CLEVELAND CLINIC BRAIN TUMOR AND NEUROONCOLOGY CENTER

PHASE I/II TRIAL OF RADIOSURGERY PLUS BEVACIZUMAB IN PATIENTS WITH RECURRENT/PROGRESSIVE GLIOBLASTOMA
Case 4309

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PHASE I/II TRIAL OF RADIOSURGERY PLUS BEVACIZUMAB IN PATIENTS WITH RECURRENT/PROGRESSIVE GLIOBLASTOMA

Patient Population: (See Section 3.0 for Eligibility)
- Histopathologically confirmed glioblastoma (WHO Grade IV)
- Completed standard concurrent conventional fractionated radiotherapy plus daily temozolomide (75 mg/m2/day)
- Radiographic evidence of tumor recurrence or progression (must be at least 12 weeks after the end of radiation therapy)
- Enhancing tumor with a maximum diameter of no greater than 3 cm.
- KPS > 60

Required Sample Size: 74 patients
1.0 INTRODUCTION

1.1 Overview

The prognosis for patients with glioblastoma remains grim, with most studies reporting a median survival of 10 to 12 months (Grossman and Batara 2004). These statistics have remained nearly unchanged since the seminal studies in the 1970s that confirmed the efficacy of external beam radiation. (Walker, Alexander et al. 1978) In those studies, the addition of chemotherapy (a nitrosourea) did not statistically improve survival compared with patients receiving radiation alone. At 2 years, less than 10% of patients were alive (Walker, Green et al. 1980). Subsequent meta-analyses of randomized trials of radiation versus radiation plus a nitrosourea-containing regimen showed only a modest improvement in 1-year survival in the patients receiving the combination regimen (Fine, Dear et al. 1993; Stewart 2002). However, Stupp and colleagues (Stupp, Dietrich et al. 2002) performed a phase II trial in patients with newly diagnosed glioblastoma, administering a daily lower dose (75 mg/m²) of temozolomide every day during the course of radiation therapy, followed by 6 months of adjuvant chemotherapy at the standard single-agent dose of 200 mg/m² for days 1 to 5 of a 28-day cycle. These phase II results were promising, demonstrating an overall median survival of 16 months.

A subsequent confirmatory, Phase III trial, performed by the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC), randomized patients with newly diagnosed glioblastoma to receive either radiation therapy alone or concurrent radiation and temozolomide followed by 6 months of adjuvant temozolomide. The study demonstrated a statistically significant improvement in median survival for the combination treatment arm (12.1 vs 14.6 months) as well as a significant increase in 2-year survival (10% vs 26%). Eighty-eight percent of the patients received the full course of concurrent temozolomide with radiation. The results of this trial were first presented at ASCO in June 2004, with the full report published in the New England Journal of Medicine (Stupp, Mason et al. 2005). This chemoradiation regimen has been widely accepted as the new standard of care for patients with newly diagnosed glioblastoma. An update from this trial was presented at the 2007 meeting of the American Society for Therapeutic Radiology and Oncology, demonstrating a 10% 5-year survival rate in patients treated with the chemoradiation regimen and providing additional evidence of the efficacy of this therapy.

Patients with recurrent glioblastoma have a median survival of 4 months despite attempts at administering a variety of chemotherapy regimens (Wong et al., 1999). Available treatments have been limited by problems with delivery to the tumor because of widespread tumor infiltration, the blood-brain barrier, and the rapid development of resistance to conventional cytotoxic agents. Therefore, there has been great interest in targeting the angiogenesis that is a prominent feature of the malignant gliomas, particularly glioblastoma. Prior studies suggest that targeting the endothelial cells involved in tumor angiogenesis is not hampered by the development of resistance (Lund et al. 1998). Further, some antiangiogenic treatments have been associated with the development of apoptosis within the tumor cells themselves.

1.1.1 Angiogenesis and invasion in glioblastoma

Available treatments have been limited by problems with delivery to the tumor because of widespread tumor infiltration, the blood-brain barrier, and the rapid development of resistance to conventional cytotoxic agents. Therefore, there has been great interest in targeting the angiogenesis that is a prominent feature of the malignant gliomas, particularly glioblastoma. Prior studies suggest that targeting the endothelial cells involved in tumor angiogenesis is not hampered by the development of resistance (Lund, Spang-Thomsen et al. 1998). Further,
some antiangiogenic treatments have been associated with the development of apoptosis within the tumor cells themselves.

The two processes, angiogenesis and tumor cell invasion, are closely associated. In gliomas, vascular endothelial growth factor (VEGF) promotes both angiogenesis and invasion of tumor cells (Machin and Plate 2000). “Invasion” of endothelial cells into the tumor is an important component of the angiogenic process. Early clinical trials attempted to block the VEGF signal transduction pathway, usually by inhibiting the VEGF receptor and/or the downstream pathway. A variety of treatments including monoclonal antibody against the receptor and small molecule receptor tyrosine kinase inhibitors have been used, with only modest success in the treatment of systemic cancers. These approaches have shown even less efficacy in the treatment of glioblastoma, likely due to limited drug delivery to the target receptor at clinically relevant concentrations and target competition with the natural ligand. A treatment that utilizes an intravascular approach would eliminate the concerns regarding drug delivery through the blood-brain or blood-tumor barrier. Bevacizumab is a humanized monoclonal antibody against VEGF (VEGF-A) (Ferrara, Hillan et al. 2005). Intravenous administration of this agent has been shown to rapidly reduce the concentration of VEGF in the circulation. Extensive investigations of bevacizumab clearly demonstrate anticancer activity in a variety of systemic cancers, including renal cell carcinoma, non-small cell lung cancer, and colorectal cancer (Yang, Haworth et al. 2003; Hurwitz, Fehrenbacher et al. 2004; Willett, Boucher et al. 2004; Miller, Chap et al. 2005).

In most studies, bevacizumab was used in combination with traditional cytotoxic agents. Randomized trials suggest that there is benefit in combining bevacizumab with cytotoxic chemotherapy drugs compared with the cytotoxic regimen alone (Gille 2006). Although the mechanism of treatment enhancement is unknown, two main hypotheses have been proposed. The first hypothesis states that there is a synergy of activity with the cytotoxic chemotherapy along with the removal of circulating VEGF leading to endothelial cell apoptosis. The second hypothesis proposes that bevacizumab selectively inhibits angiogenesis and results in the loss of markedly aberrant and tortuous intratumoral neovascularature, causing a paradoxical improvement in perfusion and delivery of the cytotoxic agent to the tumor cells. Available data support both theories, and both mechanisms may be responsible for the proven benefit of bevacizumab in the wide spectrum of cancers tested to date.

There have been small series and anecdotal reports of patients with recurrent malignant glioma, predominantly glioblastoma, who have been treated with the combination of irinotecan and bevacizumab (Stark-Vance 2005; Vredenburgh, Desjardins et al. 2007). A high objective response rate has been noted, and in some cases the responses appear to be durable. For example, a recent phase II study in patients with recurrent glioblastoma combined bevacizumab with irinotecan (Vredenburgh, Desjardins et al. 2007). The investigators reported a 57% objective response rate and a 6-month progression-free survival rate of 46%. The results of both studies compare very favorably with single-agent temozolomide in patients with no prior temozolomide exposure, where objective tumor responses were reported in less than 6% of patients and the 6-month progression-free survival rate was 21% (Yung, Albright et al. 2000). Despite concerns regarding the potential for intratumoral hemorrhages, particularly in light of an early report of bleeding in a brain metastasis in a patient on a clinical trial with bevacizumab, the preliminary reports suggest that this complication is infrequent in gliomas. Similarly, the large trials of bevacizumab in colorectal, lung, and breast cancer suggest an increase in vascular thrombotic events,
although the excess numbers appear to be arterial thromboses. Again, this problem has not been identified in the brain tumor population treated with bevacizumab.

A recent phase II study randomized patients with recurrent GBM to treatment with either bevacizumab alone or bevacizumab with CPT-11 (Cloughesy, Prados et al. 2008). A total of 163 patients were enrolled. Treatment was well tolerated; the most common serious adverse events were hypertension (8% in bevacizumab alone arm, 1% in the combination arm), fatigue (5% in bevacizumab alone arm and 6% in the combination arm), deep venous thrombosis (4% in bevacizumab alone and 8% in the combination arm), and neutropenia (1% in bevacizumab alone and 9% in the combination arm). Overall response rate, as determined by independent radiology review, was 20% in the bevacizumab alone arm and 33% with the combination. The 6-month progression-free survival rate was 35% for bevacizumab alone and 50% for the combination. Although the study was not statistically powered to compare the two arms, these results suggest a response and progression-free rate benefit to the combination of bevacizumab with a cytotoxic agent.

Laboratory and clinical imaging studies also support the potential role of antiangiogenic agents in combination with both radiation therapy and chemotherapy (Batchelor, Sorensen et al. 2007). Contrary to the early concerns that these agents would markedly reduce blood flow and therefore delivery of oxygen (for radiation-induced free radical formation) and delivery of chemotherapy, studies now clearly demonstrate that antiangiogenic agents cause vascular normalization (Jain 2005). Tumors typically demonstrate extensive neovascularization that is characterized by tortuous vessels, poorly formed basement membranes, and often by saccular structures (dead ends) and large gaps between endothelial cells. Antiangiogenic agents have been shown to eliminate many of these poorly formed vascular components, resulting in an overall enhancement of blood supply to the tumor through a process called “vascular normalization.”

1.2 Bevacizumab
1.2.1 Overview
Bevacizumab is a humanized IgG1 monoclonal antibody (MAb) that binds all biologically active isoforms of human VEGF (or VEGF-A) with high affinity (kd = 1.1 nM) (Presta, Chen et al. 1997). The antibody consists of a human IgG1 framework and the antigen-binding complementarity-determining regions from the murine anti-VEGF MAb A.4.6.1 (Kim, Li et al. 1993; Presta, Chen et al. 1997; Brochure 2006).

1.2.2 Mechanism of Action
VEGF is one of the most potent and specific angiogenic factors, and it has been identified as a crucial regulator of both normal and pathological angiogenesis. VEGF is a secreted, heparin-binding protein that exists in multiple isoforms. Action of VEGF is primarily mediated through binding to the receptor tyrosine kinases VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1). The biologic effects of VEGF include endothelial cell mitogenesis and migration, increased vascular permeability, induction of proteinases leading to remodeling of the extracellular matrix, and suppression of dendritic cell maturation. Neutralization of VEGF by A.4.6.1 or bevacizumab has been shown to inhibit the VEGF-induced proliferation of human endothelial cells in vitro and to decrease microvessel density and interstitial pressure in tumor xenografts in vivo. Preliminary results from a neoadjuvant trial in patients with rectal cancer demonstrated a decrease
1.2.3 Preclinical Studies
The murine parent MAb of bevacizumab, A4.6.1, has demonstrated potent growth inhibition in vivo in a variety of human cancer xenograft and metastasis models, including those for SK-LMS-1 leiomyosarcoma, G55 glioblastoma multiforme, A673 rhabdomyosarcoma, Calu-6, and MCF-7 cell lines (Kim, Li et al. 1993; Presta, Chen et al. 1997; Borgstrom, Gold et al. 1999). The antitumor activity was enhanced with the combination of A4.6.1 and chemotherapeutic agents compared to either agent alone. Furthermore, combined blockade of the VEGF pathway and other growth factor pathways (e.g., EGFR or PDGFR) has also demonstrated additive effects in vivo (Shaheen, Ahmad et al. 2001; Bergers, Song et al. 2003). Associated with the antitumor activity of anti-VEGF MAbs were findings of reduced intratumoral endothelial cells and microcapillary counts as well as reduced vascular permeability and interstitial pressure.

Nonclinical toxicology studies have examined the effects of bevacizumab on female reproductive function, fetal development, and wound healing. Fertility may be impaired in cynomolgus monkeys administered bevacizumab, which led to reduced uterine weight and endometrial proliferation as well as a decrease in ovarian weight and number of corpora lutea. Bevacizumab is teratogenic in rabbits, with increased frequency of fetal resorption as well as specific gross and skeletal fetal alterations. In juvenile cynomolgus monkeys with open growth plates, bevacizumab induced physeal dysplasia that was partially reversible upon cessation of therapy. Bevacizumab also delays the rate of wound healing in rabbits, and this effect appeared to be dose dependent and characterized by a reduction of wound tensile strength.

1.2.4 Clinical Studies
To date, over 3000 patients have been treated in clinical trials with bevacizumab as monotherapy or in combination regimens (Brochure 2006). The pharmacokinetics of bevacizumab have been characterized in several phase I and II clinical trials, with doses ranging from 1 to 20 mg/kg administered weekly, every 2 weeks, or every 3 weeks. The estimated half-life of bevacizumab is approximately 21 days (range 11-50 days). The predicted time to reach steady state was 100 days. The volume of distribution is consistent with limited extravascular distribution. The maximum tolerated dose of bevacizumab has not been determined; however, the dose level of 20 mg/kg was associated with severe headaches (Cobleigh, Langmuir et al. 2003). The dose schedule of either 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks is used in most phase II or III trials with only a few exceptions (e.g., the pivotal phase III trial in colorectal cancer, in which bevacizumab was given at 5 mg/kg every 2 weeks).

Clinical proof of efficacy for anti-VEGF therapy with bevacizumab has been provided by the pivotal phase III trial of bevacizumab (5 mg/kg every 2 weeks) in combination with bolus irinotecan/5-fluorouracil/leucovorin (IFL) in patients with untreated advanced colorectal cancer (Hurwitz, Fehrenbacher et al. 2004). In that study, the addition of bevacizumab to IFL was associated with an increase in objective responses (45% vs. 35%) and significant prolongations of both time to progression (10.6 vs. 6.2 months) and overall survival (20.3 vs. 15.6 months) compared with IFL. However, in the phase III trial in previously treated metastatic breast cancer, the addition of bevacizumab to capecitabine did not show a difference in time to progression despite an increase in the response rate from 9% to 20% (Miller, Chap et al. 2005).

Bevacizumab has also been studied in renal cell cancer. In a 3-arm, double-
blind, placebo-controlled phase II trial, patients with previously treated stage IV renal cell cancer were randomized to high-dose bevacizumab (10 mg/kg every 2 weeks), low-dose bevacizumab (3 mg/kg every 2 weeks), or placebo (Yang, Haworth et al. 2003). The study demonstrated a highly significant prolongation of time to progression in the high-dose arm (4.8 months) compared with the placebo (2.6 months) (hazard ratio = 2.55, \( p = 0.0002 \)); the low-dose arm was associated with a smaller difference in time to progression (3.0 months) of borderline significance. The tumor response rate was 10% in the high-dose arm but was 0% in the low-dose and placebo groups.

Additional clinical trials are ongoing in a variety of solid tumors and hematologic malignancies using bevacizumab as monotherapy or in combination with chemotherapy, radiation, or other targeted/biologic agents. Clinical trials have been reported using bevacizumab in combination with irinotecan to treat patients with recurrent malignant glioma.

Stark-Vance reported the first study in 2004 at the World Federation of Neuro-Oncology. Twenty-one patients were treated and an objective response rate, as determined by changes in cross-sectional area was demonstrated (Stark-Vance 2005). Treatment was reportedly well tolerated, although six patients were removed from the study because of medical issues, two of which were believed related to treatment (thrombosis and intestinal perforation). As described above, Vredenburgh and colleagues presented the results of 2 phase II trials from Duke University (Vredenburgh, Desjardins et al. 2007). The investigators reported a 57% objective response rate and a 6-month progression free survival rate of 46%. They report one intracranial hemorrhage among 35 treated patients and 4 incidents of thromboembolic complications.

In addition to the phase II study described above in patients with recurrent glioma, bevacizumab has been evaluated with concurrent radiation therapy and temozolomide. Preliminary data from the study by Lai and colleagues suggest that this combination is moderately well tolerated, although initiation of this combination regimen within 3 weeks of craniotomy and tumor resection may be associated with a higher rate of wound healing problems (Lai, Filka et al. 2008). A more recent update of toxicity from the initial 52 patients of the planned 70 on this trial is provided in the table below:
Radiosurgery

Radiation therapy has been long recognized to be an effective adjuvant modality in the management of GBM and the overall survival time appears to be directly correlated with the total dose delivered (Walker et al. 1979, Bleehen et al., 1991). Considering that the highest density of tumor cells are within the enhancing area of tumor, and that about 90% of recurrences are located within 2 cm of the enhancing edge of the original tumor (3) it has been suggested that a focal treatment that delivers a localized high dose to the area of the enhancing tumor with minimal irradiation of adjacent brain tissues should lead to an improved therapeutic ratio by increasing the local tumor control without an increase in the complication rate. Stereotactic radiosurgery (SRS) is a radiotherapy technique characterized by accurate delivery of high doses of radiation in a single session to small intracranial targets in such a way that the dose fall-off outside the targeted volume is very sharp. The maximal safe dosing of radiosurgery for recurrent brain tumors was shown in RTOG 9005 to be dependent upon the maximum tumor diameter (Shaw, IJROBP, 2000). Tumors with maximal diameters of less than or equal to 2.0 cm were found to have a maximal tolerate dose (MTD) of 24Gy, and those between 2.1 and 3.0 cm were found to have an MTD of 18 Gy. Of note, the MTD for tumors less than or equal to 2.0 cm was never actually reached; the investigators decided not to escalate beyond 24 Gy despite not observing dose limiting toxicity at that dose. As useful as SRS has been for treating brain metastases as well as a variety of other localized disorders, a prospective, randomized trial of SRS for the adjuvant treatment of newly diagnosed GBM (RTOG 9305) failed to show a survival advantage.

Despite this apparent setback, SRS remains an actively used modality for the treatment of patients with GBM, particularly in the recurrent setting where new enhancing disease may often consist of small, focal lesions. The American Society for Therapeutic Radiation and Oncology (ASTRO) performed an evidence based review of the use of radiosurgery for recurrent gliomas. They found that there were no randomized trials and only a sparse number of retrospective reviews and cohort studies. They concluded that

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowel perforation</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal bleed</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Renal failure</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Craniotomy wound dehiscence/infection</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Pulmonary embolus or deep vein thrombosis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Optic Neuropathy</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>
there was insufficient evidence to make any recommendations regarding the use of this modality (Tsao MN, IJROBP, 2005).

Of note, the major toxicity that has been associated with the use of radiosurgery (and other forms of radiation dose intensification) has been radionecrosis. It has been proposed that bevacizumab may be an effective therapy for treating symptomatic radionecrosis. Torcuator et al. showed that treatment of biopsy proven radionecrosis with bevacizumab resulted in symptomatic and radiographic improvement in 6 patients, with the benefit lasting up to at least 18 months (Torcuator, J NeuroOnc, 2009).

Given the continued interest in the use of SRS for recurrent GBM, and the potential synergistic benefits that may be associated with concurrent treatment with bevacizumab in terms of radiosensitization and control of radionecrosis, we propose to initiate a series of studies designed to re-evaluate the use of SRS for the treatment of localized recurrences of GBM. This first study has been designed to evaluate the safety of combining radiosurgery with bevacizumab. We also intend to obtain pilot efficacy data which will be used to decide whether to proceed with subsequent studies, which ultimately will lead to a randomized study of radiosurgery in combination with this or other chemotherapy regimens.

1.4 Summary

Bevacizumab has shown promise as an efficacious therapy for treating recurrent GBM, a disease in which there are few treatment options. There is evidence that bevacizumab treatment normalizes the tumor microvasculature in a way that enhances oxygen delivery, which makes the combination of bevacizumab and radiation an attractive combination for treating GBM. Because recurrent GBM patients have received a maximal course of radiotherapy, the combination of bevacizumab with radiosurgery is a more feasible approach in these patients. The recent completion of a randomized phase II study of bevacizumab with or without irinotecan provides us with a reasonable historical control data set to which to compare the combination of bevacizumab with radiosurgery.

2.0 OBJECTIVES

2.1 Primary

2.1.1 To determine the maximum tolerated dose of radiosurgery used to treat recurrent/progressive GBM concurrently with bevacizumab

2.1.2 To determine the overall survival of patients with recurrent/progressive GBM treated with bevacizumab and radiosurgery

2.2 Secondary

2.2.1 To evaluate the toxicities of the combination of bevacizumab and radiosurgery.

2.2.2 To evaluate the progression-free survival of patients treated with bevacizumab and radiosurgery.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

3.1.1 Histologically proven diagnosis of glioblastoma or gliosarcoma (WHO grade IV) at primary or subsequent resection.

3.1.2 Completed standard concurrent conventional fractionated radiotherapy plus daily temozolomide (75 mg/m2/day)

3.1.3 Radiographic evidence of tumor recurrence/progression as defined by a contrast enhanced MRI at least 3 months after the completion of radiation therapy

3.1.4 Unifocal enhancing disease. The enhancing focus must be <= 3 cm in maximum diameter.
3.1.5 History/physical examination within 14 days prior to registration;
3.1.6 The patient must have recovered from the effects of prior therapy before study entry. The patient must not have received chemotherapy within the following time frames:
- Non-cytotoxic agents: 2 weeks
- Cytotoxic agents: 3 weeks
- Nitrosoureas: 6 weeks
3.1.7 Must be able to undergo MRI imaging.
3.1.8 Documentation of steroid doses within 14 days prior to registration.
3.1.9 Karnofsky performance status > 60;
3.1.10 Age ≥ 18;
3.1.11 CBC obtained within 14 days prior to registration on study, with adequate bone marrow function defined as follows:
   - Absolute neutrophil count (ANC) ≥ 1,500 cells/mm³;
   - Platelets ≥ 100,000 cells/mm³;
   - Hemoglobin ≥ 10.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 10.0 g/dl is acceptable.);
3.1.12 Adequate renal function, as defined below:
   - BUN ≤ 30 mg/dl within 14 days prior to study entry.
   - Creatinine ≤ 1.7 mg/dl within 14 days prior to study entry.
   - Urine protein screened by urine analysis for urine protein creatinine (UPC) ratio. For UPC ratio > 0.5, 24-hour urine protein should be obtained and the level should be < 1000 mg.
3.1.13 Adequate hepatic function, as defined below:
   - Bilirubin ≤ 2.0 mg/dl within 14 days prior to study entry
   - ALT/AST ≤ 3 x normal range within 14 days prior to study entry
3.1.14 Electrocardiogram without evidence of acute cardiac ischemia within 14 days prior study entry
3.1.15 Prothrombin time/international normalized ratio (PT INR) < 1.4 for patients not on warfarin confirmed by testing within 14 days prior to study entry.
3.1.15.1 Patients on full-dose anticoagulants (e.g., warfarin or LMW heparin) must meet both of the following criteria:
   - No active bleeding or pathological condition that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices)
   - In-range INR (between 2 and 3) on a stable dose of oral anticoagulant or on a stable dose of low molecular weight heparin
3.1.16 Patient must provide study specific informed consent prior to study entry.
3.1.17 Women of child-bearing potential and male participants must practice adequate contraception.
3.1.18 For females of child-bearing potential, negative serum pregnancy test within 14 days prior to entry

3.2 Conditions for Patient Ineligibility
3.2.1 Prior invasive malignancy (except for non-melanomatous skin cancer) unless disease free for ≥ 3 years. (For example, carcinoma in situ of the breast, oral cavity, and cervix are all permissible).
3.2.2 More than one focus of enhancement
3.2.3 Involvement of the brainstem (defined as the midbrain or lower), or proximity to the optic chiasm/optic nerves requiring radiosurgery dose reduction.
3.2.4 Prior use of chemotherapy wafers or any other intratumoral or intracavitary treatment are not permitted. Prior radiosurgery is not permitted.
3.2.5 Prior treatment with intravenous bevacizumab
3.2.6 Severe, active co-morbidity, defined as follows:
   - Unstable angina and/or congestive heart failure within the last 6 months
   - Transmural myocardial infarction within the last 6 months
3.2.6.3 Evidence of recent myocardial infarction or ischemia by the findings of S-T elevations of $\geq 2$ mm using the analysis of an EKG performed within 14 days of entry

3.2.6.4 New York Heart Association grade II or greater congestive heart failure requiring hospitalization within 12 months prior to registration

3.2.6.5 History of stroke, cerebral vascular accident (CVA) or transient ischemic attack within 6 months

3.2.6.6 Serious and inadequately controlled cardiac arrhythmia

3.2.6.7 Uncontrolled hypertension

3.2.6.8 Significant vascular disease (e.g., aortic aneurysm, history of aortic dissection) or clinically significant peripheral vascular disease

3.2.6.9 Evidence of bleeding diathesis or coagulopathy

3.2.6.10 Serious or non-healing wound, ulcer, or bone fracture or history of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to registration, with the exception of the craniotomy for tumor resection.

3.2.6.11 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of entry

3.2.6.12 Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of entry

3.2.6.13 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects;

3.2.6.14 Acquired immune deficiency syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive.

3.2.6.15 Active connective tissue disorders, such as lupus or scleroderma that in the opinion of the treating physician may put the patient at high risk for radiation toxicity.

3.2.6.16 Any other major medical illnesses or psychiatric impairments that in the investigator’s opinion will prevent administration or completion of protocol therapy.

3.2.7 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.8 Pregnant or lactating women, due to possible adverse effects on the developing fetus or infant due to study drug.

3.2.9 Patients treated on any other therapeutic clinical trials within 30 days prior to study entry or during participation in the study.

4.0 RADIOSURGERY

Radiosurgery will be delivered 10-14 days after the start of bevacizumab therapy

4.1 Prescription Dose Determination

4.1.1 Radiosurgery dose escalation (run-in to Phase II study)

4.1.1.1 The initial prescription dose is dependent on the size of the lesion(s) as follows based on guidelines from RTOG 90-05:

<table>
<thead>
<tr>
<th>Maximum Tumor Diameter</th>
<th>Assigned Dose (tumor margin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; or $\geq 2.0$ cm</td>
<td>24 Gy</td>
</tr>
</tbody>
</table>
Dose escalation (reduction) will be performed using a 3 x 3 maximum tolerated dose design and dose escalations (reductions) will be in 2 Gy increments. Three patients will be treated at each dose level and then assessed for acute toxicity over the next 90 days. If none develop dose limiting toxicity, then dose escalation will proceed and another 3 patients will be treated at the next dose level. If one of three patients in any cohort develops dose-related toxicity, then an additional 3 patients will be treated at that dose level. If one or more additional patient develops dose-related toxicity, then that dose level will be designated as toxic and the prior dose level will be considered to be the maximum tolerated dose (MTD). A total of 6 patients must be treated at the putative MTD, with no more than one patient having dose-related toxicity, for the MTD to be confirmed. Dose escalations will be performed independently for the two tumor size cohorts. If the initial prescription doses are found to be toxic, then dose reductions will be performed as described above. There will be no dose escalations above 30 Gy for tumors ≤ 2.0 cm or 24 Gy for tumors measuring 2.1 to 3.0 cm or reductions below 14 Gy.

Unacceptable toxicity will be considered to be irreversible grade 3 (severe), any grade 4 (life threatening), or grade 5 (fatal) CNS toxicity that is considered to be related to radiosurgery occurring within 90 days of protocol radiosurgery.

Patients with tumors that are adjacent to the optic nerve and/or chiasm requiring dose reduction will not be permitted in this protocol.

The Phase II prescription doses will be determined by the results of the radiosurgery dose escalation run-in study (section 4.1.1).

Use of stereotactic frame placement for CT scan and treatment delivery, perform target localization using CT and MRI data, and have a treatment planning system capable of generating isodose distributions in three dimensions for a given treatment. Examples include Gamma Plan for the Elekta Gamma Knife System, BrainScan for the Novalis BrainLab System, or iPlan for the Novalis BrainLab System.

Target volume and isocenter determination will be based on a contrast enhanced MRI scan. This should be obtained volumetrically prior to delivery of bevacuzumab to determine true tumor extent. Fusion to CT scan will be used for proper localization in relation to stereotactic frame. Stereotactic CT or MRI slice thickness may not exceed 5 mm. The target volume will include the enhancing portion of the glioma. Surrounding areas of edema will not be considered part of the target volume.

The dose will be prescribed to the isodose surface (50-90% [maximum = 100%]) which encompasses the margin of the glioma, as defined by the imaging studies. The maximum dose will be recorded for each patient. The prescription dose shall be delivered to the 50-90% (maximum = 100%) isodose surface, and is defined as the minimum dose to the target volume. The minimum dose shall be established by the target dose-volume histogram.
4.4.2 Dose homogeneity (maximum dose/prescribed dose) should be ≤ 2

4.4.3 Conformality index (prescription isodose volume/tumor volume) should be ≤ 2

4.5 Radiosurgery Treatment Planning Data
4.5.1 Isodose distributions must be calculated, and the prescription isodose line clearly designated, for each target lesion.

4.6 Radiation Toxicities
4.6.1 Acute, < 90 days from treatment start: Possible toxicities include headache, nausea and vomiting. Reactions in the ear canals and on the ear should be observed and treated symptomatically.

4.6.2 Both acute and delayed, ≥ 90 days from treatment start (lethargy, transient worsening of existing neurological deficits) or late (radiation necrosis, cognitive dysfunction, accelerated atherosclerosis, radiation-induced neoplasms) effects of radiosurgery are to be recorded and included in the toxicity evaluation.

5.0 DRUG THERAPY

5.1 Bevacizumab
5.1.1 Bevacizumab will be administered intravenously on days 1 and 15 of each 28-day cycle.

5.1.2 The dose of bevacizumab will be 10 mg/kg of actual body weight.

5.1.2.1 The dose will be determined using body weight determined at the beginning of each treatment cycle. The daily dose will be rounded to the nearest 10 mg. The exact dose administered should be recorded in the CRF.

5.1.2.2 Bevacizumab is administered over 30 minutes.

To insure complete delivery of bevacizumab, the IV infusion line must be flushed with 0.9% sodium chloride. The following are two recommended methods for flushing the bevacizumab IV infusion line:

1. When the bevacizumab infusion is complete, add an additional 50 mL of 0.9% sodium chloride for injection to the bevacizumab infusion bag. Continue the infusion until a volume equal to that of the volume contained in the tubing has been administered.

2. Replace the empty bevacizumab infusion bag with a 50 mL bag of 0.9% sodium chloride for injection and infuse a volume equal to the volume contained in the tubing.

Please note: the flush is not included in the total recommended infusion times.

5.1.3 The first dose of bevacizumab will be administered 10 to 14 days prior to treatment with radiosurgery (defined as Study day 1)

5.1.3.1 The second dose of bevacizumab will be administered on Study day 15 and all subsequent doses will be administered on days 1 and 15 of each 28 day cycle.

5.1.4 Precautions

- General: Prior to each treatment, the patient should be carefully assessed with special attention to blood pressure, proteinuria, bleeding and cardiovascular events, as well as symptoms or signs of bowel perforation and reversible posterior leukoencephalopathy syndrome (RPLS). Decisions for retreatment or dose modification/interruption should follow the dose modification guidelines in Section 7.8.
- **Infusional reactions**: Routine premedication is not required for the first dose of bevacizumab. If infusional reactions occur, acetaminophen, diphenhydramine, steroids or other medications may be given for symptom control and for premedication as needed. Anaphylactic precautions should be observed during bevacizumab administration.
- **Hypertension**: Patients should have blood pressure monitored prior to each infusion of bevacizumab. Hypertensive medication should be initiated or increased for optimal blood pressure control according to standard public health guidelines.
- **Surgery and wound complication issues and surgery**: The appropriate interval from discontinuation of bevacizumab to subsequent elective surgery required to reduce the risk of impaired wound healing has not been determined. Decision on such an interval should take into consideration the half-life of bevacizumab. It is generally recommended that bevacizumab should be discontinued at least 4-8 weeks prior to major elective surgery. In addition, bevacizumab should not be restarted until at least 4 weeks after major surgery provided that the wound has adequately healed; in cases of high risk procedures such as liver resection, thoracotomy or neurosurgery, it is recommended that bevacizumab be resumed no earlier than 8 weeks after surgery.

5.1.5 **Bevacizumab Dose Modifications**

5.1.4.1 The dose of bevacizumab will be 10 mg/kg delivered intravenously. There will be no dose reduction for bevacizumab. Treatment should be interrupted or discontinued for certain adverse events, as described below. If bevacizumab is interrupted for ANY reason for > 8 weeks, the patient should discontinue bevacizumab therapy on protocol.

### Treatment Modification for Bevacizumab-Related Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>CTCAE.v4.0 Grade</th>
<th>Action To Be Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allergic reactions</strong> or <strong>Acute infusional reactions/ cytokine release syndrome</strong></td>
<td>Grade 1-3</td>
<td>If infusion-related or allergic reactions occur, premedications should be given with the next dose and infusion time may not be reduced for the subsequent infusion. Follow the guidelines in Section 5.1.3 for bevacizumab administration. For patients with grade 3 reactions, bevacizumab infusion should be stopped and not restarted on the same day. At the physicians’ discretion, bevacizumab may be permanently discontinued or re-instituted with premedications and at a rate of 90±15 min. If bevacizumab is re-instituted, the patient should be closely monitored for a duration comparable to or longer than the duration of the previous reactions.</td>
</tr>
<tr>
<td><strong>Arterial Thrombosis</strong></td>
<td>Grade 2 (if new or worsened since bevacizumab therapy)</td>
<td>Discontinue bevacizumab</td>
</tr>
<tr>
<td>- Cardiac ischemia/ infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- CNS ischemia (TIA, CVA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- any peripheral or visceral arterial ischemia/thrombosis</td>
<td>Grade 3-4</td>
<td>Discontinue bevacizumab</td>
</tr>
<tr>
<td>Event</td>
<td>CTCAE.v4.0 Grade</td>
<td>Action To Be Taken</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-----------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Venous Thrombosis</td>
<td></td>
<td><strong>Grade 3 OR asymptomatic grade 4</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is &lt; 2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If the planned duration of full-dose anticoagulation is &gt; 2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation <strong>IF all</strong> of the criteria below are met:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- The subject must have an in-range INR (usually 2-3) on a stable dose of warfarin or be on a stable dose of heparin prior to restarting bevacizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- The subject must not have pathological conditions that carry high risk of bleeding (eg, tumor involving major vessels or other conditions)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- The subject must not have had hemorrhagic events while on study</td>
</tr>
<tr>
<td></td>
<td>Grade 4 (symptomatic)</td>
<td><strong>Discontinue bevacizumab</strong></td>
</tr>
<tr>
<td>Hypertension*</td>
<td>Grade 1</td>
<td>Consider increased BP monitoring</td>
</tr>
<tr>
<td></td>
<td>Grade 2 asymptomatic but diastolic BP &lt; 100 mmHg</td>
<td>Begin anti-hypertensive therapy and continue bevacizumab</td>
</tr>
<tr>
<td></td>
<td>-Grade 2-3 Symptomatic OR -Diastolic BP &gt; 100 mmHg</td>
<td>• Hold bevacizumab until symptoms resolve <strong>AND BP &lt; 160/90mmHg</strong></td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td><strong>Discontinue bevacizumab</strong></td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>Grade 3</td>
<td><strong>Discontinue bevacizumab</strong></td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td><strong>Discontinue bevacizumab</strong></td>
</tr>
<tr>
<td>Proteinuria</td>
<td></td>
<td><strong>[Proteinuria should be monitored by urine analysis for urine protein creatinine (UPC) ratio prior to every other dose of bevacizumab ]</strong></td>
</tr>
<tr>
<td></td>
<td>UPC ratio &lt; 3.5</td>
<td>Continue bevacizumab</td>
</tr>
<tr>
<td></td>
<td>UPC ratio &gt; 3.5</td>
<td>Hold bevacizumab (or placebo) until UPC recovers to &lt; 3.5</td>
</tr>
<tr>
<td></td>
<td>Grade 4 or nephrotic syndrome</td>
<td><strong>Discontinue bevacizumab</strong></td>
</tr>
<tr>
<td>Hemorrhage (CNS or pulmonary)</td>
<td>Grade 2-4</td>
<td><strong>Discontinue bevacizumab</strong></td>
</tr>
<tr>
<td>Hemorrhage (non-CNS; non-pulmonary)</td>
<td>Grade 3 or 4</td>
<td><strong>Discontinue bevacizumab</strong></td>
</tr>
<tr>
<td>RPLS (reversible posterior leukoencephalopathy syndrome or PRES (posterior reversible encephalopathy syndrome)</td>
<td></td>
<td>• Hold bevacizumab in patients with symptoms/signs suggestive of RPLS; subsequent management should include MRI scans and control of HTN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <strong>Discontinue bevacizumab upon diagnosis of RPLS</strong></td>
</tr>
<tr>
<td>Event</td>
<td>CTCAE.v4.0 Grade</td>
<td>Action To Be Taken</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Wound dehiscence requiring medical or surgical intervention</td>
<td>• Discontinue bevacizumab</td>
<td></td>
</tr>
<tr>
<td>GI perforation, GI leak or fistula</td>
<td>• Hold bevacizumab until complete resolution, with a minimum of 4 weeks after surgery.</td>
<td></td>
</tr>
<tr>
<td>Bowel obstruction Grade 2 requiring medical intervention</td>
<td>• Hold bevacizumab until complete resolution</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• If surgery is required, patient may restart bevacizumab after full recovery from surgery, and at investigator’s discretion</td>
<td></td>
</tr>
<tr>
<td>Bowel obstruction Grade 3-4</td>
<td>• Hold bevacizumab until complete resolution</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• If surgery is required, patient may restart bevacizumab after full recovery from surgery, and at investigator’s discretion</td>
<td></td>
</tr>
<tr>
<td>Other unspecified bevacizumab-related AEs (except controlled nausea/vomiting). Grade 3</td>
<td>Hold bevacizumab until symptoms resolve to &lt; grade 1</td>
<td></td>
</tr>
<tr>
<td>Other unspecified bevacizumab-related AEs (except controlled nausea/vomiting). Grade 4</td>
<td>• Discontinue bevacizumab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Upon consultation with the study chair, resumption of bevacizumab may be considered if a patient is benefiting from therapy and the grade 4 toxicity is transient, has recovered to &lt; grade 1 and unlikely to recur with retreatment</td>
<td></td>
</tr>
</tbody>
</table>

*Current CTCAE definitions:*

- Grade 1: Prehypertension (systolic BP 120-139 mmHg or diastolic BP 80-89 mmHg)
- Grade 2: Stage 1 hypertension (systolic BP 140-159 mmHg or diastolic BP 90-99 mmHg); medical intervention indicated; recurrent or persistent (>=24hrs); symptomatic increase by >20 mmHg (diastolic) or to >140/90 mmHg if previously WNL: monotherapy indicated
- Grade 3: Stage 2 hypertension (systolic BP>=160 mmHg or diastolic BP>=100 mmHg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated
- Grade 4: Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated

5.1.5 Bevacizumab Agent Information

5.1.6 Bevacizumab Supply: Commercially available

5.2 Adverse Events
This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, MedDRA, version 9.0 for grading of all adverse events.

5.2.1 Adverse Events (AEs)

**Definition of an AE:** Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

5.2.2 Serious Adverse Events (SAEs)

**Definition of an SAE:** Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

5.2.3 Data Safety Monitoring Plan

This protocol will adhere to the policies of the Cancer Center Data and Safety Monitoring Plan, version 2 guidelines in accordance with NCI regulations. The Data and Safety Toxicity Committee will review all serious adverse events and toxicity reports as well as annual reviews.

6.0 OTHER THERAPY

6.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site’s source documents as concomitant medication.

6.1.1 Anticonvulsants: Anticonvulsants may be used as clinically indicated. Doses at study entry and at specific time points of the treatment must be recorded.

6.1.2 Corticosteroids: Corticosteroids may be administered at the treating physician’s discretion. Doses at study entry and at specific time points of the treatment must be recorded.

6.1.3 Antiemetics: Prophylactic antiemetics may be administered at the treating physician’s discretion.

6.1.4 Erythropoietin: Erythropoietin injections may be administered according to ASCO guidelines.

6.2 Non-Permitted Supportive Therapy

6.2.1 No other investigational drugs will be allowed during this study.

6.2.2 Surgical procedures for tumor debulking, other types of chemotherapy, and immunotherapy or biologic therapy must not be used while the patient is on protocol. Further, additional stereotactic boost radiotherapy is not allowed. If any of these treatments are required, the patient will not receive further therapy with bevacizumab according to this protocol. All further therapy is at the treating physician’s discretion, but should be recorded in the CRF.

7.0 PATIENT ASSESSMENTS: See Appendix 1 for a Summary of Assessments and Time Frames

7.1 Criteria for Evaluation of Therapy Effectiveness

7.1.1 Overall survival will be measured from study entry until death. Progression-free survival will be measured from study entry until the first occurrence of progression or death.
7.1.2 Toxicities will be measured using the CTCAE criteria, version 4.0.

7.2 Criteria for Discontinuation of Protocol Treatment

- Progression of disease as defined as a 25% increase in the bidimensional measurement of the enhancing component of the tumor attributable to tumor growth (as opposed to radionecrosis), or development of new enhancing lesions outside of the radiosurgery target volume, or neurological deterioration judged by the treating physician to be attributable to diffuse tumor progression (correlated with FLAIR changes on MRI).

- Unacceptable toxicity to the patient (at the discretion of the treating physician);

- A delay in drug therapy > 8 weeks for bevacizumab

- The patient may withdraw from the study at any time for any reason.

If protocol treatment is discontinued, follow-up and data collection will continue as specified in the protocol.

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Endpoints

8.1.1 Primary Endpoint

8.1.1.1 To determine the maximum tolerated dose of radiosurgery used to treat recurrent/progressive GBM concurrently with bevacizumab

8.1.1.2 To determine the overall survival of patients with recurrent GBM treated with bevacizumab and radiosurgery

8.1.2 Secondary Endpoints

8.1.2.1 Treatment-related toxicity.

8.1.2.2 Progression-free survival, defined as the interval from study entry to progression or death, whichever occurs first

8.2 Sample Size

Based on historical data, the median overall survival is 9 months for recurrent GBM on bevacizumab. Assuming an accrual time of 24 months and follow-up time of 18 months, a sample size of 74 (treated at the MTD for radiosurgery) would be needed to provide at least 80% power to detect a 30% reduction in risk due to the intervention using a 2-sided test at alpha = 0.05. The total sample size will be adjusted to reflect the additional patients treated in the Phase I component of this protocol.

8.3 Analysis Plan

8.3.1 Statistical Methods

Overall and progression-free survival rates will be estimated using the Kaplan-Meier method (Kaplan 1958), and the new treatment will be thought of promising and warrants further study if the median survival is at least 11.6 months. Overall survival will be measured from the date of registration to the date of death or, otherwise, the last follow-up date on which the patient was reported alive. Progression-free survival will be measured from the date of registration to the date of first progression or death or,
otherwise, the last follow-up date on which the patient was reported alive. Observed severities of toxicities (grade 3+) will be summarized by frequencies and percentages.

Multivariate analyses with the Cox proportional hazard model (Cox 1972) for overall and progression-free survival will be performed to assess the effect of patient-specific risk factors. Proportional hazard assumptions will be checked using different graphical or time-varying coefficients testing methods. If the data clearly do not follow proportional hazards, other statistical models will be used to fit the data instead. Possible alternatives are to use the stratified Cox proportional hazard model, accelerated failure model, or partition the time axis into sections where proportional hazard assumption holds.
REFERENCES


Peterson, B. and George, S.L. (1993). Sample size requirements and length of study for testing interaction in a 2 x k factorial design when time-to-failure is the outcome. Controlled Clinical Trials, 511-522.


### APPENDIX I: Study Calendar

<table>
<thead>
<tr>
<th></th>
<th>Pre-Treatment (≤ 21 d prior to first dose of bevacizumab)</th>
<th>During bevacizumab therapy (28 day cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day 1** (± 3 days)</td>
</tr>
<tr>
<td><strong>Tissue histology confirmation</strong></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>History/physical</strong></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Contrast-enhanced MRI</strong></td>
<td>X</td>
<td>X***</td>
</tr>
<tr>
<td><strong>Steroid dose documentation</strong></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Performance status</strong></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>CBC w/ diff, ANC, platelets, Hgb</strong></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>BUN</strong></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Creatine</strong></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Urine protein (random)</strong></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Bilirubin</strong></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>ALT/AST</strong></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Systolic/diastolic blood pressure</strong></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>PT INR</strong></td>
<td>X*</td>
<td>X***</td>
</tr>
<tr>
<td><strong>Serum pregnancy test (if applicable)</strong></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Informed consent</strong></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

X* - to be performed if on all patients
X** - starting with cycle 2
X*** - before every odd cycle
X**** - to be performed if patient on warfarin
# APPENDIX II

## KARNOFSKY PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal; no complaints; no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some sign or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self; unable to carry on normal activity or do active work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most personal needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospitalization is indicated, although death not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospitalization necessary; active support treatment is necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes progressing rapidly</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>

## ZUBROD PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on self-care. Totally confined to bed or (Karnofsky 10-20).</td>
</tr>
<tr>
<td>5</td>
<td>Death (Karnofsky 0).</td>
</tr>
</tbody>
</table>
APPENDIX III

ENZYME INDUCING AND NON-ENZYME ENDUCING ANTIEPILEPTIC DRUGS

The following agents are potential hepatic enzyme inducing antiepileptic drugs (EIAEDs):

Carbamazepine (Tegretol, Tegretol XR, Carbatrol)
Oxcarbazepine (Trileptal)
Phenytoin (Dilantin, Phenytek)
Fosphenytoin (Cerebyx)
Phenobarbital
Pentobarbital
Primidone (Mysoline)

The following agents are non-enzyme inducing antiepileptic drugs (non-EIAEDs):

Valproic acid (Depakote, Depakene, Depacon)
Gabapentin (Neurontin)
Lamotrigine (Lamictal)
Topiramate (Topamax)
Tiagabine (Gabitril)
Zonisamide (Zonegran)
Levetriacacetam (Keppra)
Clonazepam (Klonopin)
Clonozam (Frisium)