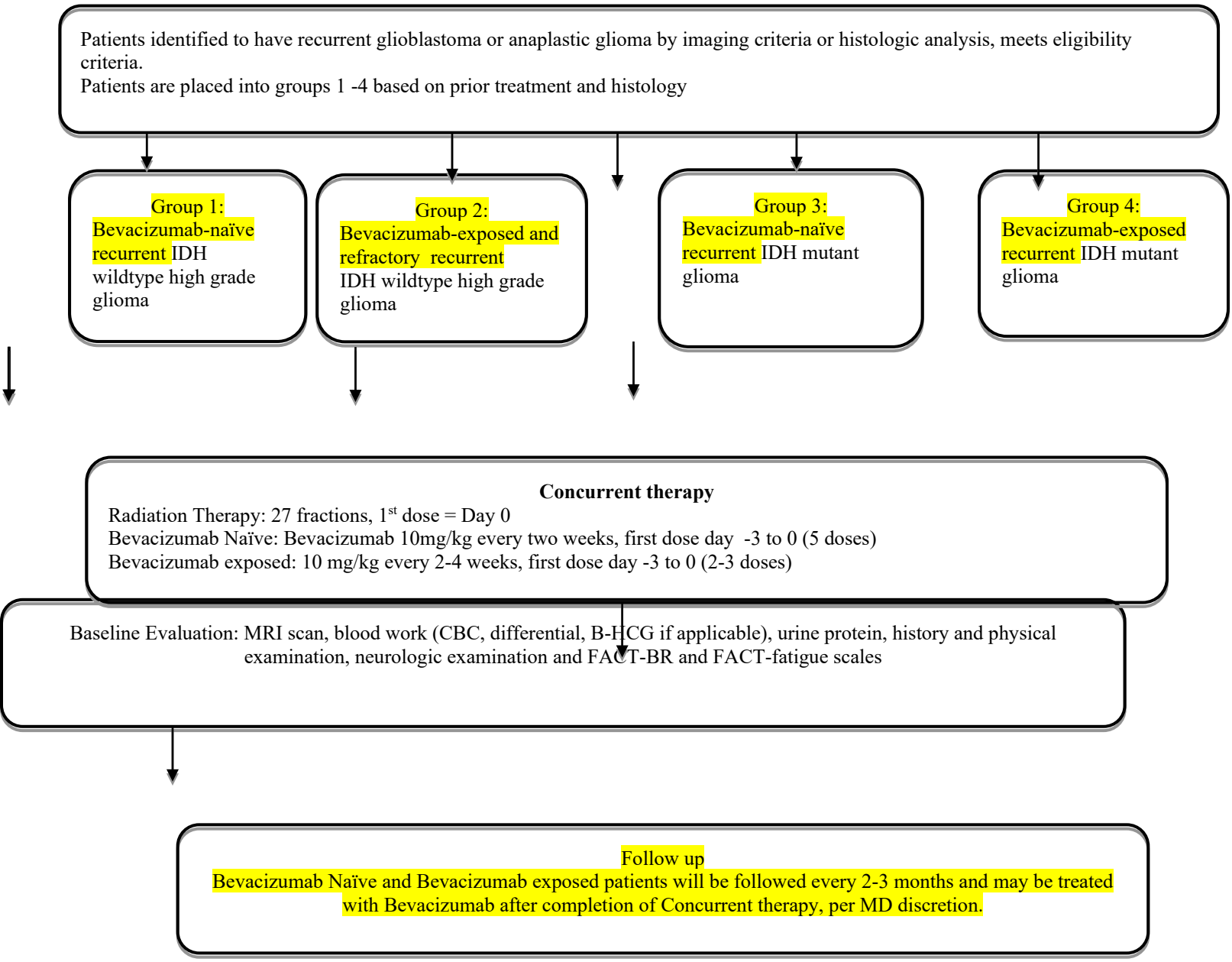
SCHEMA


Patients identified to have recurrent glioblastoma or anaplastic glioma by imaging criteria or histologic analysis, meets eligibility criteria.
Patients are placed into groups 1 -4 based on prior treatment and histology
Group 1: Bevacizumab-naïve recurrent IDH wildtype high grade glioma
Group 2: Bevacizumab-exposed and refractory recurrent IDH wildtype high grade glioma
Group 3: Bevacizumab-naïve recurrent IDH mutant glioma
Group 4: Bevacizumab-exposed recurrent IDH mutant glioma
Concurrent therapy
Radiation Therapy: 27 fractions, 1st dose = Day 0
Bevacizumab Naïve: Bevacizumab 10mg/kg every two weeks, first dose day -3 to 0 (5 doses)
Bevacizumab exposed: 10 mg/kg every 2-4 weeks, first dose day -3 to 0 (2-3 doses)
Baseline Evaluation: MRI scan, blood work (CBC, differential, B-HCG if applicable), urine protein, history and physical examination, neurologic examination and FACT-BR and FACT-fatigue scales
Follow up
Bevacizumab Naïve and Bevacizumab exposed patients will be followed every 2-3 months and may be treated with Bevacizumab after completion of Concurrent therapy, per MD discretion.

1.0 INTRODUCTION - BACKGROUND AND RATIONALE

1.1 High Grade Gliomas

High grade gliomas arise from astrocytes and oligodendrocytes. The most common type of malignant glioma is glioblastoma (GBM), which comprises 60% of gliomas. Other high grade gliomas include anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma, all of which are categorized as anaplastic gliomas.

The prognosis of patients with these diagnoses is poor. The overall survival (OS) rate for GBM is 27.2% at 2 years, 16.0% at 4 years, and 9.8% at 5 years with the standard treatment of surgical resection and adjuvant radiation therapy with concurrent and adjuvant temozolomide [1]. Patients generally undergo resection, followed by conformal radiation therapy (60 Gy) over 6 weeks with concurrent temozolomide followed by adjuvant temozolomide for a minimum of 6 months for responding patients. This regimen has also been used as "standard treatment" for patients with other forms of high grade gliomas, despite more limited data in this setting.

Addition of bevacizumab to standard first-line therapy has been shown to improve progression free survival (PFS) in the phase II setting compared to historical controls, but level 1 evidence for its use in the up-front setting does not exist, and such use is currently uncommon in most centers [2, 3]. In a single-arm study, 70 patients were treated with daily temozolomide (75 mg/m^2) and biweekly bevacizumab (10 mg/kg) with concurrent standard radiation therapy, followed by adjuvant temozolomide and bevacizumab. Median PFS was 13.6 months in the tri-modality therapy group and 7.6 months in a group of historical control patients [2].

1.2 Recurrent Disease – Systemic Agents

1.2.1 Clinical experience

Recurrent disease is almost universal in high grade gliomas [4, 5]. The current standard of care for recurrent GBM employs the use of the antiangiogenic agent bevacizumab. In the BRAIN study, a phase II, non-comparative, multicenter trial of 167 patients with recurrent GBM treated with bevacizumab alone (n=85) or in combination with irinotecan (n=82), those patients who received bevacizumab alone had a response rate of 25.9% with median duration of response of 4.2 months and 6 month PFS of 36%[6]. In an NCI-sponsored phase II study, 48 patients with recurrent GBM were treated with bevacizumab followed by bevacizumab with irinotecan at tumor progression. In these patients, the response rate was 19.6 % with a median duration of response of 3.9 months [7]. In the recurrent setting, cytotoxic chemotherapy such as CPT-11 or temozolomide is frequently combined with bevacizumab, resulting in somewhat higher response rates, and slightly increased 6 month PFS (51% with CPT-11 plus bevacizumab in the BRAIN trial) [6, 8]. In several

trials, the median survival ranges between 6.5 and 9.8 months. In the randomized BRAIN trial, median survival was approximately 9 months for both cohorts; according to the literature, the composite median survival for recurrent GBM is approximately 8 months.

Attempts have also been made to salvage recurrent GBM with temozolomide alone [9] or in combination with bevacizumab[8], and the overall data suggest modest clinical activity with 6 month PFS of 23.9% with temozolomide alone. One year OS for those patients treated with temozolomide alone was 14.8-28.6%, depending on risk stratification group.

1.2.2 Dosing & Safety of Bevacizumab

Several dosing schedules for bevacizumab have been employed. Bevacizumab has been given at 10 mg/kg every 2 weeks concurrent with and adjuvant to radiation therapy ([2, 6, 8]). Treatment with bevacizumab alone in the recurrent disease setting was associated with a 46.4% incidence of grade 3 or higher adverse events, most commonly hypertension (8.3%) and convulsion (6.0%), along with arterial thromboembolism (2.4%), venous thromboembolism (3.6%), and grade 3 GI perforations (2.5%) [6]. Adverse events resulted in termination of bevacizumab treatment in 4.8% of the bevacizumab alone patients [6].

1.2 Recurrent Disease – Re-irradiation

1.2.1 Background:

Re-irradiation has also been investigated for patients with recurrent disease. There are several studies showing that radiation therapy may be delivered safely in this setting [10-12]. . In the largest of these studies, 147 patients with recurrent GBM treated with hypofractionated radiation therapy (median dose 35 Gy in 3.5 Gy fractions), no patients experienced significant acute morbidity or required treatment breaks. One patient did experience grade 3 late central nervous system (CNS) toxicity (headaches), but no patients required hospitalization or surgical intervention for toxicity [10].

Some series suggest that those patients who receive bevacizumab and radiotherapy have improved response rates compared to those who receive either modality alone [13]. In 1 small single institution report of 25 patients (20 recurrent GBM and 5 recurrent anaplastic gliomas) treated with bevacizumab and hypofractionated radiotherapy (30 Gy in 5 fractions), the response rate for GBM was 50% with 6 month PFS of 65% and median survival of 12.5 months; this was in a cohort of well selected patients with small volume recurrence (< 3.5 cm maximum diameter) [13]. Table 1 summarizes the above data.

Table 1. Efficacy of treatment options for patients with recurrent GBM

	Response Rate (%)	6 month PFS (%)	MS (months)
Bevacizumab Alone	28.2[6]	42.6[6]	9.2[6]
Bevacizumab + CPT-11	37.8[6]	50.3[6]	8.7[6]
Bevacizumab + Chemotherapy	34.1[14]	42[14]	7.2[15]
Temozolomide Alone		23.9[9]	7.2[15]
Radiation Therapy Alone		34.8[11]	11[10]
Bevacizumab + Radiation Therapy	50[13]	65[13]	12.5[13]

Most importantly, the above trial demonstrated the safety of re-irradiation. Three of 25 patients discontinued treatment with bevacizumab due to grade 3 toxicity related to bevacizumab, but no patients experienced radiation necrosis.

1.2.1 Pulsed Reduced Dose Rate Radiation (PRDR) as an Alternate Technique for Re-irradiation

One unique approach to such recurrent glioma patients is the use of dose rate modulated re-treatment irradiation. Radiotherapy (RT) delivered below standard dose-rates reduces normal tissue toxicity and can induce significant tumor regression in some tumor types including glioma. By reducing the effective dose-rate and increasing the treatment time, it becomes possible for repair processes to be active during irradiation. This reduction in dose-rate can result in a therapeutic advantage, as repair of sub-lethal damage in normal neural tissues is greater for late complications than for neoplastic cells; furthermore tumor cells (that have received prior RT) can accumulate in a sensitive phase of the cell cycle, e.g., G_2, thus leaving them at risk for radiation induced killing.

1.2.2.1 Biological Basis for PRDR

The general concept for RT dose rate modulation relates to exploiting the biological differences between normal neural tissue and glial neoplasms in terms of repair of radiation damage and the induction of radiation-induced lethal lesions. In this regard, it is of interest to note that low dose rate interstitial brachytherapy has been used for the treatment of recurrent glioma with reported improved median survivals [9]. The radio-biological properties of low dose-rate radiation have long been established relative to tumor/tissue sparing. Currently, a superior dose distribution is felt to be the reason for the efficacy and tolerance observed with brachytherapy as a treatment for malignant glioma. Beyond this, however,

there is theoretical and experimental evidence relating to lower dose-rates potentially providing more efficient radiation damage. Indeed, there is increasing experimental evidence as well as clinical observations suggesting that reduced dose-rate irradiation may be a biologically different and distinct process in contrast to acute high dose rate fractionated irradiation.

Shultz and Geard [16] evaluated 2 human glioblastoma cell lines relative to the effects of dose rate on radiosensitivity. Dose rates ranged from 0.2 Gy/h to 5.4 Gy/h. An inverse dose rate effect, (i.e., a paradoxical increase in cell killing within a narrow range of decreasing dose-rate) was demonstrated at approximately 0.4 Gy/h [16]. This phenomenon is thought to be a consequence of the accumulation of cycling cells at the G2M checkpoint. During continuous low dose-rate irradiation, the G2M blocked cells are preferentially killed as they are relatively more radiosensitive than cells in G1 and S phase. In support of this concept, Shultz and Davies, performed cell cycle analysis which revealed maximal accumulation of cells at G2M checkpoint at a dose rate of 0.4 Gy/h [17, 18]. Based on these experimental observations, one can extrapolate to the hypothesis that actively proliferating glial tumors may be selectively more radiosensitive to continuously delivered low dose-rate irradiation than the quiescent surrounding normal brain tissue.

Beyond the aforementioned considerations, breaking each fraction of radiation into a number of subfractions takes advantage of a second intriguing radiation phenomenon known as low-dose hyper-radiosensitivity (LDHRS), (i.e., increased radiosensitivity to doses <0.3–0.5 Gy). This translates to a cell survival that is considerably lower than that which would be predicted from extrapolation of the survival curves derived from higher doses. Such data are available (i.e., low-dose responses) for many human cell lines [19], most of which have demonstrated LDHRS [20, 21]. As alluded to above, low dose hypersensitivity might be a product of radiation-damaged G2 cells entering mitosis prematurely [20]. That is to say there was inefficient cell cycle arrest of irradiated cells as a result of the inverse dose effect [20]. Short *et al.* [22] have hypothesized that low-dose hypersensitivity can be thought of as the constitutive response of cells without the enabling of repair mechanisms triggered by higher doses. Modeling of these phenomena has been accomplished by Short and colleagues [23].

Building on the above concepts, Tomé and Howard used modeling to develop a treatment strategy for gliomas that employs both a reduced dose-rate and pulsed treatment dose delivery [24]. Using five established glioma cell lines they demonstrated that a pulsed delivery scheme can yield a substantial increase in tumor control probability. They proposed a pulsed delivery scheme for the treatment of gliomas in which the daily treatment fraction is delivered using 0.20 Gy pulses, separated by three minutes for a time-averaged dose-rate of 0.0667 Gy/min. The dose per pulse of 0.2 Gy was near or below the transition dose observed *in vitro* for four of the five glioma cell lines studied [24].

Although most evidence for low-dose hypersensitivity has been demonstrated *in vitro*, analysis of LDHRS in metastatic tumors (i.e., breast, melanoma, and sarcoma involving skin and subcutaneous tissue) has revealed a

potential advantage to low-dose ultrafractionated therapy compared with more standard fraction sizes [21].

In the next section the technical aspects of applying these radio-biological concepts to clinical practice are described, as well as the clinical experience regarding their application to recurrent glioma patients.

1.2.2.2 **The University of Wisconsin (Madison) Clinical Experience with PRDR- RT**

We have recently reported on a series of 103 recurrent glioma patients using a dose modulation technique we designated this technique as PRDR-RT as described in section II above [11]. Histologies included: low-grade glioma (n=25); grade 3 oligodendroglioma (n=3); grade 3 oligoastrocytoma (n= 3); grade 3 astrocytoma (n=25), grade 4 oligoastrocytoma (n= 1), grade 4 astrocytoma (n= 44); brainstem glioma (n=1); (pineal tumor (n=1). Strikingly, the mean treatment volume was 403.5 ± 189.4 cm^3 according to T2-weighted magnetic resonance imaging and a 2-cm margin. The PRDR-RT regimen was well tolerated, and no patient discontinued treatment because of associated toxicity.

Autopsy of the brain was performed in 15 patients, of which 4 had notable necrosis. In 2 of these 4 patients the PRDR dose was 50 Gy in 2 patients originally treated to a dose of 54 Gy and 59.4 Gy, with an interval of 12 and 40 months to PRDR-RT. In the other 2 of 4 patients, the PRDR dose was 54 Gy in 2 patients originally treated to 60 Gy, with an interval of 11 and 28 months to PRDR-RT. In addition, one of these patients received stereotactic radiosurgery to 12 Gy prescribed to the 50% isodose line 25 months after initial RT to 60 Gy. Other pathological findings only included punctuate necrosis in the presence of recurrent tumor, usually associated with mitoses or vascular endothelial proliferation. Follow-up MRI scans in this series revealed changes consistent with disease progression, pseudo-progression, or necrosis. Clinical deterioration was treated with increases in steroid dosage and supportive care. Three patients underwent post-PRDR-RT subtotal resection with the pathologic findings revealing progressive disease without treatment related necrosis. Although no formal endocrine, neuro-cognitive, or visual testing was performed, no patient manifested obvious blindness from treatment.

Multivariate analysis revealed age at the initial diagnosis, initial low-grade disease, and KPS of ≥80 to be significant predictors of survival after initiation of PRDR. No significant survival difference (from the initiation of PRDR) was observed for patients who had previously been treated with no systemic therapy (including temozolomide), one previous regimen, two previous regimens, three previous regimens, or four or more previous regimens (as described below) .

Regarding GB patients, we found that time from initial RT (≥14 months) was prognostic, and the OS of these patients compared favorably relative to palliative chemotherapy [25]. Such PLDR-RT patients had a median survival of 28 weeks; patients reirradiated within 14 months of previous therapy had a median survival of only 21 weeks ($p = 0.004$). It is noteworthy that 77% of the patients treated in the Phase II drug studies [25] had received previous chemotherapy, 25% of whom had received at least two regimens. In the UW series, 92% of patients had received

previous chemotherapy, and 45% had received at least two regimens. Of parenthetical interest, *de novo* GB patients were compared with those who were initially diagnosed with a lower grade glioma and transformed to grade 4 (confirmed by the biopsy); there was no significant difference in survival from the initiation of PRDR-RT (median survival 5.2 vs. 5.9 months, p = .12)

In considering histologic findings at the initial diagnosis, median survival for those with low-grade glioma from the initiation of PRDR-RT was 11.4 months (range, 1–33.8); for those with Grade 3 glioma: 5.6 months (range, 1.2–23.7); for those with GB: 5.1 months (range, 1–48.4). The 6-month and 1-year actuarial survival rate after retreatment with PRDR was 73.9% and 47.8% for those with low-grade glioma, 38.2% and 9.7% for those with Grade 3 glioma, and 34.8% and 4.4% for those with GB, respectively. For the entire cohort, the median survival from the initiation of PRDR-RT was 5.8 months (range, 1–48.4), and the 6-month and 1-year actuarial survival rate was 44.7% and 15.9%, respectively.

For the reader's interest, a series of MRI's demonstrating a typical PRDR-RT response was published in 2007 as part of a case report [26].

In summary, PRDR as a reirradiation strategy was well tolerated, allowing for safe retreatment of larger target volumes to high doses (>100 Gy) with palliative benefit.

1.3 Bevacizumab and Treatment of Radiation Necrosis

It is important to recognize the role of bevacizumab in treating and effectively reversing radiation-induced cerebral necrosis[27]. A randomized double-blind placebo-controlled trial with cross-over design of radiation therapy for radiation necrosis of the CNS involved 14 patients with radiation necrosis in the CNS with associated neurologic signs and symptoms. Five of 5 patients who were randomized to initial treatment with bevacizumab had improvement in their neurologic signs and symptoms, and 7 of 7 who were initially randomized to the control group had no improvement. After crossover, all patients had symptomatic improvement. Bevacizumab is thought to be effective in treatment of central nervous system radiation necrosis by restoring the blood brain barrier which is made dysfunctional by radiation therapy, causing edema and neurologic symptoms.

1.4 Rationale for the Current Trial

Based upon the modest activity of both treatment modalities (bevacizumab, and radiotherapy), possible synergy as demonstrated in several pre-clinical models, and data supporting that the use of bevacizumab is also likely protective against brain necrosis, we propose to combine these in a bi- modality approach for patients with recurrent malignant glioma. We propose to conduct a phase II trial of concurrent radiation and bevacizumab followed by adjuvant bevacizumab in patients with recurrent high grade gliomas including GBM and anaplastic glioma. Patients will be stratified into 4 groups on the basis of histology and prior therapy:

bevacizumab-naïve with recurrent GBM (Group 1), bevacizumab-exposed with refractory recurrent GBM (Group 2), bevacizumab-naïve with recurrent anaplastic glioma (Group 3), and bevacizumab-exposed with recurrent anaplastic glioma (Group 4). We will assess survival and toxicity endpoints for this regimen in the recurrent setting.

Bevacizumab dosing and schedule in both the primary and recurrent disease settings have been somewhat standard; thus we will utilize this standard dose of 10 mg/kg biweekly throughout both treatment periods [2, 6, 8].

In summary recent approval of bevacizumab for the treatment of recurrent GB has yielded a new clinical cohort of patients with a uniquely poor prognosis, i.e., patients who have progressed after bevacizumab therapy [28, 29]. The 6-month progression free survival (PFS) for these patients is negligible. Relative to this, anecdotal experience at the UW (Howard and Robins, unpublished 2011) suggests that PRDR-RT does provide some palliation and even responses in this patient population. Beyond this, our experience with continuing bevacizumab with PRDR RT after progression on bevacizumab may have utility. Additionally, adding bevacizumab to PRDR-RT in bevacizumab naïve patients may provide durable responses in excess of the typical PFS (i.e., ~ 4 months) seen with bevacizumab [6, 7]. These observations may in part relate to the potential for bevacizumab to prevent, and or treat, radiation induced necrosis[27].

1.4.1 Updated Experience with Bevacizumab and PRDR-RT June 2014 (see reference 31)

Our recent published retrospective review in the Journal of Neuro-oncology demonstrated that in patient who have progressed on bevacizumab 2 to 3 cycles of bevacizumab at 10mg/kg/ every 4 weeks is adequate to salvage patients and improve survival. The abstract of that paper appears below:

> "Outcomes after bevacizumab failure for recurrent glioblastoma (GBM) are poor. Our analysis of 16 phase II trials (n = 995) revealed a median overall survival (OS) of 3.8 months (±1.0 month SD) after bevacizumab failure with no discernible activity of salvage chemotherapy. Thus, the optimal treatment for disease progression after bevacizumab has yet to be elucidated. This study evaluated the efficacy of reirradiation for patients with GBM after progression on bevacizumab. An IRB approved retrospective (2/2008–5/ 2013) analysis was performed of 23 patients with recurrent GBM (after standard radiotherapy/temozolomide) treated with bevacizumab (10 mg/kg) every 2 weeks until progression
> (median age 53 years; median KPS 80; median progression free survival on bevacizumab 3.7 months). Within 7–14 days of progression on bevacizumab, patients initiated reirradiation to a dose of 54 Gy in 27 fractions using pulsed-reduced dose rate (PRDR) radiotherapy. The median planning target volume was 424 cm3. At the start of reirradiation, bevacizumab (10 mg/kg) was given every 4 weeks for two additional cycles. The median OS and 6 month OS after bevacizumab failure was 6.9 months and 65 %, respectively. Reirradiation was well tolerated with no symptomatic grade 3–4 toxicities. Favorable outcomes of reirradiation after bevacizumab failure in patients with recurrent GBM suggest its role as a treatment option for large volume recurrences not amenable to stereotactic radiosurgery.
> As PRDR is easily accomplished from a technological standpoint, we are in the process of expanding this approach to a multi-institutional cooperative group trial."

1.4.2 2017 Updated rationale for "A Phase II Study of Pulsed Reduced Dose-Rate Radiation Therapy with Bevacizumab for Recurrent High-Grade Gliomas"

CO11374; "A Phase II Study of Pulsed Reduced Dose-Rate Radiation Therapy with Bevacizumab for Recurrent High-Grade Gliomas" has been open and actively accruing 4 to 5 patients per year for the past five years. This accrual rate reflects the limited numbers of this small patient population. Since we opened CO11374 at the University of Wisconsin, numerous small retrospective, mostly single institution studies have suggested that re-irradiation is a feasible treatment option achieving both a palliative benefit and prolongation of survival (1) However, the recent 2017 ASCO radiotherapy guidelines by expert consensus panel (2) regards re-irradiation of recurrent high-grade glioma as "experimental" and acknowledges that there is minimal high-quality evidence regarding re-irradiation which creates a need for guidance in the form of prospective clinical trials. Furthermore, this 2017 report also stresses that the majority of the published re-irradiation experience is in patients with small volume recurrences. The current trial, CO11374 is evaluating PRDR as a reirradiation strategy for safe retreatment of larger treatment volumes to high doses (>100 Gy). The rationale for the continued accrual of patients to CO11374 continues to be significant in 2017.

(1) The evolving role for re-irradiation in the management of recurrent grade 4 glioma. Howard SP, Krauze A, Chan MD, Tsien C, Tomé WA. J Neurooncol. 2017 Apr 6. doi: 10.1007/s11060-017-2392-1. PMID: 28386661

(2) Sulman EP, Ismaila N, Armstrong TS, Tsien C, Batchelor TT, Cloughesy T, Galanis E, Gilbert M, Gondi V, Lovely M, Mehta M, Mumber MP, Sloan A, Chang SM. Radiation Therapy for Glioblastoma: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Guideline. J Clin Oncol. 2017 Jan 20;35(3):361-369. doi: 10.1200/JCO.2016.70.7562.

(3) Tipping M, EichoFF JC, Robins HI, Clinical Outcomes in Recurrent Glioblastoma with BEV therapy: An Analysis of the Literature. J Clin Neuro-Science 2017, in press

2.0 OBJECTIVES

2.1 Primary Objective:

The primary objective of this phase II study will be to determine the overall survival (OS) for patients with recurrent high grade malignant gliomas treated with concurrent radiation, and bevacizumab followed by adjuvant bevacizumab. OS is the most appropriate endpoint for this trial given that response rates are very low and do not serve as a useful surrogate. Additionally, PFS is confounded on the MRI due to changes consistent with pseudo-progression, a well-described phenomenon in this disease.

2.2 Secondary Objectives:

Secondary objectives will include the following:

2.2.1 Determine the safety profile of this regimen.

2.2.2 Determine the progression free survival (PFS) at 6 and 12 months (all patients) as well as at 3 months (bevacizumab-exposed patients only).

2.2.3 Qualitatively compare the results of brain autopsy in patients who have received PRDR-RT /Bevacizumab to prior results (n=15) obtained with PRDR-RT

2.2.4 Determine the impact of this regimen on neurologic symptoms via FACT-Br and FACT-Fatigue scales and Karnofsky performance status (KPS).

3.0 SELECTION OF PATIENTS

Potentially eligible patients will be identified by their treating physicians in the Neuro-Oncology outpatient clinic of the University of Wisconsin or at Aspirus Regional Cancer Center. Approximately 60 to 80 patients fitting the criteria listed above are seen per year. We estimate that we will accrue approximately 1-2 patients per month to this trial.

3.1 Inclusion Criteria

3.1.1 Patients must have histologically or molecularly confirmed Grade 3 or Grade 4 glioma, IDH mutant or wildtype, as defined by the 2021 WHO guidelines.

3.1.2 Patients must have measurable or non-measurable (evaluable) disease recurrence.

3.1.2.1 Recurrence must be documented based on a combination of clinical and imaging parameters, consistent with routine clinical practice, with or without histologic confirmation.

3.1.2.2 Patients may have had any number of relapses and be eligible for the study.

3.1.3 Patients must have been previously treated with radiation therapy and temozolomide (bevacizumab-naïve – Groups 1 and 3) or radiation therapy, temozolomide and bevacizumab (bevacizumab-exposed – Groups 2 and 4). Therapy with these agents may be given together or sequentially in the past.

3.1.4 All patients may have had prior surgery, chemotherapy, and radiation therapy. Patients with prior VEGF inhibitor exposure will be placed in the Bevacizumab exposed group (Groups 2 and 4). Prior treatment with Gliadel is permitted for all groups.

3.1.5 Prior radiation requirements

- For bevacizumab-naïve patients (Groups 1 and 3) a minimum of 5 months must have elapsed since completion of initial radiation therapy for study entry, and there is no minimum time since completion of last chemotherapy.
- For bevacizumab-exposed patients (Groups 2 and 4) minimum of 3 months must have elapsed since completion of initial radiation therapy and there is no minimum time since completion of last chemotherapy

3.1.6 Patients must be 18 years or older.

3.1.7 Patients must have a KPS performance status of ≥ 60.

3.1.8 Patients must have adequate bone marrow function (within 14 days prior to registration) defined as:
3.1.8.1 Hemoglobin ≥ 10
3.1.8.2 Platelets $\geq 100{,}000/mm^3$
3.1.8.3 Absolute neutrophil count $\geq 1500/mm^3$

3.1.9 Urine protein via dipstick $\leq$ 2+or $\leq$ 100mg/d

3.1.10 Patients' baseline blood pressure must be adequately controlled with or without antihypertensive medications prior to registration (systolic $\leq$ 160 mmHg, diastolic $\leq$ 90 mmHg).

3.1.11 Patients must have a baseline evaluation including history and physical examination with neurological evaluation and MRI of the brain (with and without gadolinium-based contrast), all completed within 30 days prior to registration.

3.1.12 Females of child-bearing potential, based on institutional guidelines, must have a negative pregnancy test within 14 days prior to registration.

3.1.13 Females of child-bearing potential and sexually active males must consent to follow acceptable birth control methods to avoid conception while on treatment.

3.1.14 All subjects must have given signed, informed consent prior to registration on study.

3.1.15 Patients previously treated outside of the UW must have their pathology slides sent to the UW for review and confirmation. (see section 12)
3.1.15.1 NOTE: A copy of the pathology report is sufficient for registration.

3.2 Exclusion Criteria

3.2.1 Patients who are pregnant or breast-feeding will NOT be eligible for participation.

3.2.2 Patients with a prior malignancy will NOT be eligible for participation aside from the following exception:
3.2.2.1 Patients who have had any curatively treated invasive malignancy and have been disease free without treatment for 1 year prior to study entry ARE eligible for participation.

3.2.3 Patients with an active second malignancy (other than non-melanoma skin cancer or cervical cancer in situ) are NOT eligible for participation.

3.2.4 Patients with uncontrolled hypertension (> 160/90 mmHg) are NOT eligible for participation.

3.2.5 Patients who exhibit any other serious concurrent active infection or other medical illness which would jeopardize their ability to receive the therapy outlined in this protocol with reasonable safety will NOT be eligible for participation.

4.0 PATIENT REGISTRATION

Patients *may not* begin protocol treatment prior to registration.

- All patients must meet eligibility criteria listed in Section 3 and provide written informed consent. Eligibility will be verified by UW Radiation Oncology Coordinators prior to study registration. Email completed protocol checklist to: dho-datamgrs@lists.humonc.wisc.edu UW Radiation Coordinators will verify that the checklist is completed, will assign a case number and arm for ONCORE Registration
- Each center is responsible for registration directly into UWCCC ONCORE database prior to study treatment. The following information will be recorded:
    - Protocol number
    - Patient's name and initials
    - Patient's medical record number
    - Patient demographic data, including gender, birth date, and race.

5.0 TREATMENT PLAN

5.1 Overview

This will be a phase II trial to assess the survival and toxicity associated with concurrent re-irradiation plus bevacizumab, followed by adjuvant bevacizumab in patients with recurrent high grade gliomas. A total of 80 patients will be enrolled on this trial. Patients will be stratified into 4 groups on the basis of histological diagnosis (IDH wild type high grade or IDH mutant high grade glioma) and prior therapies received (bevacizumab-naïve or bevacizumab-exposed). Treatment will be divided into 2 phases. The first phase (initial phase) will include all treatments (bevacizumab) given during (concurrently with) re-irradiation therapy, whereas the second phase (adjuvant phase) will consist of treatments (bevacizumab) given after re-irradiation therapy is completed. Re-irradiation therapy will last for 5.5 weeks. One cycle of systemic therapy in the adjuvant phase will be defined as 4 weeks in duration. Patients may continue on adjuvant therapy(MD discretion) until disease progression or removal due to toxicity. Overall survival will be the primary endpoint of this phase II trial.

5.2 Administration

5.2.1 PRDR Re-irradiation Therapy

The first day of re-irradiation therapy will be considered Day 0. Re-irradiation therapy will be given using the UW PRDR-RT technique, with a total daily dose of 2.0 Gy delivered in .2 Gy pulses for 27 fractions to a total dose of 54 Gy delivered to the MR FLAIR abnormality (the T2 may substitute for FLAIR, if the FLAIR sequence is not available) as the clinical target volume (CTV). There will be a minimal expansion from

each CTV to planning target volume (PTV) of at most 2mm. At least 90% of each CTV should receive 90% of the prescribed dose. In the rare instance of the presence of extensive disease requiring essentially whole brain radiation, a total daily dose of 1.8 Gy delivered in .2 Gy pulses for 23 fractions to a total dose of 41.4 Gy will be utilized.

It is reasonable to assume that during the initial course of radiation therapy, the optic nerves and chiasm would have received approximately 50 Gy. Therefore, no more than an additional 30 Gy to the optic nerves or chiasm will be permitted during re-irradiation with the caveat that the total cumulative dose to these structures will not exceed 70 Gy.

5.2.1.1 Technique for pulsed reduced-dose-rate (PRDR)- RT

The technique at the University of Wisconsin (UW) for pulsed reduced-dose-rate (PRDR) RT [11, 30] is to generate 0.2-Gy pulses separated by 3-min intervals, thus creating an apparent average dose rate of 0.0667 Gy/min [24]. The dose rate of the linear accelerator is reduced to 1 Gy/min during each 0.2-Gy pulse. In a large series (n=103) of glioma patients [11] described in the next section, the median dose was 50 Gy (range, 20–60) delivered in 1.8–2.0-Gy fractions; with a mean treatment volume of 403.5 ± 189.4 cc^3 according to T2-weighted magnetic resonance imaging and a 2-cm margin.

5.2.2 Bevacizumab or FDA approved Biosimilar

Bevacizumab is commercially available and FDA approved for use in recurrent gliomas. The Bevacizumab biosimilars - MVASI™ and Zirabev™is also approved for us as a substitute for Avastin and can be administered for use in recurrent gliomas.

Commercial drug will be used and drug preparation will be per package insert and infused per institutional guidelines.

Bevacizumab will be administered intravenously at a dose of 10 mg/kg every 2-4 weeks; the timing of the infusions will vary depending on the treatment phase (see below). Bevacizumab will be diluted in a total volume of 100 mL of 0.9% sodium chloride Injection, USP. Anaphylaxis precautions should be observed during drug administration. The dose will be based on current weight at each dosing time point. It is not necessary to correct dosing based on ideal weight.

Bevacizumab will be administered per institutional practice. If a patient experiences an infusion-associated adverse event, he/she may be premedicated for the next bevacizumab administration per institutional practice.

5.2.2.1 Protocol Therapy:

The first dose of bevacizumab will be given between Days -3 & 0.

Bevacizumab Naïve patients: Patients will receive 10mg/kg which will continue every 2 weeks (+/- 3 days) during re-irradiation therapy as long as no severe toxicity occurs. Protocol therapy will be considered complete after a total of 5 doses of Bevacizumab are given.

Bevacizumab Exposed Patients: Patients will receive 10mg/kg of bevacizumab every 2-4 weeks (+/- 3 days) for 2-3 cycles, per MD discretion, during re-irradiation therapy as long as no severe toxicity occurs. Protocol therapy will be considered complete after the last fraction of PRDR is given (+/-3 days to account for the last dose of concurrent therapy Bevacizumab administration). Any dose given after the end of PRDR, will be considered SOC during the follow-up phase.

After completion of protocol therapy, patient will be moved to study follow-up and Bevacizumab may be continued, per MD discretion, and administered per institutional guidelines.

5.3 Dose Modifications

All toxicities will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

5.3.1 Bevacizumab

The bevacizumab dose may be reduced if any of the criteria outlined in Table 2 below are met. There will be no difference in dosing between the initial and adjuvant phases of treatment for bevacizumab. If adverse events occur that require holding bevacizumab, treatment may resume when all toxicities have resolved to ≤ grade 1 or baseline. Up to 2 scheduled doses of bevacizumab may be missed, but treatment may not be held for > 6 weeks due to toxicity. Please refer to Table 2 for adverse events requiring delays or permanent discontinuation of bevacizumab treatment. Regardless of the reason for holding bevacizumab treatment, the maximum allowable length of bevacizumab treatment interruption is ≤ 6 weeks.

Any toxicities related or possibly related to bevacizumab treatment should be managed according to standard medical practice.

Discontinuation of bevacizumab will have no immediate therapeutic effect. Bevacizumab has a terminal half-life of 21 days; therefore, its continuation results in slow elimination over several months. There is no available antidote for bevacizumab.

Patients will be assessed clinically for toxicity prior to, during, and after each infusion. If unmanageable toxicity occurs because of bevacizumab at any time during the study, treatment with bevacizumab should be discontinued. Please refer to Table 2 below for guidelines regarding management of bevacizumab with regards to adverse events.

Table 2: Bevacizumab dose management due to adverse events

Event	Grade	Action to be Taken
Hypertension	1 or 2	No dose modification required.
	3	If not controlled to < 160/90 mm/Hg with medication, hold bevacizumab until BP improved to institutional goal.
	4 (including hypertensive encephalopathy)	Discontinue bevacizumab.
Hemorrhage: non-pulmonary & non-CNS events	1 or 2	No dose modification required.
	3	***All patients***: hold bevacizumab until all of the following criteria are met: • Bleeding is resolved and Hgb is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage

		recurrence. ***Patients who experience a repeat Grade 3 hemorrhagic event will be discontinued from bevacizumab***.
(cont) **Hemorrhage: non-pulmonary & non-CNS events**	4	Discontinue bevacizumab.
Hemorrhage: pulmonary or CNS	1	***All patients***: hold bevacizumab until all of the following criteria are met: • Bleeding is resolved and Hgb is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.
	2, 3, or 4	Hold bevacizumab until recovery to ≤ Grade 1..
Venous thrombosis	1 or 2	No dose modification required.
	3 or 4	Hold bevacizumab until recovery to ≤ Grade 1..
Arterial thromboembolic event (new onset, worsening, or unstable angina, myocardial infarction, transient	Any grade	Discontinue bevacizumab.

ischemic attack, cerebrovascular accident, or any other arterial thromboembolic event)		
Congestive heart failure (left ventricular systolic dysfunction)	1 or 2	No dose modifications required.
	3 or 4	Hold bevacizumab until recovery to ≤ Grade 1..
Proteinuria		
	Proteinuria Dipstick ≧100mg/dl	Patients on bevacizumab having a spot urinary protein of ≧100mg/dl may be delayed up to 2 weeks at the investigator's discretion.
	4 (nephrotic syndrome)	Discontinue bevacizumab.
GI perforation	Any grade	Discontinue bevacizumab.
Fistula	Any grade (TE fistula)	Discontinue bevacizumab.
	Other Grade 4 fistula	Discontinue bevacizumab.
Bowel obstruction	1	Continue bevacizumab for partial obstruction NOT requiring medical intervention.
	2	Hold bevacizumab for partial obstruction requiring medical intervention – resume upon complete resolution.
	3 or 4	Hold bevacizumab for complete obstruction. If surgery is necessary, patient may restart bevacizumab after full recovery from surgery if within allowed time frame and at the investigator's discretion.
Wound dehiscence	Any grade	Discontinue

	(requiring medical or surgical therapy)	bevacizumab.
Reversible posterior leukoencephalopathy	Any grade (confirmed by MRI)	Discontinue bevacizumab.
Other unspecified bevacizumab-related adverse events	Grade 3	Hold bevacizumab until recovery to ≤ Grade 1.
	Grade 4	Discontinue bevacizumab.

5.3.2.1 Infusion reactions

Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. Patients who experience Grade 3 or 4 allergic reaction/hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment.

The infusion should be slowed to 50% or less or interrupted for patients who experience any infusion-associated symptoms not specified above. When symptoms have completely resolved, the infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well-tolerated. Infusions may be restarted at the full rate during the next infusion.

5.3.3 Radiation Therapy

There will be no dose modifications to the radiation therapy treatment.

5.4 Supportive Care Guidelines & Use of Concomitant Medications

All medications taken during study participation, including reasons for use, will be recorded in the appropriate eCRF. For all subsequent visits, all concomitant therapy that is continuing or has been added, discontinued, or had a dosage change since the previous visit must also be recorded.

5.4.1 **Corticosteroids** should be used in the smallest dose to control symptoms of cerebral edema and mass effect and should be discontinued if possible.

5.4.2 **Anti-seizure medications** should be used as indicated.

5.4.3 If **neurosurgical intervention** is required for indications not related to tumor progression, these procedures must be documented, including indications for surgery, surgical operative note, and pathology report. In such situations, bevacizumab will be held and may be restarted at the discretion of the investigator

5.4.4 **Other therapies** considered necessary for the well-being of the patient may be given at the discretion of the investigator.

5.4.5 Any use of **complementary or alternative medications** should be cleared

by the Principal Investigator.

5.5 Criteria for Discontinuation of Treatment and Withdrawal from Study

5.5.1 Criteria for Discontinuation of Treatment

5.5.1.1 Clinical or radiographic disease progression. Patients will be treated clinically as indicated thereafter and will be tracked for survival.

5.5.1.2 Severe toxicity in which continuing treatment poses a safety risk. Please refer to Sections 5.3.1 and 5.3.2 for additional guidelines concerning treatment discontinuation due to toxicity.

5.5.2 Criteria for Withdrawal from Study

Patients who discontinue treatment for any reason, but have demonstrated stable disease or response from treatment, will be followed on study until disease progression unless one of the following occurs:

5.5.2.1 The patient or his/her legally authorized representative requests to discontinue protocol therapy or withdraws consent.

5.5.2.2 The decision is made by the treating physician to remove the patient from study due to patient non-compliance or lack of follow-up.

5.6 Follow-Up

Long-term follow-up after concurrent therapy treatment discontinuation will occur every 2-3 months (or as clinically indicated) via clinic visit or phone calls; follow-up will continue until death to assess for survival endpoints.

6.0 ENDPOINT ASSESSMENT

Response to therapy will require completion of the initial phase of therapy (consisting of concurrent re-irradiation, and bevacizumab) with a follow up MRI scan that can be compared to the pre-treatment scan. Tumor measurements and assessments will be based on Updated Response Assessment Criteria of High Grade Gliomas- Neuro-Oncology Working Group (RANO criteria). Tumor assessments may include either a CT or MRI scan of the brain; however the same method should be used throughout the treatment period for each patient.

6.1 Definitions

6.1.1 Measurable Disease

Measurable disease is defined as bi-dimensionally measurable lesions with clearly defined margins by CT or MRI scan and 2 perpendicular diameters of at least 10 mm.

6.1.2 Nonmeasurable Disease (Evaluable disease)

Nonmeasurable disease is defined as either uni-dimensionally measurable

lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters less than 10 mm.

6.1.3 Overall Survival

Overall survival (OS) will be defined as the time from first re-irradiation treatment until death from any cause.

6.1.4 Progression Free Survival

Progression free survival (PFS) will be defined as the time from the first study treatment to the first occurrence of disease progression or death.

6.2 Primary Endpoint

The primary objective is to determine the OS of patients on this study. Please refer to Section 6.1 for definition.

6.3 Secondary Endpoints

6.3.1 Change in neurological status

One secondary objective of this study is to determine the change in neurological status associated with this treatment regimen in this population. This will be assessed in several ways:

6.3.1.1 Examination

Changes in neurological and physical exam, as compared to baseline assessment.

6.3.1.2 Patient-reported outcomes

FACT-BR and FACT-fatigue scales will be obtained at baseline (pre-therapy), end of PRDR, and at the time of each subsequent MRI or CT scan.

6.3.1.3 Performance Status

Patients will be graded according to Karnofsky Performance Status, at baseline and at each bevavizumab infusion timepoint (while receiving PRDR).

6.3.2 Safety profile

Another secondary objective is to determine the safety profile of this tri-modality approach. Toxicity will be assessed using the NCI CTCAE version 5.0 criteria (see appendices). Toxicity assessments will occur weekly during the initial phase of treatment, and then prior to the start of each cycle during the adjuvant phase of treatment. Assessments may occur more frequently if needed.

6.3.3 Determine the PFS

PFS will be calculated at the 6 and 12 month time points for all patients. For the bevacizumab-exposed patients (Groups 2 and 4), PFS will also be

calculated at the 3 month timepoint. Please refer to 6.4 below for evaluation of response.

6.4 Evaluation of Response

Response will be evaluated using RANO criteria. If there are multiple contrast-enhancing lesions, a minimum of the 2 largest lesions should be measured, and the sum of the products of the perpendicular diameters of these lesions should be determined. A maximum of 5 of the largest lesions may be measured; the largest enlarging lesion(s) should be selected, with emphasis placed on lesions that allow reproducible repeated measurements.

For patients with recurrent disease who have multiple lesions of which only 1 or 2 are increasing in size, the enlarging lesions should be considered the target lesions for evaluation of response. The other lesions will be considered nontarget lesions and should also be recorded. Rarely, unequivocal progression of a nontarget lesion requiring discontinuation of therapy or development of a new contrast enhancing lesion may occur, even in the setting of stable disease or partial response in the target lesions. These changes would qualify as progression. Please refer to Table 3 below for response criteria and categories.

Table 3: Evaluation of Response by RANO Criteria

Criterion	Response Category			
	CR	**PR**	**SD**	**PD**
T1 gadolinium enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥ 25% ↑
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑
New lesion	None	None	None	Present[1]
Corticosteroids	None	Stable or ↓	Stable or ↓	n/a
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓
Requirement for response	***All***	***All***	***All***	***Any[1]***

[1] Progression occurs when this criterion is present

↓ = decreased, ↑ = increased, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease

7.0 STUDY PARAMETERS

	Screening/Baseline[1]	Concurrent (PRDR & BEV)[3]	Follow-up[13]
Re-irradiation		X[4]	
Bevacizumab		X[5]	X[14]
Informed consent	X		
Neurologic/ physical examination, vitals, and KPS	X[2]	X[10]	X
QOL evaluations (MMSE, FACT-Br & FACT-Fatigue)[12]	X	End of PRDR	X
MRI with contrast or CT[6]	X		X
Hematology[7]	X	as clinically indicated	
Urinalysis, no microscopy (for urine protein)[8]	X	X	
Pregnancy test [9]	X		
Symptom and toxicity assessment[11]	X	X	X

[1] Unless otherwise noted, screening assessments must be done within 30 days prior to registration.
[2] Baseline exam will include medical history and documentation of concomitant medications.
[3] For Bev naïve: treatment will last approximately 10 weeks and will consist of 27 fractions of radiation and 5 doses of bevacizumab.
For Bev exposed: treatment will consist of 27 fractions of radiation and 2-3 doses of bevacizumab.
[4] Re-irradiation will begin on Day 0 and will consist of a dose of 27 fractions (total of 54Gy) over 5.5 weeks using PRDR-RT.
[5] For Bev naïve: Bevacizumab will be administered at a dose of 10 mg/kg IV for 2-week cycles. The 1st dose will occur between Days -3 and 0 and will continue every 2 weeks (+/- 3 days) during the concurrent phase for a total of 5 doses.
For Bev exposed: Bevacizumab will be administered at a dose of 10 mg/kg every 2-4 weeks (+/- 3 days) for a total of 2-3 cycles. The 1st dose will occur between Days -3 and 0. Any dose given after end of PRDR, will be considered SOC during the follow-up phase.
[6]
[7] CBC with differential drawn at baseline then as clinically indicated.
[8] UA no micro within 28 days of registration and prior to each dose of bevacizumab starting with subsequent cycle/day after C1D1.
[9] Females of childbearing potential must have a negative serum or urine pregnancy test within 14 days of registration.
[10] Neurologic, physical examination (with KPS) and vitals will be performed prior to each bevacizumab dose.
[11] Patients will be assessed prior to each protocol infusion of bevacizumab, at completion of PRDR, and each follow-up MRI appointment.
[12] QOL's and MMSE will be performed at baseline, end of PRDR-RT, and each follow-up MRI appointment if patient has not progressed.
[13] Long-term follow-ups after completion of PRDR therapy or early treatment discontinuation will occur every 2-3 months (or as clinically indicated) via clinic visit or phone calls; follow-up will continue until death to assess for survival endpoints.
[14]After completion of Concurrent therapy (see footnote 3), the patient will be moved to study follow-up and Bevacizumab may be continued, per MD discretion, and administered per institutional guidelines.

8.0 DRUG FORMULATION AND PROCUREMENT

8.2 Bevacizumab

8.2.1 Other Names

Avastin

8.2.2 Classification – type of agent

Bevacizumab is a vascular endothelial growth factor- specific angiogenesis inhibitor.

8.2.3 Mode of Action

Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in *in vitro* models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

8.2.4 Storage and Stability

Upon receipt of the study drug, vials are to be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. Vials should be protected from light. Opened vials must be used within 8 hours. VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 subject may not be used for any other subject. Once study drug has been added to a bag of sterile saline, the solution must be administered within 8 hours.

8.2.5 Protocol Dose

Bevacizumab will be administered at a dose of 10 mg/kg every 2 weeks (+/- 3 days). The first dose will occur between Days -3 and 0 during the initial phase of study treatment. During the adjuvant phase of treatment, there will be 4 infusions per cycle.

8.2.6 Preparation

Bevacizumab will be diluted in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP.

8.2.7 Protocol Administration

Protocol Administration: Administration will be as an intravenous infusion.

8.2.8 Incompatibilities

Bevacizumab should not be diluted in dextrose.

8.2.9 Availability

Bevacizumab is commercially available and will not be provided by the study.

8.2.10 Side Effects

8.2.10.1 Allergy/Immunology

Allergic reaction/hypersensitivity. infusion-related reactions.

8.2.10.2 Blood/Bone marrow
Leukopenia, neutropenia, thrombocytopenia

8.2.10.3 Cardiac
Hypertension/hypertensive crisis, cardiac ischemia/infarction, supraventricular arrhythmia, left ventricular dysfunction (congestive heart failure), hypotension, and syncope

8.2.10.4 Constitutional symptoms
Asthenia, fever, rigors/chills, weight loss

8.2.10.5 Dermatology/skin
Exfoliative dermatitis, complications with wound healing, rash, skin ulceration, urticaria

8.2.10.6 Gastrointestinal
GI perforation and wound dehiscence, sometimes complicated by intra-abdominal abscesses, large bowel leakage, GI fistula, intestinal obstruction, intestinal necrosis, mesenteric venous occlusion, colitis, mucositis/stomatitis, nausea, vomiting, anorexia, constipation, diarrhea, heartburn/dyspepsia, dry mouth, taste disturbance.

8.2.10.7 Hemorrhage/Bleeding
Life-threatening or fatal pulmonary hemorrhage (primarily in lung cancer patients), CNS bleeding, GI hemorrhage, subarachnoid hemorrhage, hemorrhagic stroke, epistaxis (nose bleeds), vaginal bleeding, gum bleeding.

8.2.10.8 Infection
Infection with normal ANC.

8.2.10.9 Metabolic
Increased: alkaline phosphatase, ALT (SGPT), AST (SGOT), bilirubin, serum creatinine. Hyponatremia and hypokalemia.

8.2.10.10 Neurology
Cerebrovascular ischemia, dizziness, abnormal gait, confusion.

8.2.10.11 Ocular
Excessive lacrimation.

8.2.10.12 Pain
Abdominal pain, chest/thoracic pain, headache, arthralgias, myalgias, generalized.

8.2.10.13 Pulmonary/Upper respiratory
Dyspnea, cough, bronchospasm/wheezing, voice changes (hoarseness).

8.2.10.14 Renal/Genitourinary
Proteinuria, nephrotic syndrome

8.2.10.15 Vascular

Life-threatening and potentially fatal arterial thromboembolic events: cerebral infarction, transient ischemic attacks, myocardial infarction, angina. Venous thromboembolic events: deep vein thrombosis, intra-abdominal thrombosis

8.2.10.16 Reversible Posterior Leukoencephalopathy Syndrome

There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with RPLS, a rare neurologic disorder that can present with the following signs and symptoms (among others): seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Brain imaging is mandatory to confirm the diagnosis of RPLS. In patients who develop RPLS, treatment of specific symptoms, including control of hypertension, is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known.

8.2.11 Nursing Implications

Monitor patient closely during infusion, for infusion related events and for bleeding.

Monitor blood pressure prior to each dose to assess for development of hypertension.

Instruct patient to monitor and report signs/symptoms of bleeding (nose bleeds, blood in sputum), wound healing problems, abdominal pain, thromboembolic problems (chest or leg pain, dyspnea, vision changes, severe headache, cough, swelling).

9.0 STATISTICAL CONSIDERATIONS

9.1 Endpoints

The primary endpoint in this phase II study will be overall survival (OS). Secondary endpoints will be hematologic and neurologic toxicities, progression free survival (PFS), and survival after re-irradiation.

9.2 Sample Size Justification & Assumptions

9.2.1 Glioblastoma (Groups 1 and 2)

Using the limited data available in similar groups of patients, as noted above in Table 1, those who have received systemic therapy alone have

median survival ranging from 7.2-9.2 months [6, 15], and those who have received radiation seems to be in the range of 11-12.5 months [10, 13]. Those patients with GBM who are bevacizumab-naïve (Group 2) will presumably have improved overall outcomes compared to those who have been previously treated with bevacizumab (Group 1).

In Group 1, the primary hypothesis will be a 40% prolongation of survival (although we will measure survival as a hazard function, this is expected to shift median from an anticipated 8 to 11.2 months). To have at least 80% power to observe this delta, with a one-sided significance level of 0.1, a minimum of 24 patients will be required, and allowing for approximately 15% non-evaluability/drop-off, we anticipate a cohort size of 28.

In Group 2, the primary hypothesis will be a 50% prolongation of survival (although we will measure survival as a hazard function, this is expected to shift median from an anticipated 10 to 15 weeks. To have at least 80% power to observe this delta, with a one-sided significance level of 0.1, a minimum of 19 patients will be required, and allowing for approximately 15% non-evaluability/drop-off, we anticipate a cohort size of 22.

9.2.2 Anaplastic Glioma (Groups 3 and 4)

There are no relevant clinical data to truly estimate the PFS in these patients. The purpose of enrolling these patients is to generate preliminary descriptive data and statistics for future clinical trial design. Therefore, in Groups 3 and 4, up to 15 patients will be enrolled in each group to determine response, PFS, and OS endpoints.

9.3 Analysis

Data will be analyzed using Kaplan-Meier curves for overall survival and the median survival will be determined from these curves.

9.4 Reporting and Exclusions

9.4.1 Evaluation of toxicity

All patients will be evaluable for toxicity from the time of their first treatment with bevacizumab, or radiation therapy.

9.4.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 8) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 8

usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria should be included in the main analysis of the survival and response endpoints. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-8 will be protocol specific.

All conclusions should be based on all eligible patients. Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub-analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals for response rate should also be provided.

All patients enrolled on this study will be provided a separate consent that will allow for a brain autopsy at the time of death which is standard clinical consent at the University of Wisconsin. Patients will be encouraged to take the brain autopsy consent home and review it with family and friends. Their decision to consent or not consent will have no impact on this clinical trial. It is anticipated that approximately 50% of subjects will consent to a brain autopsy. This will allow us qualitatively compare the results of brain autopsy in patients who have received PRDR-RT /Bevacizumab to prior results (n=15) obtained with PRDR-RT

10.0 ADVERSE EVENT MONITORING & REPORTING

The ongoing review of safety data will include review of clinical adverse events (AEs) and serious adverse events (SAEs) including skin-related toxicity assessment and laboratory studies. The CTCAE version 5.0 will be used to grade all AEs.

10.1 Definition

An AE is an undesirable medical occurrence (sign, symptom, or diagnosis) or worsening of a pre-existing medical condition (diabetes, congestive heart failure, rheumatoid arthritis) that occurs after initiation of the investigational product whether or not it is considered to be investigational product related. A worsening of an existing medical condition is one that was present at baseline (e.g., cancer, diabetes, migraine headaches, gout) and became more severe, more frequent, or increased in duration during investigational product treatment.

An SAE is defined by regulatory agencies as one that suggests a significant hazard or side effect, regardless of the investigator or sponsor's opinion on the relationship to

investigational product. This includes, but may not be limited to, any event that (at any dose):

1. Is fatal
2. Is life threatening (places the subject at immediate risk of death)
3. Requires inpatient hospitalization or prolongation of existing hospitalization
4. Is a persistent or significant disability/incapacity
5. Is a congenital anomaly/birth defect
6. A hospitalization meeting the regulatory requirement for the "serious" criteria is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility
7. Any event that does not exactly meet this definition yet, in the investigator's opinion represents a significant hazard can be assigned the "other significant hazard" regulatory reporting serious criteria
8. Additionally, important medical events that may not be immediately life threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the outcomes listed above, or result in urgent investigation, may be considered serious. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

Serious adverse events

Serious adverse events will be collected and recorded at least throughout the study period beginning with the signing of the informed consent through 30 days after the end of the treatment phase or through the safety follow-up visit, whichever is longer.

All serious adverse events that occur after the subject has signed the informed consent form must be reported to UWCCC Data Safety and Monitoring Board and other regulatory agencies as per appendix 1.

Serious adverse events occurring after conclusion of the study AND thought to be possibly related to the investigational study will be collected and reported within 10 working days of discovery or notification of the event via the same mechanism.

11.0 RECORDS TO BE KEPT

This protocol will be conducted according to Good Clinical Practice Guidelines. Participating investigators/institutions agree to permit trial related monitoring, audits, IRB review, and regulatory inspections, providing direct access to source

documents/data.

All data identified in patient evaluation table, Section 7.0 will be collected. The planning data, simulation films, isodose distributions (axial, coronal, and sagittal planes through the PTV) will be archived per radiation therapy standard clinical practice

Eligibility Checklist	Submitted prior to registration
On Study Forms: -Baseline Form -Pre-Study Labs -Imaging form -QOL's (MMSE, FACT-BR and FACTIT-Fatigue)	Within 2 weeks of Registration
End of Radiation: -XRT summary form -Appropriate Bevacizumab treatment form - QOL's (MMSE, FACT-BR and FACTIT-Fatigue) -AE form	Within 2 weeks of Completion
For patients in follow-up: -AE form -MRI form (if patient hasn't progressed) - QOL's (if patient hasn't progressed) (MMSE, FACT-BR and FACTIT-Fatigue)	Every 2-3 months
Time of Death -Follow-up form	Within 2 weeks

Follow-up data and signed informed consents will be kept for a minimum of five years. Forms will be labeled with study number, subject initials sequence numbers assigned sequentially when subjects are registered.

12.0 PATHOLOGY REQUIREMENTS

All patients who had surgery outside of UW Hospital will be asked to submit 1 H&E slide for review at UW for confirmation of diagnosis. A copy of the pathology report from the primary surgery is sufficient for registration. Biopsy proof of recurrent disease is not required. Dr. Shahriar Salamat and Dr. Jeffrey Helgager are the designated Neuro-Oncology Neuropathologists. Send slide to Marissa Weiss. See protocol cover page for mailing address.

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Appendix I – Data and Safety Monitoring Plan

Oversight And Monitoring Plan

The UWCCC Data and Safety Monitoring Committee (DSMC) is responsible for the regular review and monitoring of ongoing clinical research in the UWCCC. A summary of DSMC activities are as follows:

- Review clinical trials conducted at the UWCCC for subject safety, protocol compliance, and data integrity.
- Review Serious Adverse Events (SAE) requiring expedited reporting, as defined in the protocol, for clinical trials conducted at the UWCCC, and studies conducted at external sites for which the UWCCC acts as an oversight body.
- Review reports generated through the UWCCC DSMS elements (Internal Audits, Quality Assurance Reviews, Response Reviews, Compliance Reviews, and Protocol Summary Reports).
- Notify the protocol Principal Investigator of DSMC decisions and, if applicable, any requirements for corrective action related to data or safety issues.
- Work in conjunction with the UW Health Sciences IRB in the review of relevant safety information as well as protocol deviations, non-compliance, and unanticipated problems reported by the UWCCC research staff, when appropriate.
- Ensure notification of SAEs which require expedited reporting are provided to external sites participating in multi-institutional clinical trials coordinated by the UWCCC.

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Monitoring And Reporting Guidelines

UWCCC quality assurance and monitoring activities are determined by study sponsorship and risk level of the protocol as determined by the PRMC. Protocols (including Intervention Trials, Non-Intervention Trials, Behavioral and Nutritional Studies, and trials conducted under a Training Grant) are evaluated by the PRMC at the time of committee review. UWCC monitoring requirements for trials without an acceptable external DSMB are as follows

Intermediate Monitoring

Protocols subject to intermediate monitoring generally include UW Institutional Phase I/II and Phase II Trials. These protocols undergo review of subject safety at regularly scheduled DOT meetings where the results of each subject's treatment are discussed and the discussion is documented in the DOT meeting minutes. The discussion includes the number of subjects enrolled, significant toxicities, dose adjustments, and responses observed. Protocol Summary Reports are submitted on a semi-annual basis by the study team for review by the DSMC.

I. REVIEW AND OVERSIGHT REQUIREMENTS

II.

a) Serious Adverse Event – Reported Within 24 Hours

Serious Adverse Events requiring reporting within 24 hours (as described in the protocol) must also be

reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu within one business day. A 24 hr. initial "SAE Details" Report, generated in the UWCCC database, must be attached to the email along with any pertinent information available at the time of initial reporting. The DSMC Chair will review the information and determine if immediate action is required. Within 10 working days, all subsequent SAE documentation must be submitted electronically along with a 24 hour follow-up "SAE Details" Report and a completed UWCCC SAE Routing Form to saenotify@uwcarbone.wisc.edu. All information is entered and tracked in the UWCCC database.

If the SAE occurs on a multiple-institutional clinical trial coordinated by UW Radiation Oncology, the UW Radiation Oncology coordinators should be notified by phone (see cover page) and email at: dho-datamgrs@lists.humonc.wisc.edu who will ensure that all participating sites are notified of the event and resulting action within one working day of the determination.

b) Serious Adverse Event – Reported within 10 Days

Serious Adverse Events requiring reporting within 10 working days (as described in the protocol) will also be sent to the UWCCC DSMC Chair via email to saenotify@uwcarbone.wisc.edu. A 10 day "SAE Details" report, generated in the UWCCC database must be attached to the email along with pertinent information regarding the SAE and the UWCCC SAE Routing Form. The Committee Chair will review the information and determine if further action is required. This information is entered and tracked in the UWCCC database.

If the SAE occurs on a multiple-institutional clinical trial coordinated by UW Radiation Oncology, the UW Radiation Oncology coordinators should be notified by phone (see cover page) and email at: dho-datamgrs@lists.humonc.wisc.edu who will ensure that all participating sites are notified of the event and resulting action within one working day of the determination.

c) Study Progress Review

Study Progress Review- Protocol Summary Reports

Protocol Summary Reports (PSR) are required to be submitted to the DSMC commensurate with the Phase of the study. The PSR provides a cumulative report of serious adverse events, as well as any protocol violations, deviations or unanticipated problems, toxicities and responses that have occurred on the protocol in the timeframe specified. PSRs are reviewed at each DSMC meeting.

Protocol Summary Reports enable DSMC committee members to assess whether significant benefits or risks are occurring that would warrant study closure. This information is also provided by Disease Oriented Working Group meeting minutes, internal audit and/or response review reports. In addition, the DSMC requires the DOWG or protocol Study Chair to submit external DSMB reports or any other significant study-related information.

In the event that there is significant risk warranting study suspension or closure, the DSMC will notify the PI of the DSMC findings. The DSMC ensures that the PI reports any temporary or permanent suspension of a clinical trial to the sponsor (e.g., NCI Program Director, Industry Sponsor Medical Monitor, Cooperative Group Study Chair, etc.) and other appropriate agencies.

II EXPEDITED REPORTING OF SERIOUS ADVERSE EVENTS

Depending on the nature, severity, and attribution of the serious adverse event an SAE report will be phoned in, submitted in writing, or both according to Table *C* below. All

serious adverse events must also be reported to the UWCCC Data and Safety Monitoring Committee Chair. All serious adverse events must also be reported to the UW IRB (if applicable), and any sponsor/funding agency not already included in the list.

Determine the reporting time line for the SAE in question by using the following table. Then refer to sections A and B below if the SAE occurred at the UWCCC or sections C and D if the SAE occurred at 1 South Park, Johnson Creek, or a WON Site.

Expedited Reporting Requirements for Adverse Events that Occur in Non-IND/IDE Studies Within 28 Days Post Commercial Drug Therapy

Reporting Requirements for Serious Adverse Events

NOTE: Investigators MUST immediately report to the *UWCCC DSMC, and the IRB (if applicable)* ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention. See below.
An adverse event is considered serious if it results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse event.
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria* MUST be immediately reported to the UWCCC within the timeframes detailed in the table below:

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour; 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

** Hospitalization for medical management of grade 1-2 seizure disorders does not require reporting as an SAE and consideration of a seizure as an Important Medical Event is at the discretion of the treating physician.**

Expedited AE reporting timelines are defined as:

- **24-Hour; 5 Calendar Days** – The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- **10 Calendar Days** – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 28 days after study intervention and have an attribution of possibly, probably, or definitely related study will be reported as follows:

Expedited 24-hour notification followed by complete report within 10 calendar days for:

- All Grade 4, and 5 SAEs

A. <u>SAE Requiring 24 Hour Reporting Occurs at UWCCC:</u>

a. To the IRB:

Consult the UW-IRB website for reporting guidelines.

b. To the UWCCC:

Reference the **SAE SOP** (Standard Operating Procedure) and the **SAE Reporting Workflow for DOWGs** on the UWCCC website (http://www.uwccc.wisc.edu) for specific instructions on how and what to report to the UWCCC for *[24]* hour initial and follow-up reports. **A follow-up report is required to be submitted within 10 days of the initial *[24]* hour report.**

For this protocol, the following entities are required to be notified:

1. saenotify@uwcarbone.wisc.edu
2. Steve Howard, MD: PI
3. Diana Trask Research Program Manager

SAE Requiring *[10]* Day Reporting Occurs at UWCCC:

a. To the *FDA:*

Report the SAE using the online FDA Med Watch form available at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm. Also print the report or save it as a pdf for reporting to the *IRB (see section b)* UWCCC (see section c).

b. To the IRB:

Consult the UW-IRB website for reporting guidelines.

c. To the UWCCC:

Reference the **SAE SOP** (Standard Operating Procedure) and the **SAE Reporting Workflow for DOWGs** on the UWCCC website (http://www.uwccc.wisc.edu) for specific instructions on how and what to report to the UWCCC for *[24]* hour initial and follow-up reports. **A follow-up report is required to be submitted within 10 days of the initial *[24]* hour report.**

For this protocol, the following entities are required to be notified:

1. saenotify@uwcarbone.wisc.edu
2. Steve Howard, MD: PI
3. Diana Trask Research Program Manager

Appendix IV – FACT-Br & FACT-Fatigue Scales

Below is a list of statements that other people with your illness have said are important**.**
Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy.....	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends.....	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness.....	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support).....	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					

GS7	I am satisfied with my sex life.....	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness.....	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling.....	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF4	I have accepted my illness.....	0	1	2	3	4
GF5	I am sleeping well.....	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now.....	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

ADDITIONAL CONCERNS

		Not at all	A little bit	Some-what	Quite a bit	Very much
Br1	I am able to concentrate	0	1	2	3	4
Br2	I have had seizures (convulsions)	0	1	2	3	4
Br3	I can remember new things	0	1	2	3	4
Br4	I get frustrated that I cannot do things I used to	0	1	2	3	4
Br5	I am afraid of having a seizure (convulsion)	0	1	2	3	4
Br6	I have trouble with my eyesight	0	1	2	3	4
Br7	I feel independent	0	1	2	3	4
NTX6	I have trouble hearing	0	1	2	3	4
Br8	I am able to find the right word(s) to say what I mean	0	1	2	3	4
Br9	I have difficulty expressing my thoughts	0	1	2	3	4
Br10	I am bothered by the change in my personality	0	1	2	3	4
Br11	I am able to make decisions and take responsibility	0	1	2	3	4
Br12	I am bothered by the drop in my contribution to the family	0	1	2	3	4
Br13	I am able to put my thoughts together	0	1	2	3	4
Br14	I need help in caring for myself (bathing, dressing, eating, etc.)	0	1	2	3	4
Br15	I am able to put my thoughts into action	0	1	2	3	4
Br16	I am able to read like I used to	0	1	2	3	4
Br17	I am able to write like I used to	0	1	2	3	4
Br18	I am able to drive a vehicle (my car, truck, etc.)	0	1	2	3	4
Br19	I have trouble feeling sensations in my arms, hands, or legs	0	1	2	3	4
Br20	I have weakness in my arms or legs	0	1	2	3	4
Br21	I have trouble with coordination	0	1	2	3	4
An10	I get headaches	0	1	2	3	4

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

English (Universal)
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