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A Phase II Study of Bevacizumab, Temozolomide and Hypofractionated Radiotherapy for Patients with Newly Diagnosed Glioblastoma.

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a pilot study to evaluate the feasibility and efficacy of a novel treatment regimen for newly diagnosed glioblastoma patients. In this study, patients will receive hypo-fractionated radiotherapy (RT) in combination with temozolomide and bevacizumab followed by adjuvant therapy with bevacizumab and temozolomide. This treatment regimen is novel in that it delivers the initial course of RT over 2 weeks instead of 6 weeks; also, the addition of bevacizumab during and after RT is a new approach. This approach has the potential to be an improvement on the effectiveness of current therapy as it is designed to target tumor stem cells and endothelium in addition to the primary tumor.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary objective:

- To test the safety and feasibility of delivering bevacizumab and temozolomide in combination with hypo-fractionated radiotherapy to patients with newly diagnosed glioblastoma.

Secondary objectives:

- Progression free survival
- Overall survival
- Neurocognitive outcome

3.0 BACKGROUND AND RATIONALE

3.1 Background

The treatment of glioblastoma represents a therapeutic challenge, even with maximal treatment at diagnosis, malignant gliomas have a dismal prognosis. Standard management is optimal surgical resection followed by a combination of temozolomide and involved field radiotherapy followed by adjuvant temozolomide. (Stupp 2005) However, median survival for glioblastoma remains poor at 14.6 months and average time to tumor progression is approximately 6 months.

Several recent phase II studies have shown that bevacizumab is an active agent in the treatment of recurrent malignant glioma either as a single agent or in combination with irinotecan; radiographic response rates range from 30 to 60% and 6 month progression free survival (PFS) is approximately 40%. (Vrendenburgh 2007, Cloughesy 2008, Norden 2008). The benchmark for success in recurrent glioma trials is typically given as a response rate of 10-15% and a 6 month PFS of 20-30%. As a result of this promising data, bevacizumab has been widely adopted as salvage therapy for patients with recurrent malignant glioma and current clinical trials seek to address the optimal way to integrate bevacizumab into the management of treatment naïve patients.

Standard radiation therapy (RT) for glioblastomas is 60Gy divided into 30 fractions of 2 Gy each. This is typically delivered 5 days a week over 6 weeks. Side effects can include fatigue, headache, nausea, vomiting and worsening of neurologic function if edema occurs during treatment. Side effects are typically well managed by steroids that are administered at initiation of treatment. Dose escalation and alternative fractionation studies done with both external beam RT and brachytherapy have not improved outcomes and produced higher toxicity in some studies.

Although RT is the most effective treatment for gliomas, recurrences are most likely to recur within the field of full dose radiation. The addition of temozolomide to RT has improved survival modestly but the outcome is still dismal. Thus, alternate treatment strategies must be investigated to improve the effectiveness of RT.

In addition to bevacizumab, hypofracionated RT is an attractive treatment strategy. Hypofracionated RT may be biologically more effective in killing glioma cells than standard fractionation RT as glioma cells are relatively radioresistant. There are clear fractionation studies that show that radioresistant cell lines such as melanoma and renal cell cancer are clearly more responsive to hypofractionated RT versus standard fractionation RT.

Short and long-term side effects of RT are related to both volume and fractionation. Hypofractionated RT has not been used as a standard approach for gliomas due to concern about toxicity given the relatively extensive nature of these tumors. However, in our MSK 05-092 experience with recurrent glioma patients treated with concurrent bevacizumab and hypofractionated RT, the radiation was tolerated very well. Most of the patients did not need steroids to manage side effects from treatment and patients had minimal fatigue during the course of RT. Follow-up MRI's indicated that bevacizumab decreases tumor related edema and thus may be the reason why the hypofractionated RT was so well tolerated even in this group of previously irradiated patients.

3.2 Rationale for the proposed study

This study builds on the results of our recently completed trial, MSK 05-092, which demonstrated that the combination of bevacizumab and hypofractionated re-irradiation is both safe and effective for patients with recurrent malignant glioma. (Mohile 2007) Radiographic response rates were excellent at 73% and 6m PFS was 76%. This success is due in large part to the combination of bevacizumab with high dose per fraction radiotherapy. Therefore, we have designed this study to build on these results for patients with newly diagnosed glioblastoma. This represents a novel treatment strategy that is both scientifically and clinically attractive for several reasons:

1. The combination of bevacizumab and high dose fraction RT targets tumor endothelium. Tumor endothelium has been shown by Fuks and Kolesnick and their coworkers at Sloan-Kettering to be a prime target for radiotherapy, particularly at high dose fractions. Vascular endothelial growth factor (VEGF) prevents radiation-induced endothelial cell death after being induced by HIF-1a, itself being induced by hypoxia and by reactive oxygen species in reoxygenating tumor tissue. Blockade of VEGF via antibody binding of its VEGFR2 receptor sensitizes tumor vessels to irradiation. Such antibody treatment may also "prune" the VEGF-dependent structurally abnormal and highly inefficient neovessels and may thereby increase the efficiency of oxygen delivery and improve radiosensitivity of the tumor cells themselves. Therefore, VEGF blockade may sensitize tumor endothelium and tumor cells.

Malignant gliomas are highly hypoxic tumors with high endogenous expression of HIF-1a and of VEGF and its receptors, with a consequently vigorous angiogenic phenotype. These are the perfect tumors against which to test the hypothesis that VEGF blockade can sensitize tumors to irradiation. The synergy of anti-angiogenic agents with radiation has been shown in many preclinical studies, including with experimental brain tumors. There has been only a single clinical trial testing an anti-angiogenic agent (angiostatin) with radiotherapy.

2. ***Targeting the perivascular niche is critical to eradicating glioblastoma stem cells.*** Tumor stem cells are increasingly recognized as a critical element of tumorigenesis and resistance to current therapeutic approaches. In particular, for malignant gliomas, the tumor related stem cells largely reside in and are dependent on the perivascular microenvironment and VEGF signaling for survival. (Gilbertson and Rich, Nature Reviews 2007) The proposed treatment strategy will intensely target this perivascular tumor microenvironment and we are hopeful that this will result in synergistic impact on the tumor, tumor vasculature and tumor stem cell population.

Clinically, the current standard of care for patients with newly diagnosed glioblastoma is to treat with concurrent low dose temozolomide and radiotherapy (60Gy) over approximately 6 weeks followed by at least 6 months of adjuvant monthly temozolomide. Our proposed regimen would significantly alter the standard treatment regimen in 3 critical ways:

1. Radiotherapy will be delivered using hypo-fractionated stereotactic IMRT with dose painting

Radiotherapy to the brain can now be given with great precision and with sparing of the surrounding tissues using dynamic multileaf collimation with intensity modulated radiotherapy (IMRT). Our experience with the use of 30Gy to the tumor given in 5 fractions over two and a half weeks (two fractions per week) using 6 Gy per fraction has indicated that this regimen is safe and effective in previously-irradiated patients with malignant glioma as well as in large lesions located close to the brain stem or involving the brain stem.

Several studies have shown that hypo-fractionated radiotherapy is feasible and safe for primary high-grade gliomas. The radiation will also be delivered with "dose painting" achieved through IMRT so that the gadolinium-enhancing region of the tumor would receive 6 Gy per fraction and the edematous regions as defined on FLAIR sequences would receive 4 Gy per fraction. This hypo-fractionated dose is equivalent to 60Gy over 6 weeks by conventional radiotherapy, but has the advantage of convenience to the patient, decreased acute toxicity, less steroid dependency and better tolerance.

2. ***Bevacizumab will be administered in combination with radiotherapy.***

The results of our initial study demonstrated that this combination is safe even in the treatment of previously radiated patients and we did not observe an increased risk of CNS hemorrhage or radiation necrosis.

3. ***Bevacizumab will be administered in combination with temozolomide both during and after radiotherapy.***

To date, bevacizumab has been administered safely and successfully in combination with multiple different chemotherapeutic agents. In most solid tumors it has been critical to combine bevacizumab with an active chemotherapy agent in order to obtain clinically meaningful benefit. The initial reports in GBM combined bevacizumab with irinotecan which is not a particularly active agent in malignant glioma with response rates below 10% as a single agent. Temozolomide is the most effective chemotherapy currently available for the treatment of glioblastoma and therefore would be the ideal drug to test in combination with bevacizumab to optimize benefit. Specific combinations of bevacizumab and temozolomide are currently being studied at several sites (RTOG, Duke, UCLA, U of Chicago), to the best of our knowledge no unexpected toxicities have been reported (Lai 2008). However, we recognize that the particular combination proposed here is novel and will require careful monitoring for acute and delayed toxicity.

Rationale for neurocognitive assessments:

As new treatments that may increase survival for GBM patients are developed, it is important to assess cognitive outcome and quality of life in the context of prospective clinical trials. The National Cancer Institute (NCI) Brain Tumor Progress Review Group Report has recommended that routine cognitive and QOL assessment become the standard of care for patients with brain tumors (BTPRG, 2000). This is particularly relevant for the novel treatment with BV in combination with TMZ and RT, considering the preliminary evidence of increased survival but unknown long-term neurotoxicity of this regimen. Cognitive dysfunction is common in brain tumor patients, and can be related to both the disease and the adverse effects of treatment including surgery, RT and chemotherapy. Cognitive difficulties often have an impact on quality of life and interfere with the patient's ability to function at premorbid levels (Weitzner & Meyers, 1997). The literature suggests that whole-brain RT alone or in combination with

chemotherapy often result in more pronounced cognitive dysfunction (Correa et al., 2004; Harder et al., 2004) than either partial RT or chemotherapy alone (Armstrong et al., 2000; Taphoorn et al., 1994; Correa et al., 2007; Fliessbach et al., 2005). The cognitive domains suggested to be particularly sensitive to treatment-induced cognitive dysfunction include several aspects of attention and executive functions, learning and retrieval of new information, and psychomotor speed.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

- This will be a pilot study to address the safety and feasibility of delivering bevacizumab and temozolomide in combination with hypo-fractionated radiotherapy to patients with newly diagnosed glioblastoma. There is no planned randomization. All patients enrolled on the study will be included in the analysis in an intent to treat fashion

4.2 Intervention

Screening (w/in 2 weeks of enrollment): Gadolinium-enhanced brain MRI with perfusion, neurological/physical examination, neurocognitive assessment, laboratory values and blood pressure measurement.

Treatment:
Bevacizumab10 mg/kg IV once every two weeks on days 1 and 15 of every cycle (Cycle defined as 28 days). Temozolomide 75mg/m^2 daily beginning on day 1 through completion of radiotherapy. Hypofractionated dose painting IMRT will start on day 1 and will be delivered on a Monday, Wednesday, Friday schedule for a total of 6 fractions.

Post RT therapy: Bevacizumab 10mg/kg IV every two weeks. Temozolomide 150-200mg/m^2 daily for 5 consecutive days will be given on 28 day cycles as detailed in section 9.2.

Follow up: CBC weekly, comprehensive panel and urinalysis monthly, blood pressure every other week. Neurological/physical examination monthly. Gd-enhanced MRI with perfusion every 2 cycles. Neurocognitive assessment will be performed as per section 10.0.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 BEVACIZUMAB

Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution for intravenous (IV) infusion. Bevacizumab may be supplied 20-cc (400-mg) glass vials containing 16 ml bevacizumab, at 25 mg/ml). Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and sterile water for injection (swfi), usp. Vials contain no preservative and are suitable for single use only. For further details and molecule characterization, see the bevacizumab investigator brochure.

5.1.1 Bevacizumab Administration

Bevacizumab will be diluted in a total volume of 100mL of 0.9% Sodium Chloride Injection, USP. Administration will be as a continuous IV infusion. Anaphylaxis precautions should be observed during study drug administration. It is not necessary to correct dosing based on ideal weight. Dose administration will follow institutional guidelines.

If a subject experiences an infusion–associated adverse event, he or she may be premedicated for the next study drug infusion; however, the infusion time may not be decreased for the subsequent infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30±10 minutes as long as the subject continues to be premedicated. If a subject experiences an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90±15 minutes. Similarly, if a subject experiences an infusion-associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60±10 minutes.

5.1.2 Bevacizumab Storage

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.

5.2 TEMOZOLOMIDE

Temozolomide is an oral cytotoxic alkylating agent which undergoes spontaneous conversion to MTIC, the active metabolite of dacarbazine, at physiologic pH. It has demonstrated activity against and is approved for the treatment of newly diagnosed glioblastoma.

Temozolomide is manufactured by Schering Plough, Inc. It is available as 5, 20, 100, 140, 180 and 250 mg capsules. The 20mg and 100mg capsules are projected to be stable for at least 30 months when stored between 2 and 30°C in amber glass bottles. The 5mg and 250mg capsules are projected to be stable for at least 12 months under the same conditions.

Commercially available drug supply will be used for this study.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

Any adult patient with a newly diagnosed glioblastoma would be a candidate to participate in this study.

6.1 Subject Inclusion Criteria

- Pathologic diagnosis of glioblastoma or grade IV glioma.
- Tumor volume should be less than 60 cc (approximately 5cm maximum diameter).
- Age $\geq$ 18
- KPS $\geq$70
- Granulocyte count >1.5 X 10^9/L
- Platelet count >99 X 10^9/L
- SGOT < 2.5X upper limit of normal (ULN).
- Serum creatinine < 2X ULN.
- Bilirubin < 2X ULN.
- All patients must sign written informed consent.

6.2 Subject Exclusion Criteria

- Any prior chemotherapy, radiotherapy and biologic therapy for glioma.
- Any prior experimental therapy for glioma.
- Tumor invasion of the corpus callosum.
- Multicentric glioma
- Other concurrent active malignancy (with the exception of cervical carcinoma in situ or basal cell ca of the skin).
- Serious medical or psychiatric illness that would in the opinion of the investigator interfere with the prescribed treatment.
- Pregnant or breast feeding women.

- Refusal to use effective contraception.
  Inadequately controlled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure > 100 mmHg)
- Prior history of hypertensive crisis or hypertensive encephalopathy
- New York Heart Association (NYHA) Grade II or greater congestive heart failure (see Appendix E)
- History of myocardial infarction or unstable angina within 12 months prior to Day 1
- History of stroke or transient ischemic attack
- Significant vascular disease (e.g., aortic aneurysm, requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1
- History of hemoptysis (≥ 1/2 teaspoon of bright red blood per episode) within 1 month prior to Day 1
- Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 1 of treatment or anticipation of need for major surgical procedure during the course of the study
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to Day 1
- History of abdominal fistula or gastrointestinal perforation within 6 months prior to Day 1
- Serious, non-healing wound, active ulcer, or untreated bone fracture
- Proteinuria as demonstrated by a UPC ratio ≥ 1.0 at screening
- Known hypersensitivity to any component of bevacizumab

7.0 RECRUITMENT PLAN

Patients will be recruited from the neurology, radiation oncology and neuro-surgery services at MSKCC. All patients will be seen by a neuro-oncology attending. All patients entered in the protocol will give written informed consent. There are no gender or racial restrictions.

8.0 PRETREATMENT EVALUATION

The following studies are required within two weeks prior to starting concurrent immunochemotherapy and radiotherapy:

- Complete history and physical exam including vitals signs and neurologic exam.
- Height and weight.
- CBC including WBC differential and platelet count.

- Comprehensive chemistry panel.
- Urine protein: creatinine ratio or urinalysis.
- Gadolinium enhanced MRI brain with perfusion
- Neurocognitive assessment (Time 1, see details in section 10)

9.0 TREATMENT/INTERVENTION PLAN

9.1 Concurrent immunochemotherapy and radiotherapy

This treatment should start approximately 4 to 6 weeks after surgical resection. Bevacizumab may NOT be given until day 29 post resection.

Bevacizumab 10mg/kg will be administered on day 1 and15.

Temozolomide will be given at a dose of 75mg/m2 daily for the complete course of radiotherapy. Patients will start temozolomide on day 1 and take the last dose on the final day of radiotherapy; temozolomide should be taken at least 1 hour before RT is administered. Patients will dose on weekdays, weekends and holidays when radiotherapy is not scheduled. Supportive anti emetic therapy will be prescribed per institutional guidelines or at the discretion of the treating physician.

Hypofractionated radiotherapy will start on day 1 and will be delivered on a Monday, Wednesday, Friday schedule for a total of 6 fractions

Patients will be simulated with a 5 point Aquaplast face-mask and an ACQSim CT scan with IV contrast (unless contraindicated). The T1 post-contrast images from the most recent MRI will be fused to the treatment planning CT to define the GTV_1 (gross tumor volume).

The GTV_1 will be defined as any post-operative residual contrast enhancing tumor and should represent a single structure (ie the GTV_1 should not be multifocal). If a gross total resection was performed, the GTV_1 will be defined as the post-operative cavity. A 5mm margin will be added to create a CTV_1 and an additional 5mm will be added to create a PTV_1. The PTV_1 will be treated with 600 cGy per fraction. Thus, the PTV_1 will receive a total dose of 3600cGy.

The flair images from the post-operative MRI will be fused to the treatment planning CT scan as well. The GTV_2 will be defined as the flare abnormality as defined on that post-operative MRI. A 2cm margin will be added to create a CTV_2 and an additional 5mm will be added to create a PTV_2. The PTV_2 will be treated with 400 cGy per fraction. Thus, the PTV_2 will receive a total dose of 2400cGy.

A dose-painting technique with intensity modulated radiation therapy (IMRT) will be used to for treatment in order to achieve a homogeneous dose distribution to the above defined volumes. A plan entailing the treatment goals within 10% of the prescribed dose will be accepted.

The optic structures (chiasm and optic nerves) will be kept to <3.5Gy per fraction and the brainstem should have a D05 of 6Gy per fraction (so that no more than 5% of the brainstem receives 6 Gy per fraction).

9.2 Adjuvant bevacizumab and temozolomide

This therapy will begin approximately 3 weeks after the completion of radiotherapy and will last for a total of 6 cycles (1 cycle = 28 days). Additional cycles may be administered at the discretion of the treating physician.

Bevacizumab 10mg/kg will be administered on day 1 and 14 (+/- 3 days) of each cycle.

Temozolomide

Cycle 1: TMZ will be delivered at the standard dose of 150mg/m^2 daily for days 1-5.

Cycle 2+: TMZ may be escalated to full dose 200mg/m^2 daily for days 1-5 of each cycle if no grade 3 toxicity was seen in cycle one. Further rules for dose modification are outlined in section 11.0.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

During concurrent immunochemotherapy and radiotherapy:

- CBC weekly (this should continue during the 3 weeks between completion of RT and adjuvant therapy).
- Brief physical exam including vital signs weekly by radiation oncology.

During adjuvant bevacizumab and temozolomide:

Within one week prior to initiation of adjuvant therapy a new contrast enhanced MRI with perfusion will be obtained – this will be considered a new baseline MRI and all patients should continue to adjuvant therapy regardless of MRI result.

- Weekly CBC and monthly comprehensive chemistry panel.
- Monthly exam including vital signs
- Urine protein:creatinine ratio or urinalysis for proteinuria monthly

- Contrast enhanced MRI with perfusion after every 2 cycles of therapy
- Neurocognitive testing (approximately 4months post RT, 1 year after diagnosis and then annually in long term survivors)
- After completion of protocol treatment all patients will be followed for survival and delayed toxicity; patients who completed treatment without evidence of tumor progression will also be followed for disease control. MRI and clinical evaluation including neurologic exam will be performed approximately every 3 months.

Neurocognitive testing

Patients will undergo a brief neuropsychological test battery subsequent to surgery and prior to initiation of BV, TMZ and RT (Time 1). Patients without evidence of recurrent disease will be seen for neuropsychological re-evaluations approximately 4 to 5 months after surgery (Time 2), 8 months post surgery (Time 3) and about 1 year post-surgery (Time 4). Cognitive re-evaluations will be performed on a yearly basis subsequently in long-term survivors without evidence of disease recurrence.

All cognitive measures selected have appropriate norms (i.e., considering age and education), and the majority have published high construct validity, and test/re-test reliability. Patients will also complete self-report measures of fatigue and mood. The entire evaluation can be completed in approximately 60 minutes. The neuropsychological test battery will be re-administered at each of the follow-up visits, and alternate forms of tests will be used whenever available to avoid practice effects.

11.0 TOXICITIES/SIDE EFFECTS

11.1 Radiation

Radiation: the expected acute side effects include

- Fatigue (grade 1-2)
- Alopecia (partial)
- Headache (grade 1)

Radiation: other possible but unlikely acute side effects include

- Headache (grade 2 or higher)
- Nausea/vomiting
- Exacerbation of existing neurologic symptoms
- Development of new focal neurologic symptoms

Radiation: possible but unlikely long-term side effects include

- White matter changes
- Changes in memory or thought processes

- <10%:Necrosis

11.2 Temozolomide

Temozolomide: the most common grade 3 or 4 toxicities reported include:

- <10%: nausea/vomiting, elevated liver enzymes, elevated BUN/Cr, constipation.
- <5%: lymphopenia, thrombocytopenia, rash, headache, alopecia, fatigue.
- <1%: lethargy.

NCI CTC version 3.0 will be used to grade all toxicity.

Temozolomide dose modification:

If hematologic toxicity grade 3 or higher occurs, patients may be treated with appropriate growth factors. If clinically indicated the dose of temozolomide may be reduced by 25mg/m^2/day.

If grade 3 or 4 treatment related non-hematologic toxicity occurs the dose of temozolomide may be reduced by 25mg/m2/day. Temozolomide will be held until all related non-hematologic toxicity has resolved to a grade 2 or lower.

11.3 Bevacizumab: Safety Profile

In the initial Phase I and II clinical trials, four potential bevacizumab-associated safety signals were identified: hypertension, proteinuria, thromboembolic events, and hemorrhage. Additional completed Phase II and Phase III studies of bevacizumab as well as spontaneous reports have further defined the safety profile of this agent. Bevacizumab-associated adverse events identified in phase III trials include congestive heart failure (CHF) primarily in metastatic breast cancer, gastrointestinal perforations, wound healing complications, and arterial thromboembolic events (ATE). These and other safety signals are described in further detail as follows and in the bevacizumab Investigator Brochure.

Hypertension: An increased incidence of hypertension has been observed in patients treated with bevacizumab. Grade 4 and 5 hypertensive events are rare. Clinical sequelae of hypertension are rare but have included hypertensive crisis, hypertensive encephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS) (Ozcan et al., 2006; Glusker et al., 2006).

There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Therefore, caution should be exercised before initiating bevacizumab therapy in these patients. Monitoring of blood pressure is recommended

during bevacizumab therapy. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.

Temporary interruption of bevacizumab therapy is recommended in patients with hypertension requiring medical therapy until adequate control is achieved. If hypertension cannot be controlled with medical therapy, bevacizumab therapy should be permanently discontinued. Bevacizumab should be permanently discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy.

Proteinuria: An increased incidence of proteinuria has been observed in patients treated with bevacizumab compared with control arm patients. In the bevacizumab-containing treatment arms of clinical trials (across all indications), the incidence of proteinuria (reported as an adverse event) was up to 38% (metastatic CRC Study AVF2192g). The severity of proteinuria has ranged from asymptomatic and transient events detected on routine dipstick urinalysis to nephrotic syndrome; the majority of proteinuria events have been grade 1. NCI-CTC v. 3.0 Grade 3 proteinuria was reported in up to 3% of bevacizumab-treated patients, and Grade 4 in up to 1.4% of bevacizumab-treated patients. The proteinuria seen in bevacizumab clinical trials was not associated with renal impairment and rarely required permanent discontinuation of bevacizumab therapy. Bevacizumab should be discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome).

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence from the dose-finding, Phase II trials (AVF0780g, AVF0809s, and AVF0757g) suggesting that Grade 1 proteinuria may be related to bevacizumab dose.

Proteinuria will be monitored by urine protein:creatinine (UPC) ratio at least every 6 weeks. If the UPC ratio is not available, a dipstick urinalysis may be used to allow treatment to proceed.

Thromboembolic Events: Both venous and arterial thromboembolic (TE) events, ranging in severity from catheter-associated phlebitis to fatal, have been reported in patients treated with bevacizumab in the colorectal cancer trials and, to a lesser extent, in patients treated with bevacizumab in NSCLC and breast cancer trials.

Venous thromboembolism (including deep venous thrombosis, pulmonary embolism, and thrombophlebitis: In the phase III pivotal trial in metastatic CRC, there was a slightly higher rate of venous TE events in patients treated with bevacizumab plus chemotherapy compared with chemotherapy alone (19% vs. 16%).

In Study AVF2107g, a Phase III, pivotal trial in metastatic CRC, VTE events, including deep venous thrombosis, pulmonary embolism, and thrombophlebitis, occurred in 15.2% of patients receiving chemotherapy alone and 16.6% of patients receiving chemotherapy + bevacizumab.

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The incidence of NCI-CTC v. 3.0 Grade ≥ 3 venous VTE events in one NSCLC trial (E4599) was higher in the bevacizumab-containing arm compared to the chemotherapy control arm (5.6% vs. 3.2%). One event (0.2%) was fatal in the bevacizumab-containing arm; not fatal events were reported in the carboplatin/paclitaxel arm (see Bevacizumab Investigator Brochure).
In metastatic CRC clinical trials, the incidence of VTE events was similar in patients receiving chemotherapy + bevacizumab and those receiving the control chemotherapy alone.

In clinical trials across all indications the overall incidence of VTE events was 2.8%−17.3% in the bevacizumab-containing arms compared with 3.2%−15.6% in the chemotherapy control arms. The use of bevacizumab with chemotherapy does not substantially increase the risk of VTE event compared with chemotherapy alone. However, patients with metastatic CRC who receive bevacizumab and experienced a VTE event may be at higher risk for recurrence of VTE event.

Arterial Thromboembotic Events: An increased incidence of ATE events was observed in patients treated with bevacizumab compared with those receiving control treatment. ATE events include cerebrovascular accidents, myocardial infarction, transient ischemic attacks (TIAs), and other ATE events. In a pooled analysis of data from five randomized Phase II and III trials (mCRC [AVF2107g, AVF2192g, AVF0780g]; locally advanced or metastatic NSCLC [AVF0757g]; metastatic breast cancer [AVF2119g]), the incidence rate of ATE events was 3.8% (37 of 963) in patients who received chemotherapy + bevacizumab compared with 1.7% (13 of 782) in patients treated with chemotherapy alone. ATE events led to a fatal outcome in 0.8% (8 of 963) of patients treated with chemotherapy + bevacizumab and 0.5% (4 of 782) of patients treated with chemotherapy alone. Cerebrovascular accidents (including TIAs) occurred in 2.3% of patients treated with chemotherapy + bevacizumab and 0.5% of patients treated with chemotherapy alone. Myocardial infarction occurred in 1.4% of patients treated with chemotherapy + bevacizumab compared with 0.7% of patients treated with chemotherapy alone (see the Bevacizumab Investigator Brochure for additional details).

Aspirin is a standard therapy for primary and secondary prophylaxis of arterial thromboembolic events in patients at high risk of such events, and the use of aspirin ≤ 325 mg daily was allowed in the five randomized studies discussed above. Use of aspirin was assessed routinely as a baseline or concomitant medication in these trials, though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and arterial thromboembolic events, retrospective analyses of the ability of aspirin to affect the risk of such events were inconclusive. However, similarly retrospective analyses suggested that the use of up to 325 mg of aspirin daily does not increase the risk of grade 1-2 or grade 3-4 bleeding events, and similar data with respect to metastatic colorectal cancer patients were presented at ASCO 2005 (Hambleton et al., 2005). Further analyses of the effects of concomitant use of bevacizumab and aspirin in colorectal and other tumor types are ongoing.

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Gastrointestinal perforation Patients with metastatic carcinoma may be at increased risk for the development of gastrointestinal perforation and fistula when treated with bevacizumab and chemotherapy. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation. A causal association of intra-abdominal inflammatory processes and gastrointestinal perforation to bevacizumab treatment has not been established. Nevertheless, caution should be exercised when treating patients with intra-abdominal inflammatory processes with bevacizumab. Gastrointestinal perforation has been reported in other trials in non-colorectal cancer populations (e.g., ovarian, renal cell, pancreas, breast, and NSCLC) and may be higher in incidence in some tumor types.

Fistula: Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae in the GI tract are common (1%–10% incidence) in patients with metastatic CRC, but uncommon (0.1%−1%) or rare (0.01%–0.1%) in other indications. In addition, fistulae that involve areas of the body other than the GI tract (e.g., tracheoesophageal, bronchopleural, urogenital, biliary) have been reported uncommonly (0.1%–1%) in patients receiving bevacizumab in clinical studies and postmarketing reports. Events were reported at various timepoints during treatment, ranging from 1 week to > 1 year following initiation of bevacizumab, with most events occurring within the first 6 months of therapy.

Permanently discontinue bevacizumab in patients with tracheoesophageal fistulae or any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

Wound healing complications: Wound healing complications such as wound dehiscence have been reported in patients receiving bevacizumab. In an analysis of pooled data from two trials in metastatic colorectal cancer, patients undergoing surgery 28-60 days before study treatment with 5-FU/LV plus bevacizumab did not appear to have an increased risk of wound healing complications compared to those treated with chemotherapy alone (Scappaticci et al., 2005). Surgery in patients currently receiving bevacizumab is not recommended. No definitive data are available to define a safe interval after bevacizumab exposure with respect to wound healing risk in patients receiving elective surgery; however, the estimated half-life of bevacizumab is 21 days. Bevacizumab should be discontinued in patients with severe wound healing complications.

If patients receiving treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4–8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin or restart bevacizumab until 4 weeks after that procedure (in the case of high-risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 weeks and bevacizumab no earlier than 8 weeks after surgery).

Amended: 4/28/09

Hemorrhage: Overall, grade 3 and 4 bleeding events were observed in 4.0% of 1132 patients treated with bevacizumab in a pooled database from eight phase I, II, and III clinical trials in multiple tumor types (bevacizumab Investigator Brochure, October 2005). The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage (see below) and minor mucocutaneous hemorrhage.

Tumor-Associated Hemorrhage: Major or massive pulmonary hemorrhage or hemoptysis has been observed primarily in patients with NSCLC. Life-threatening and fatal hemoptysis was identified as a bevacizumab-related adverse event in NSCLC trials. These events occurred suddenly and presented as major or massive hemoptysis. Among the possible risk factors evaluated (including squamous cell histology, treatment with anti-rheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, bevacizumab therapy, previous medical history of atherosclerosis, central tumor location, and cavitation of tumors during therapy), the only variables that showed statistically significant correlations with bleeding were bevacizumab therapy and squamous cell histology.

Of patients experiencing pulmonary hemorrhages requiring medical intervention, many had cavitation and/or necrosis of the tumor, either preexisting or developing during bevacizumab therapy. Patients developing lung cavitation on treatment should be assessed by the treating physician for risk-benefit.

In Study E4599, in which squamous cell carcinoma was excluded, the rate of any type of Grade ≥ 3 hemorrhage was 1.0% in the control arm (carboplatin and paclitaxel) versus 4.1% in the carboplatin and paclitaxel + bevacizumab arm (Sandler et al. 2006).

GI hemorrhages, including rectal bleeding and melena have been reported in patients with CRC, and have been assessed as tumor-associated hemorrhages.

Tumor-associated hemorrhages were also seen rarely in other tumor types and locations, including a case of CNS bleeding in a patient with hepatoma with occult CNS metastases and a patient who developed continuous oozing of blood from a thigh sarcoma with necrosis.

Mucocutaneous Hemorrhage: Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly NCI-CTC v. 3.0 Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen.

There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

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 (Glusker et al. 2006; Ozcan et al. 2006).

Congestive heart failure: In clinical trials, CHF was observed in all cancer indications studied to date, but predominantly in patients with metastatic breast cancer. In the Phase III clinical trial of metastatic breast cancer (AVF2119g), 7 (3%) bevacizumab-treated patients experienced CHF, compared with two (1%) control arm patients. These events varied in severity from asymptomatic declines in left ventricular ejection fraction (LVEF) to symptomatic CHF requiring hospitalization and treatment. All the patients treated with bevacizumab were previously treated with anthracyclines (doxorubicin cumulative dose of 240−360 mg/m^2). Many of these patients also had prior radiotherapy to the left chest wall. Most of these patients showed improved symptoms and/or left ventricular function following appropriate medical therapy (Miller et al. 2005).

In a randomized, Phase III trial of patients with previously untreated metastatic breast cancer (E2100), the incidence of LVEF decrease (defined as NCI-CTC v. 3.0 Grade 3 or 4) in the paclitaxel + bevacizumab arm was 0.3% versus 0% for the paclitaxel alone arm

No information is available on patients with preexisting CHF of New York Heart Association (NYHA) Class II−IV at the time of initiating bevacizumab therapy, as these patients were excluded from clinical trials.

Prior anthracyclines exposure and/or prior radiotherapy to the chest wall may be possible risk factors for the development of CHF. Caution should be exercised before initiating bevacizumab therapy in patients with these risk factors.

A Phase II trial in patients with refractory acute myelogenous leukemia reported 5 cases of cardiac dysfunction (CHF or LVEF decrease to < 40%) among 48 patients treated with sequential cytarabine, mitoxantrone, and bevacizumab. All but 1 of these patients had significant prior exposure to anthracyclines as well (Karp et al. 2004).

Two additional studies investigated concurrent administration of anthracyclines and bevacizumab. In 21 patients with inflammatory breast cancer treated with neoadjuvant docetaxel, doxorubicin, and bevacizumab, no patients developed clinically apparent CHF; however, patients had asymptomatic decreases in LVEF to < 40% (Wedam et al. 2004). In a small Phase II study in patients with soft tissue sarcoma, 2 of the 17 patients treated with

bevacizumab and high-dose doxorubicin (75 mg/m^2) developed CHF (one Grade 3 event after a cumulative doxorubicin dose of 591 mg/m^2, one Grade 4 event after a cumulative doxorubicin dose of 420 mg/m^2); an additional 4 patients had asymptomatic decreases in LVEF (D'Adamo et al. 2004).

Other studies in patients with various tumor types and either a history of anthracycline exposure or concomitant use with bevacizumab are ongoing.

Patients receiving concomitant anthracyclines or with prior exposure to anthracyclines should have a baseline MUGA scans or echocardiograms (ECHOs) with a normal LVEF.

Neutropenia: Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone (Sandler et al. 2006).

Additional Adverse Events: See the bevacizumab Investigator Brochure for additional details regarding the safety experience with bevacizumab.

Bevacizumab Dose Modification and Toxicity Management

There are no reductions in the bevacizumab dose. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes.

Any toxicities associated or possibly associated with 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 discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab.

Subjects should 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.

Infusion Reaction: Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. Subjects who experience a NCI CTCAE v. 3.0 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 subjects who experience any infusion-associated symptoms not specified above. When the subject's 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 cycle.

Adverse events requiring delays or permanent discontinuation of bevacizumab are listed in Table 1. Regardless of the reason for holding study drug treatment, the maximum allowable length of treatment interruption is 2 months.

If patients on treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4-8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 4 weeks after that procedure (in the case of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 wk and bevacizumab no earlier than 8 wk after surgery).

Table1:
Bevacizumab Dose Management Due to Adverse Events

Event	Action to be Taken
Hypertension	
No dose modifications for grade 1/2 events	
Grade 3	If not controlled to 150/100 mmHg with medication, discontinue bevacizumab.
Grade 4 (including hypertensive encephalopathy)	Discontinue bevacizumab.
Hemorrhage	
No dose modifications for grade 1/2 non-pulmonary and non-CNS events	
Grade 3 Non-pulmonary and non-CNS hemorrhage	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab held until all of the following criteria are met: • The bleeding has resolved and hemoglobin 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. Subjects who experience a repeat Grade 3 hemorrhagic event will be discontinued from receiving bevacizumab.
Grade 4 non-pulmonary or non-CNS hemorrhage	Discontinue bevacizumab.
Grade 1pulmonary or CNS hemorrhage	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab held until all of the following criteria are met: • The bleeding has resolved and hemoglobin 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.
Grade 2, 3, or 4 pulmonary or CNS hemorrhage	Discontinue bevacizumab

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Table 1

Bevacizumab Dose Management due to Adverse Events (continued)

Venous Thrombosis	
No dose modifications for grade 1/2 events	
Grade 3 or 4	Hold study drug treatment. If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation if all of the following criteria are met: • The subject must have an in-range INR (usually between 2 and 3) if on warfarin; LMWH, warfarin, or other anticoagulant dosing must be stable prior to restarting bevacizumab treatment. • The subject must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation.
Arterial Thromboembolic event	
(New onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)	
Any grade	Discontinue bevacizumab.
Proteinuria	
No dose modifications for grade 1/2 events	
Grade 3 (UPC> 3.5, urine collection > 3.5 g/24 hr)	Hold bevacizumab treatment until ≤ Grade 2, as determined by either UPC ratio ≤ 3.5 or 24 hr collection ≤ 3.5 g
Grade 4 (nephritic syndrome)	Discontinue bevacizumab
GI Perforation	Discontinue bevacizumab.
Fistula	
Any grade (TE fistula)	Discontinue bevacizumab.
Grade 4 fistula	Discontinue bevacizumab.

Bowel Obstruction	
Grade 1	Continue patient on study for partial obstruction NOT requiring medical intervention.
Grade 2	Hold bevacizumab for partial obstruction requiring medical intervention. Patient may restart upon complete resolution.
Grade 3/4	Hold bevacizumab for complete obstruction. If surgery is necessary, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion.
Wound dehiscence Any grade (requiring medical or surgical therapy)	**Discontinue 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.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

All patients will have their tumor measurements recorded at baseline and at the time of each MRI scan. Lesions must be measured in two dimensions. The dose of gadolinium must be held constant from scan to scan.

Complete response (CR) is the total disappearance of all measurable contrast-enhancing tumor on two MRIs separated by at least 4 weeks. The patient must have no clinical neurologic deterioration or decrease in performance status. The patient must be off dexamethasone.

Partial response (PR) is at least a 50% reduction in the size of measurable contrast enhancement (the sum of the products of the greatest length and maximum width of all measurable lesions). No lesion may progress and no new lesions may appear. All PR should be confirmed by repeat MRI separated by at least 4 weeks. The dose of dexamethasone must be the same or lower than at baseline.

Stable disease (SD) exists when a patient fails to qualify for partial response or progressive disease.

Progressive disease (PD) is an increase of 25% or more in the size of any lesion or the appearance of a new site of tumor.

Because the first MRI obtained after radiotherapy often shows an increased pattern/area of enhancement of indeterminant significance this scan will not be used to assess response to therapy or to make a decision as to whether or not a patient remains on study. The first MRI after radiotherapy will be used as a new baseline scan for subsequent MRI assessments.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If the patient develops progressive disease he/she will be taken off study treatment and referred for alternative therapy.

If the patient develops unacceptable toxicity he/she will be removed from study treatment.

If the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (i.e., a change in diagnosis), the patient will be removed from the study.

A patient can be removed from the study treatment at any time if the study doctor believes it is in their best interest.

14.0 BIOSTATISTICS

This is a pilot study to evaluate the safety of and feasibility of delivering bevacizumab and temozolomide in combination with hypo-fractionated radiotherapy to patients with newly diagnosed glioblastoma. Twenty-five patients will be accrued to the study. It is anticipated that twenty patients will receive the treatment and be assessable for safety based on prior studies of newly diagnosed glioblastoma at MSKCC (eg. 05-079). Safety and tolerability will be measured by the presence of grade 3 or 4 non-hematologic toxicity (NCI Common Toxicity Criteria version 3.0). The trial will be terminated if 5 treatment-related grade 3 or 4 non-hematologic toxicities (excluding hypertension) are observed. The table below provides the probability of stopping the trial early for various hypothetical toxicity rates for a sample size of 20 patients and 5 toxic events, excluding hypertension and wound healing complications (column 2). All adverse events will be monitored in an ongoing manner.

The toxicity of greatest concern is wound healing complications. This toxicity will be treated separately from the above specified nonhematologic toxicities. If 3 or more treatment-related grade 2 or higher symptomatic wound dehiscence (requiring medical intervention) are observed

then the trial will be terminated. The third column of the table below provides the probability of stopping the trial early for various hypothetical toxicity rates for a sample size of 20 patients and 3 wound dehiscence events requiring medical intervention.

True Toxicity	Probability of Early Stopping	Probability of Early Stopping Wound-related
5%	0.3%	8%
10%	4.3%	32%
20%	37.0%	79%
30%	76.2%	96%
40%	94.9%	99.6%
50%	99.4%	99.9%

Frequencies of toxicities will be tabulated. The grade 3 /4 non-hematologic toxicity rate will be estimated at the end of the trial along with a 95% confidence interval. With 20 patients this can be estimated to within +/- .22.

Efficacy measures (secondary endpoints) including response rate or survival will be estimated. Estimated accrual is approximately two patients patient per month and the study is expected to be completed in approximately 2 years.

The primary goal of this study is to test the safety of bevacizumab in patients with recurrent glioblastomas in preparation for a larger study to test the efficacy of this approach used for the initial treatment of these tumors if safety is confirmed in the present trial. We will review all adverse event data recorded from this study. If four or fewer grade 3 or higher nonhematologic adverse events occur, and 3 or fewer treatment-related grade 2 or higher wound healing issues (requiring medical intervention) are observed, we will propose a larger randomized phase II or III protocol.

Neurocognitive endpoint:
This is a prospective study with repeated measures of several neuropsychological test scores. The test battery will be administered: prior to initiation of treatment; approximately 4-5 months after surgery; 1 year post surgery; and for long term survivors on a yearly basis thereafter. The primary outcome to be evaluated is prevalence of neuropsychological deficits at initial examination, as defined by test scores that are deviant from age and gender mean values, and changes (differences) in test scores at a subsequent follow-up evaluations relative to baseline for each patient, adjusted for possible prognostic factors. These will yield "snap-shot," within patient measures of rates of progression of toxicity later in the clinical time course.

An assessment of the relationships between patients' demographic, clinical, and treatment characteristics and both baseline scores and on-study changes in scores will be performed. Although repeated measures analysis of covariance would be a preferred statistical approach if complete data were available, the applicability of such methods is limited since data may be missing in a non-random way. We will be vigilant for possible statistical biases that may arise due to selective initial participation in the study and selective dropping out of the study, insofar as it correlates with progression of disease or therapy-induced neurotoxicity. Statistical power considerations depend on both sample sizes and effect sizes. The typical levels of scores on the administered tests are not accurately known, and in fact their estimation is a primary aim of this study. The variability of these estimates among study patients and the degree of relationship with other patient characteristics is even more difficult to specify a priori. In any case, the overall goals of this endpoint are descriptive and hypothesis-generating more than hypothesis testing.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

As per face-sheet

Confirm in the electronic medical record that the patient has received the Notice of Privacy Practice. This must be obtained before the eligibility confirmation and obtaining of the research informed consent.

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain written informed consent, by following procedures defined in section entitled Informed Consent Procedures.

All particpants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am - 5:30pm at (646) 735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the informed consent form, the completed signature page of the Research Authorization and a completed Eligibility Checklist must be faxed to PPR.

During the registration process registering individuals will be required to answer specific eligibility questions and provide the following information:

Registering Individual	[Last, First Name]
Notice of Privacy Status	[Yes, No, N/A]
Research Authorization	[Date]
MSKCC IRB Protocol#	
Attending of Record (if applicable)	[Last, First Name]
Consenting Professional	[Last, First Name]
Informed Consent Date	
Participant's Full Name	[Last, First Name]
Participant MRN	

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and

Safety Monitoring Plans can be found on the MSKCC Intranet at:
http://mskweb2.mskcc.org/irb/index.htm

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

Inclusion of Children in Research

This protocol/project does not include children because the number of children is limited and because the majority are already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

17.1 Privacy

It is the responsibility of the Research Staff to ensure that protocol subjects received the Center's Notice of Privacy Practices. If the subject has not received one, MSK personnel must provide a Notice of Privacy Practices and obtain acknowledgment before the subject participates in the study.

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB as soon as possible but no later than 5 calendar days. The IRB requires a Clinical Research Database (CRDB) AE report to be delivered to the Institutional SAE Manager (307 East 63rd Street, 1st Floor) containing the following information:

Fields populated from the CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following information:
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form

The PI's signature and the date it was signed are required on the completed report.

17.2.1 Genentech Safety Reporting Requirements for Investigator Sponsored Studies

For Investigator Sponsored IND Exempt Studies**, the Sponsor-Investigator is required to notify Genentech of any fatal or life-threatening adverse event that is** unexpected and assessed by the investigator to be possibly related to the use of Bevacizumab**. An unexpected adverse event is one that is not already described in the Investigator Brochure.**

All Serious Adverse Events must be faxed to:

Genentech Drug Safety

Amended: 4/28/09

Fax: (650) 225-4682 or (650) 225-5288

For questions related to safety reporting, contact:

Genentech Drug Safety
Tel: 1-888-835-2555
or

Fax: (650) 225-4682 or (650) 225-5288

Genentech may contact the reporter for additional information, clarification, or current status of the subject for whom and adverse event was reported.

Genentech Adverse Event Reporting Definitions

A serious treatment emergent adverse event (STEAE) is any sign, symptom or medical condition that emerges during Bevacizumab treatment or during a post-treatment follow-up period that (1) was not present at the start of Bevacizumab treatment and it is not a chronic condition that is part of the patient's medical history, OR (2) was present at the start of Bevacizumab treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy, AND that meets any of the following regulatory serious criteria:

- Results in death
- Is life-threatening
- Requires or prolongs inpatient hospitalization
- Is disabling
- Is a congenital anomaly/birth defect
- Is medically significant or requires medical or surgical intervention to prevent one of the outcomes listed above.

Assessing Causality:

The event should be assessed to decide whether there is a reasonable possibility that bevacizumab caused or contributed to an adverse event. The following general guidance may be used.

Yes: if the temporal relationship of the clinical event to bevacizumab administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

Amended: 4/28/09

No: if the temporal relationship of the clinical event to bevacizumab administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

18.0 INFORMED CONSENT PROCEDURES

All patients must provide written informed consent prior to registration and treatment. Those physicians authorized to obtain informed consent are listed on the title page of this document. The patient will sign three copies of the informed consent. One copy will become part of the patient's medical record, one copy will be stored in the patient's research file and one copy will be given to the patient to keep.

18.1 Research Authorization

Procedures for obtaining Research Authorization: Before any protocol-specific procedures are carried out, investigators and/or designated staff will fully explain the details of the protocol, study procedures, and the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must sign the Research Authorization component of the informed consent form. The Research Authorization requires a separate set of signatures from the patient. The original signed documents will become part of the patient's medical record, and each patient will receive a copy of the signed documents.

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20.0 APPENDICES

Appendix 1: Neuropsychological Test Battery