Abbreviated Title: Ph II Ependymoma

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Title: Phase II trial of Carboplatin and Bevacizumab for the Treatment of Recurrent Low-grade and Anaplastic Supratentorial, Infratentorial and Spinal Cord Ependymoma in Adults: A Multi- Center Trial

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Commercial Agents: Bevacizumab and Carboplatin will be dispensed by the participating site's pharmacy and will be charged to the patient's medical insurance carrier.

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP) and the following:

1. United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

PRÉCIS

Background:

- Ependymomas are glial based tumors arising from the ependymal lining of the ventricular system and central canal of the spinal cord
- These tumors affect both adults and children and represent approximately 1.2%-7.8% of all intracranial cancers
- Currently, the standard therapy for newly diagnosed low-grade ependymoma includes total surgical excision, when possible, followed by radiation therapy. Complete surgical resection is often not possible because of the location of the tumor and the concern for damage to surrounding eloquent brain during surgery. The situation is even more critical for patients with anaplastic ependymomas because of the higher proliferative rate and greater propensity for tumor infiltration into surrounding normal brain, preventing any possibility of complete tumor removal by surgery.
- For patients with the more aggressive anaplastic ependymoma, chemotherapy is often administered either before or after the radiation in the hope that infiltrating tumor cells will be eliminated.
- Extensive experience has been gathered with the use of bevacizumab in other neuroepithelial tumors such as malignant gliomas. Based on the interesting results observed in the reported small series of patients with recurrent ependymomas treated with bevacizumab, as well as on the evidence of VEGF-promoted angiogenesis in these tumors, we designed a phase II study to test the efficacy of bevacizumab in patients with recurrent ependymoma. As results in most types of tumors have indicated that anti-angiogenesis therapies are more effective when given in combination with cytotoxic chemotherapy, in this study bevacizumab will be combined with carboplatin. The choice of carboplatin is justified by the fact that, as detailed above, this remains the most effective agent in this disease, and extensive toxicity data is available for the combination of bevacizumab and carboplatin in a variety of tumor types, including GBMs.

Objective:

- To evaluate the efficacy of carboplatin and bevacizumab for the treatment of recurrent low grade or anaplastic ependymoma. The primary endpoint will be progression-free survival (PFS) at one year.

Eligibility:

- Histologically proven intra-cranial or spinal ependymoma or anaplastic ependymoma. There must be pathologic or imaging confirmation of tumor progression or regrowth.
- Patients must be ≥18 years old.
- Patients must have a Karnofsky performance status of ≥ 60.
- Patients must have adequate bone marrow function, adequate liver function and adequate renal function before starting therapy.
- Patients must have recovered from the toxic effects of prior therapy:

- Patients having undergone recent resection of recurrent or progressive tumor will be eligible
- Patients must have failed prior radiation therapy and must have an interval of greater than or equal to 42 days from the completion of radiation therapy to study entry.
- Women of childbearing potential must have a negative B-HCG pregnancy test documented within 14 days prior to registration.
- Women of childbearing potential and male participants agree to practice adequate contraception.
- Patients must not have any significant medical illnesses or active infection
- Patients must not have history of any other cancer
- Patients must not be pregnant/breast feeding.
- Patients must not have received prior therapy with bevacizumab, or related drugs
- No active bleeding or pathological condition that carries a high risk of bleeding
- No major surgical procedure, open biopsy, or significant traumatic injury within 28 days.

Design:

- This is a phase II study to evaluate the efficacy of carboplatin and bevacizumab for the treatment of recurrent low grade or anaplastic ependymoma. This trial is designed utilizing a Simon optimal two-stage design.
- Carboplatin will be given on day 1 of each cycle. Bevacizumab will be administered on days 1 and 15 of each cycle. The total duration of treatment will be 6 cycles. After cycle 6, carboplatin should be discontinued, but bevacizumab may be continued at the discretion of the treating physician.
- Patients will be monitored for hematologic or serologic evidence of myelosuppression, hepatic injury, renal injury, and electrolyte disturbances and for clinical evidence of other toxicity.

TABLE OF CONTENTS

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

To evaluate the efficacy of carboplatin and bevacizumab for the treatment of recurrent low grade or anaplastic ependymoma. The primary endpoint will be progression-free survival (PFS) at one year.

1.1.2 Secondary Objectives

1.1.2.1 To evaluate response rates to this chemotherapy.

1.1.2.2 To evaluate overall survival in this population.

1.1.2.3 To evaluate toxicity profile of this combination.

1.1.2.4 To longitudinally evaluate patient reported outcome measures using self-reported symptom severity and interference with daily activities using the MDASI-BT and/or MDASI-SP instrument.

1.1.3 Exploratory Objectives

1.1.3.1 To evaluate safety and preliminary efficacy of this treatment in patients with recurrent Ependymomas according to anatomical location (supratentorial, posterior fossa and spinal cord).

1.1.3.2 To evaluate paraffin embedded tissue samples (and frozen samples, if available) utilizing gene expression profiling (Illumina technology), immunohistochemistry and/or RT-PCR. Analysis will focus on expression of genes involved in angiogenesis and hypoxia-related tissue factors. This component of the research will be overseen by Dr. Kenneth Aldape.

1.2 BACKGROUND AND RATIONALE

1.2.1 Background on Ependymomas

Ependymomas are glial based tumors arising from the ependymal lining of the ventricular system and central canal of the spinal cord, and can therefore be found in the supratentorial, posterior fossa and spinal compartments. These tumors affect both adults and children and represent approximately 1.2%-7.8% of all intracranial tumors. The WHO classifies ependymomas into low grade (WHO grade II) and the more malignant – anaplastic ependymomas (WHO grade III). Anaplastic ependymomas are more common in adults.

Currently, the standard therapy for newly diagnosed low-grade ependymoma includes total surgical excision followed by radiation therapy. Complete surgical resection is often not possible because of the location of the tumor and the concern for damage to surrounding eloquent brain during surgery. The situation is even more critical for patients with anaplastic ependymomas because of the higher proliferative rate and greater propensity for tumor infiltration into surrounding normal brain, preventing any possibility of complete tumor removal by surgery. For patients with the more aggressive anaplastic ependymoma, chemotherapy is often administered either before or after the radiation in the hope that infiltrating tumor cells will be eliminated. Unfortunately, even for patients with low-grade ependymoma, survival can be poor when the tumor is not totally surgically resected. There have only been a limited number of reports describing chemotherapy treatments for patients with recurrent ependymoma, either low grade or anaplastic. As a consequence, optimal therapy for this group remains unknown. Most reported regimens are based on platinum compounds (carboplatin or cisplatin) and have been developed in children.[1, 2] Many of these regimens are associated with a high incidence of

moderate to severe toxicity, and applying such treatments to adults can be challenging.[3] The largest experience with chemotherapy in adult ependymoma patients was reported by Brandes et al.[4] That study included 28 adult patients who had recurrent ependymoma (n = 17) or anaplastic ependymoma (n = 11) after initial treatment with surgery and radiation. One-half of the patients had undergone multiple tumor resections. A wide variety of regimens were used ranging from single agent temozolomide to the "8 in 1" regimen that combines 8 different chemotherapy agents. The overall objective response rate was 20% (complete response [CR] and partial response [PR]). The 12 month PFS rate was 44% (95% CI, 29%-68%). The median time to progression was 9.9 months and the median overall survival (OS) was 40.4 months. Analysis of outcomes in patients who received platinum-based chemotherapy regimens (N=13) in comparison to patients treated with regimens without platinum (N=15) showed that platinum-containing regimens are associated with higher response rates (30.8% vs. 13.3%), confirming the activity of platinum agents in this disease. However, there were no significant differences in PFS or OS between the two groups, although interpretation of these results is limited by the low number of patients.

1.2.2 Rationale for bevacizumab and anti-angiogenesis strategies in ependymomas

Bevacizumab (Avastin™, Genentech Inc., South San Francisco, CA) is a humanized monoclonal anti-VEGF antibody with demonstrated efficacy in a variety of solid tumors. It was first approved by the FDA in 2004 for first line chemotherapy for colorectal cancer. Since then, FDA approval has been obtained for the treatment of advanced NSCLC and metastatic HER-2 negative breast cancer and, more recently, progressive glioblastoma (GBM).

1.2.2.1 Pre-clinical data

A number of studies have investigated angiogenic patterns in ependymomas. The largest study evaluated paraffin embedded tissue in a series of 100 patients with ependymoma, obtained at the time of diagnosis.[5] This included 73% of patients with WHO grade II tumors and 27% with grade III tumors. In spite of the low prevalence of high grade tumors, microvascular proliferation could eventually be documented in 42% of patients in various patterns, whereas necrosis was present in 57% of patients. VEGF expression, as evaluated by in situ hybridization, was detected in 88% of patients. CA9 was expressed in 84% of patients, but HIF1-alpha was seen in only 42% of patients. This suggested that VEGF expression is frequent in ependymomas, and may not result from hypoxia (as in GBMs), but rather from oncogenic activation. In that same study, a high hypoxic score (defined as expression of more than two hypoxia-related tissue factors) was associated with worse prognosis on univariate, but not multivariate analysis, whereas elevated MIB-1 index remained a significant marker of poor prognosis in the multivariate setting. VEGF expression was associated with a trend in decreased OS (p= 0.06).[5] In another study, VEGF expression in ependymomas was associated with tumor grade, and predicted shorter PFS (p=0.003).[6] In a smaller study, VEGF was found to be strongly expressed in 8/10 ependymomas, all of them with extensive necrosis and vascular proliferation; VEGF expression was mainly observed around the necrotic areas, and most tumors also displayed strong expression of VEGFR (Flt-1 and KDR).[7] Taken together, these studies suggest that anti-VEGF treatments such as bevacizumab are an attractive strategy for the treatment of ependymomas, particularly in the recurrent setting where tumors are associated with a more aggressive behavior.

1.2.2.2 Clinical data

Clinical experience with bevacizumab in ependymomas is limited. A single, small, retrospective study has been reported.[8] That study reported on eight adult patients with recurrent ependymoma treated at

several different institutions. In three patients, bevacizumab was given in combination with CPT-11, in two patients with carboplatin, in one patient with temozolomide and in two patients as a single agent. Patients tolerated treatment well. Six of the 8 patients achieved a partial response, disease was stable in one patient and one patient progressed. The median TTP in that heavily pre-treated population was 6.5 months and the overall survival was 9.4 months.

Conversely, extensive experience has been gathered with the use of bevacizumab in other neuroepithelial tumors such as malignant gliomas and glioblastomas. After anecdotal experience suggested high response rates,[9] a phase II study was conducted in recurrent glioma.[10] Impressive response rates were confirmed, with 63% of the 32 enrolled patients demonstrating at least a PR. PFS, and to a lesser extent OS, were also increased in comparison to historical controls (GBM patients: median PFS- 20 weeks; median OS- 10 months; N=23). Preliminary results of a phase II randomized trial comparing single-agent bevacizumab versus the combination of bevacizumab with irinotecan indicate that both arms achieved superior outcomes in comparison to historical controls. The group receiving the combination of drugs achieved higher response rates (33% vs 20%) and 6 month-PFS (50% vs 35%), although OS was slightly longer in the single agent arm (8.9 vs 9.7 months).[11] Based on such results, bevacizumab was approved for the treatment of recurrent malignant gliomas. Importantly, such studies have demonstrated that bevacizumab can be safely given to patients with brain tumors, and that concerns of intracranial bleeding should not preclude their use, including in patients receiving anticoagulation.[12]

1.2.3 Rationale for this study

Based on the interesting results observed in the reported small series of patients with recurrent ependymomas treated with bevacizumab, as well as on the evidence of VEGF-promoted angiogenesis in these tumors, we designed a phase II study to test the efficacy of bevacizumab in patients with recurrent ependymoma. As results in most types of tumors have indicated that anti-angiogenesis therapies are more effective when given in combination with cytotoxic chemotherapy, in this study bevacizumab will be combined with carboplatin. The choice of carboplatin is justified by the fact that, as detailed above, this remains the most effective agent in this disease, and extensive toxicity data is available for the combination of bevacizumab and carboplatin in a variety of tumor types, including GBMs. The study will include a comprehensive translational component for the evaluation of treatment effects on advanced MRI imaging parameters (perfusion and spectroscopy) as well as serum levels of angiogenesis-related factors as potential biomarkers.

A large number of manuscripts have been published outlining the toxicities associated with bevacizumab use in patients with cancer. A recent publication by Armstrong, et al specifically describes the well-known toxicities and their incidence and management in the brain tumor patient population [24] These include hypertension which is refractory in a small percentage of patients, thromboembolic disease which occurs in the venous system in 8-10% of patients and arterial (mostly cerebral) in 1-2%, significant intracranial hemorrhage in less than 2%, renal dysfunction in less than 2% and wound dehiscence in less than 2% (partially dependent on time from craniotomy). Intestinal perforation also occurs in less than 2%.

1.2.3.1 Rationale for the patient-reported outcomes:

Although rare, ependymal tumors have a recognized impact on the patients physical and neurologic function[13, 14]. Despite aggressive therapy at diagnosis, many ependymomas recur [15]. Currently,

no standard therapy at recurrence has been established, and the impact of chemotherapy at recurrence has been limited[15].

This study seeks to establish effective therapies at recurrence and improve on current clinical results. We hypothesize that using a combination of carboplatin and bevacizumab will result in improved survival. However, given the intensive nature of this regimen, it will be important to determine whether if any determined survival benefit is associated with improvements in symptoms or does a worsening of these parameters offset the increase in survival.

Precedence for measuring "non-therapeutic" endpoints exists in oncology research. For example, Gemcitabine was approved by the FDA partially as a consequence of the decrease in pain reported in pancreatic patients who were treated, not on the basis of survival improvement which was modest, at best [16]. There have been efforts in neuro-oncology to evaluate secondary endpoints using validated instruments as an additional indicator of benefit.

The M.D. Anderson Symptom Inventory-Brain Tumor Module or M.D. Anderson Symptom Inventory Spine Tumor Module (MDASI-BT or SP, respectively) allows the self-reporting of symptom severity and interference with daily activities. The MDASI-BT or SP has demonstrated reliability and validity in the adult primary brain tumor patient population [17] [18]. This tool represents a modification of the widely used and validated MDASI, with particular attention to symptoms common in patients with brain tumors. The availability of validated instruments provides an opportunity to prospectively assess the impact of treatment, both positive and negative, on patients. This evaluation of symptom burden in this study will assist in finding the best possible treatment with the least toxicity.

1.2.4 Rationale for the correlative studies

Although bevacizumab has been extensively utilized for the treatment of GBM and several other types of cancer, to date, no predictive biomarker has been validated for selection of patients likely to benefit from treatment or that could be used for follow-up and to guide treatment decisions. In order to identify validate such potential biomarkers in this trial the following studies will be performed:

1.2.4.1 Baseline tumor expression of hypoxia-related factors

In a recent retrospective study conducted by Sathornsumetee et al[19] in GBM patients undergoing treatment with bevacizumab, the authors found that high VEGF expression levels in the tumor was associated with radiographic responses but not OS. This finding is in line with the normalization of vasculature and decreased permeability observed with anti-VEGF strategies, which translates into radiographic response, but that may or may not be associated with anti-tumor effect. In contrast, expression of hypoxia-related factors CA9 and HIF-2 expression was associated with poor survival, suggesting that such factors may be better predictive markers for anti-angiogenic strategies. However, such findings may not be applicable in ependymomas, as the VEGF expression may not be dependent on hypoxia, but rather to oncogenic activation, as detailed above. To investigate these aspects in this study paraffin embedded tissue or frozen tissue from all patients will be evaluated for the expression of hypoxia-related and angiogenesis factors such as VEGF, VEGFR-2/KDR, CD31, CA9, HIF-2α and others, utilizing immunohistochemistry, RT-qPCR and gene expression profiling (Illumina technology). This component of the study will be performed by Dr. Kenneth Aldape (Section **5.1**) who has extensive experience in the molecular characterization of ependymomas in the setting of prior CERN studies.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Histologically proven intra-cranial or spinal ependymoma or anaplastic ependymoma. There must be pathologic or imaging confirmation of tumor progression or regrowth. The patient's histologic diagnosis must be confirmed on Central Pathology Review prior to registration Step 2.

> *If a patient has already had central pathology review at MDACC (for example, from a previous enrollment to protocol CERN08-02), the central pathology does not need to be repeated. Previous pathology confirmation can be utilized for this study's pathology eligibility testing.

2.1.1.2 The patient must have at least 1 block of tissue or 15 unstained slides at a minimum available for central pathology review and molecular profiling of the tissue sample.

2.1.1.3 All patients must sign an informed consent indicating that they are aware of the investigational nature of this study. Patients must have signed an authorization for the release of their protected health information.

2.1.1.4 Patients must be ≥ 18 years old.

2.1.1.5 Patients must have a Karnofsky performance status of ≥ 60.

2.1.1.6 Patients must have adequate bone marrow function (WBC ≥ 3,000/µl, ANC ≥ 1,500/mm^3, platelet count of ≥ 100,000/mm^3, and hemoglobin ≥ 10 gm/dl), adequate liver function (SGOT [AST <92.5 Units/L] and bilirubin ≤ 1.5 mg/dL), and adequate renal function (creatinine < 1.5 mg/dL and calculated creatinine clearance ≥ 60 cc/min) before starting therapy. Eligibility level for hemoglobin may be reached by transfusion.

2.1.1.7 Patients must have shown unequivocal radiographic evidence for tumor progression by MRI or CT scan as defined by Section **6.3.1.6**. If an MRI is being obtained to verify eligibility, it is recommended that the MRI parameters follow the specifications detailed in Appendix **15.4** so that the patient will not require a repeat MRI prior to treatment start.

2.1.1.8 At the time of registration: Patients must have recovered from the toxic effects of prior therapy: ≥ 28 days from any investigational agent, ≥28 days from prior cytotoxic therapy, ≥14 days from vincristine, ≥42 days from nitrosoureas, ≥21 days from procarbazine administration, and ≥7 days for non-cytotoxic agents, e.g., interferon, tamoxifen, thalidomide, cis-retinoic acid, etc. (radiosensitizer does not count). Any questions related to the definition of non-cytotoxic agents should be directed to the Principal Investigator.

2.1.1.9 Patients having undergone recent resection of recurrent or progressive tumor will be eligible as long as all of the following conditions apply:

- They have recovered from the effects of surgery.
- A minimum of 28 days have elapsed from the day of surgery to the day of registration Step 2. For core or needle biopsy, a minimum of 7 days must have elapsed prior to registration Step 2.
- Residual disease following resection of recurrent ependymoma is not mandated for eligibility into the study. To best assess the extent of residual disease post-operatively, a CT/ MRI

should be done no later than 96 hours in the immediate post-operative period or at least 4 weeks post-operatively, within 14 days prior to consent. If the "within 96-hour after surgery" scan is more than 14 days before consent the scan needs to be repeated. If the steroid dose is increased between the date of imaging and consent, a new baseline MRI/CT is required on a stable steroid dosage for at least 5 days.

2.1.1.10 Patients must have failed prior radiation therapy* and must have an interval of greater than or equal to 42 days from the completion of radiation therapy to study entry.

*Note: Patients with an indication for craniospinal radiotherapy (i.e., extensive leptomeningeal disease) but have refused palliative craniospinal radiotherapy are eligible.

2.1.1.11 Patients with prior therapy that included interstitial brachytherapy or stereotactic radiosurgery must have confirmation of true progressive disease rather than radiation necrosis based upon either PET or Thallium scanning, MR spectroscopy, or surgical/pathological documentation of disease.

2.1.1.12 Women of childbearing potential must have a negative B-HCG pregnancy test documented within 14 days prior to registration.

2.1.1.13 Women of childbearing potential and male participants agree to practice adequate contraception.

2.1.2 Exclusion Criteria

2.1.2.1 Patients with any significant medical illnesses that in the investigator's opinion cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate this therapy.

2.1.2.2 Patients with a history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission and off of all therapy for that disease for a minimum of 3 years are ineligible.

2.1.2.3 Patients with an active infection or serious intercurrent medical illness.

2.1.2.4 Patients found to be pregnant/breast feeding. Patients must not be pregnant because animal studies show that carboplatin and bevacizumab are teratogenic

2.1.2.5 Patients with any disease that will obscure toxicity or dangerously alter drug metabolism.

2.1.2.6 Patients who have received prior therapy with bevacizumab, or related drugs (previous therapy with carboplatin is allowed).

2.1.2.7 Inadequately controlled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure > 100 mmHg) despite antihypertensive medication.

2.1.2.8 New York Heart Association (NYHA) Grade II or greater congestive heart failure.

2.1.2.9 History of myocardial infarction or unstable angina within 12 months prior to Day 1.

2.1.2.10 History of stroke or transient ischemic attack.

2.1.2.11 Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1.

2.1.2.12 History of hemoptysis (≥ 1/2 teaspoon of bright red blood per episode) within 1 month prior to Day 1.

2.1.2.13 Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation). (To be eligible, Prothrombin time/international normalized ratio (PT INR) should be < 1.4 for patients not on warfarin.)

2.1.2.14 Patients receiving full dose anticoagulation therapy (e.g., warfarin or LMW heparin) and does not 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 (usually between 2 and 3) on a stable dose of oral anticoagulant or on a stable dose of low molecular weight heparin.

2.1.2.15 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.

2.1.2.16 Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to Day 1.

2.1.2.17 History of abdominal fistula or gastrointestinal perforation within 6 months prior to Day 1.

2.1.2.18 Serious, non-healing wound, active ulcer, or untreated bone fracture.

2.1.2.19 Proteinuria as demonstrated by a UPC ratio ≥ 1.0 at screening, or Urine dipstick for proteinuria ≥ 2+ (patients discovered to have ≥2+ proteinuria on dipstick urinalysis at baseline should undergo a 24 hour urine collection and must demonstrate ≤ 1g of protein in 24 hours **to be eligible**).

2.1.2.20 Known hypersensitivity to any component of bevacizumab.

2.1.2.21 Patients has current active hepatic or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, or stable chronic liver disease per investigator assessment)

2.2 SCREENING EVALUATION

2.2.1 A complete medical history and review of concomitant medications, physical exam (height, weight, vital signs and BSA) and neurological examination (to include documentation of the patients Karnofsky Performance Status per Appendix **15.1**), as well as neuro-imaging confirming tumor progression shall be performed on all patients. The scan done prior to study entry documenting progression will be reviewed by the patient's principal investigator. The baseline scan should be obtained within 14 days before registration step 2, and should follow the instructions described in Appendix **15.4.**

2.2.2 Pre-study laboratory tests shall include CBC, differential, platelets, PT/PTT and INR, serum creatinine, calculated creatinine clearance, bilirubin, SGOT, urine protein/ creatinine ratio (or urinalysis) and serum pregnancy test for women of childbearing potential. Pre-study laboratory tests must be obtained within 14 days before registration step 2.

2.2.3 Documentation of tumor diagnosis. Following registration step 1, slides from the most recent pre-registration biopsy must be submitted for review.

Fifteen unstained paraffin slides, or a paraffin tissue block, will be obtained in all study patients from original surgery or definitive surgery or the surgery closest to initiation of this clinical trial and in those patients who will be undergoing resection at time of treatment failure.

In this study, paraffin embedded tissue or frozen tissue (or 15 unstained slides at a minimum) will be collected from all patients, for evaluation of expression of hypoxia-related and angiogenesis factors such as VEGF, VEGFR-2/KDR, CD31, CA9, HIF-2α and others, utilizing immunohistochemistry, RT-qPCR and gene expression studies. Tissue evaluation will be required for every case before study registration Step 2 (see Section **5.1**):

2.3 REGISTRATION PROCEDURES

2.3.1 Registration at NCI

Not applicable. As of Amendment C (Version Date 04/24/2017), participants will not be enrolled at the Clinical Center, NIH.

2.3.2 Participating Site Registration

All patients must be registered through the NCI Coordinating Center's Research Nurse. The Coordinating Center is open from 8:30am to 5:00pm EST Monday through Friday, excluding federal holidays. An Eligibility Checklist and cover memo will be supplied by the Coordinating Center, NCI CCR and updates will be provided as needed. Subject eligibility (including source documents as described in section **6.1.1**) and demographic information is required for registration. To initially register a subject, after the participant has signed consent, complete the top portion of the eligibility checklist form (step 1) and send via encrypted email to Coordinating Center's Research Nurse, 240-760-6428, nci_bttc@mail.nih.gov. Once eligibility is confirmed, complete the remainder of the eligibility checklist form and send via encrypted email. If patient is not eligible, please notify the Coordinating Center, 240-760-6428, nci_bttc@mail.nih.gov. The Coordinating Center will review the registration form and forward it to the NCI Central Registration Office for processing. NCI Central Registration Office (CRO) will assign a unique patient/subject ID number for each subject that will be used to enter data into the C3D data base. Participating sites will receive a copy of the CRO's confirmation of registration from the Research Nurse. Questions about eligibility should be directed to the Coordinating Center's Research Nurse.

Registration Step 1

Registration step 1 must be completed:

- After the patient has signed the informed consent.
- Before study related research tests and/or procedures are obtained.
- Before tissue/slides are submitted for analysis and histologic diagnosis confirmation.

Confirmation of histology by Central Review will not be known at this time point. At the time of registration step 1, the following information will be requested by the Research Nurse:

- A faxed or emailed copy of a completed and signed, protocol specific, Step 1 Eligibility Checklist Form.
- One copy of a Pathology report from the patient's most recent surgery or biopsy.
- One copy of the signed and dated Informed Consent/Authorization.

The Eligibility Checklist form should be prepared and signed prior to faxing or emailing to the Research Nurse.

If the patient fails eligibility screening, do not proceed to Step 2 of the registration process.

Subjects that do not meet screening criteria should be removed from the study following the procedure in section **3.6.3.2**.

Registration Step 2

Registration step 2 must be completed:

- After eligibility screening has been completed and the local investigator has determined that the patient meets eligibility requirements.
- After centralized review and confirmation of histologic diagnosis.
- Before initiation of study treatment of any modality.

Confirmation of histologic diagnosis at this time point must be known. Protocol treatment may not be initiated until Step 2 of the registration process has been completed by the Research Nurse. At the time of registration step 2, the following information will be requested:

- A faxed or emailed copy of a completed and signed, protocol specific, Step 2 eligibility checklist form
- One copy of the Central Pathology Review results

The Eligibility Checklist form should be prepared and signed prior to faxing or emailing to the Research Nurse.

2.3.3 Initiation of Therapy

Treatment may not be initiated until the participating institution receives a faxed or emailed copy of the patient's Registration Verification Letter from the NCI Registration Office.

All Patients that are eligible to receive therapy must initiate treatment <u>within 96 hours</u> after the registration Step 2.

2.3.4 Treatment Assignment

Cohorts

Number	Name	Description
1	First cohort	Patients with Recurrent Low-grade and Anaplastic Supratentorial, Infratentorial and Spinal Cord Ependymoma

Arms

Number	Name	Description
1	Experimental	Carboplatin will be given on day 1 of each cycle. Bevacizumab will be administered on days 1 and 15 of each cycle. The total duration of treatment will be 6 cycles. After

		cycle 6, carboplatin should be discontinued, but bevacizumab may be continued at the discretion of the treating physician.

Stratifications

None.

Arm Assignment

Patients in cohort 1 will be directly assigned to arm 1.

2.4 BASELINE EVALUATION

2.4.1 Patients will complete a baseline MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT or MDASI-SP) (Appendix **13.2** or **13.3**) within 14 days (+ 3 working days) after enrollment on the clinical trial. The MDASI-BT or MDASI-SP will be completed only by the patient, unless changes in vision or weakness make this difficult. If this occurs, then the caregiver or research assistant may read the questions to the patient or assist with marking the severity number or score as described by the patient. A patient caregiver may complete the questionnaires as a patient-preference proxy if the patient's deficits preclude self-report.

2.4.2 Prior to treatment start, a baseline MRI of the brain including diffusion, perfusion and spectroscopy should be obtained as specified in Appendix **13.4**. This MRI should be performed within 14 days prior to registration step 2. In case of contra-indication to an MRI, a CT of the head with and without contrast should be performed. The same type of scan, i.e., MRI or CT must be used throughout the period of protocol treatment for tumor measurement.

2.4.3 Prior to treatment start, a baseline creatinine clearance should be obtained from a 24-hour urine collection or calculated using the Cockcroft-Gault equation (see section **3.2**). The maximum CrCl used should be 125 ml/min. The creatinine to be used for this baseline calculation should be obtained on the day of treatment or within 3 days prior.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a phase II study to evaluate the efficacy of carboplatin and bevacizumab for the treatment of recurrent low grade or anaplastic ependymoma after failure of one line of chemotherapy. This trial is designed utilizing a Simon optimal two-stage design, as described in Section 8. **Patients must initiate study treatment within 96 hours after registration Step 2.** If the patient has undergone surgery, treatment should start no sooner than 28 days after surgery. All efforts should be made to obtain a post-operative scan within 96 hours following surgery for evaluation of extent of surgery. A pre-treatment MRI must be obtained/repeated within 14 days prior to start of treatment, following the parameters established in Appendix **13.4.**

Eligible patients will be treated as described below. One cycle will correspond to 4 weeks. A treatment window of +/- 3 days is acceptable for all treatments and procedures. Carboplatin will be given on day 1 of each cycle. Bevacizumab will be administered on days 1 and 15 of each cycle. The total duration of treatment will be 6 cycles. After cycle 6, carboplatin should be discontinued, but bevacizumab may be continued at the discretion of the treating physician. Patients will be monitored for hematologic or serologic evidence of myelosuppression, hepatic injury, renal injury, and electrolyte disturbances and for clinical evidence of other toxicity as is described in sections **3.2.1, 3.2.2, 11.1** and **11.2**.

3.2 DRUG ADMINISTRATION

3.2.1 **Carboplatin** will be given on day 1 of each cycle. For cycle 1, the dose will be given at an AUC=5 mg/mL/min. If no toxicity higher than grade 1 is observed during cycle 1, the dose of carboplatin will be increased to AUC=6 mg/mL/min for cycle 2 and onwards.

The carboplatin dose should be calculated using the Calvert formula: Carboplatin dose (mg) = target AUC x (CrCl + 25).

The maximum CrCl used should be 125 ml/min. The creatinine to be used for calculation of AUC should be obtained on the day of treatment or within 3 days.

The Cr Cl should be calculated using the Cockroft-Gault equation:

Male: CrCl (ml/min) = (140-age) X (Actual weight in kg) / 72 x serum Creatinine (mg/dl).

Female: CrCl (ml/min) = (140-age) X (Actual weight in kg) X 0.85 / 72 x serum Creatinine (mg/dL)

A measured CrCl from a 24 hour urine collection may also be used.

3.2.1.1 Special considerations with the use of the Cockcroft-Gault (CG) in estimating GFR:

3.2.1.1.1 Adjustments for extremes of weight

- Actual weight is to be used unless patient has BMI> 25
- In patients with BMI > 25, using the adjusted body weight should be considered.
- If using other weight, please justify rationale.

3.2.1.1.2 Serum creatinine details

- IDMS creatinine is preferred; back-calculating to a non-IDMS creatinine will not be permitted.
- Lower limits of reported serum creatinine: Recommendation is 0.7 mg/dL be the lower limit

If using lower serum creatinine value, please justify rationale.

3.2.1.1.3 Use of capping GFR (at 125) or Carboplatin dose or both.

3.2.1.2 Adjustments for first cycles compared with subsequent cycles.

At the discretion of the treating physician, deviations to the rules described for carboplatin dose

Calculation may be proposed and discussed with the study PI**.**

3.2.2 **Bevacizumab** will be administered at a dose of 10 mg/kg on days 1 and 15 of each cycle.

The total duration of treatment will be 6 cycles. After cycle 6, carboplatin should be discontinued, but bevacizumab may be continued at the discretion of the treating physician. Patients who have completed the maximum number of Carboplatin cycles will remain on-study and should be followed with MRI and correlative blood tests per protocol every 8 weeks (+/- 30 days), until withdrawal of consent or radiographic progression of disease. Patients who have completed the maximum number of Carboplatin cycles and are continuing on Bevacizumab should have CBC, pregnancy test (β-HCG), creatinine clearance, UPC or urinalysis at the discretion of the treating physician. If carboplatin is discontinued prior to completion of 6 cycles due to toxicity, patients may continue with single-agent bevacizumab until disease progression, at the discretion of the treating physician.

3.2.3 Dose Modifications

Patients with stable or responding disease may be retreated at the same dose or at a reduced dose level, depending upon the adverse events observed in the current cycle and any adverse events present on the first day of the next cycle. If multiple toxicities are seen, the dose administered in a subsequent cycle should be based on the most severe toxicity experienced in the current cycle. Dose modifications or delays should be made based upon whether toxicities occur within a 4-week treatment cycle or at the expected start of the next treatment cycle.

Patients who experience dose-limiting toxicity should have laboratory testing at least weekly until the toxicity has resolved.

There will be no dose modifications of the bevacizumab. After the 1st year of treatment (the primary endpoint), treating physicians can decide to stop or modify the dose and or interval of bevacizumab as clinically indicated. The protocol does not prescribe a schedule for this, but recognizes the common practice of tapering the dose/schedule to provide continued therapy once disease control is established but hopefully reducing the toxicity risk imposed by prolonged treatment at the full dose regimen.

3.2.3.1 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 toxicity 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 weeks. 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 4.0 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).

Table 1: Bevacizumab Dose Management Due to Adverse Events

Event per CTCAEv4	Action to be Taken
Hypertension	
No dose modifications for grade 1 or 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 or 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
Venous Thrombosis	
No dose modifications for grade 1 or 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 or 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

3.2.3.2 Carboplatin Dose Modification and Toxicity Management

Recommendation for the management of carboplatin-related toxicities and required dose reductions for hematologic and non-hematologic toxicities are detailed below. Because dose levels may be important for achieving adequate brain penetration, all efforts will be taken to avoid dose reductions. Whenever required, the following dose levels will be utilized for dose reductions:

Dose level 1	AUC 6 mg/mL/min
Dose level 0	AUC 5 mg/mL/min
Dose level -1	AUC 4 mg/mL/min
Dose level -2	AUC 3 mg/mL/min
Dose level -3	Discontinue treatment (bevacizumab may be continued)

3.2.3.3 Hematologic Toxicity:

Dose Modifications Based on Weekly ANC and Platelet Counts:

ANC (/mcL)		**Platelets (/mcL)**	**% of Planned Carboplatin Dose**
> 1000	and	> 75,000	100%
750-999	or	50,000 to < 75,000	hold*
< 750	or	< 50,000	hold**

*Upon recovery to ANC ≥ 1,000/mcL and platelets to ≥ 100,000/mcL, the same dose level will be administered.

** Upon recovery to ANC ≥ 1,000/mcL and platelets to ≥ 100,000/mcL, one lower dose levels will be administered. If ANC < 750 but platelets >75,000, at the investigator's discretion, prophylactic G-CSF may be used and the same dose may be administered.

3.2.3.4 Non-hematologic Toxicity:

Dose Modifications Based on carboplatin-related Non-Hematologic Toxicities:

CTCAEv4 Grade	**% of Planned Carboplatin Dose**
0-2∞	100%∞
3*	hold**
4	hold**

∞For symptomatic CTCAEv4 Grade 2 toxicity, the dose may be held until recovery to CTCAEv4 Grade 0-1, then resume at one dose lower, at the investigator's discretion.

*Except nausea/vomiting (unless patients are on optimal antiemetic therapy)

**Hold until recovery to CTCAEv4 Grade 0-1 (or to within 1 grade of starting values for pre-existing laboratory abnormalities), and then resume at one dose level lower.

*** Hold until recovery to CTCAEv4 Grade 0-1 (or to within 1 grade of starting values for pre-existing laboratory abnormalities), and then resume at two dose levels lower.

3.2.3.5 At the Start of the Next Treatment Cycle:

A new course of treatment may begin when the ANC is at least 1000/mm^3 and the platelet count is at least 100,000/mm^3 and any other treatment-related toxicities are less than or equal to grade 1. If after a one-week delay all treatment related toxicities are less than or equal to grade 1, proceed with treatment at the dose level dictated by the modifications outlined above. If treatment related toxicities have not resolved to less than or equal to grade 1 after a one-week delay, treatment will be held again, and the patient will be evaluated weekly. If treatment will be held for 2 weeks for treatment related toxicities, reduce the Carboplatin dose by one dose level beyond that indicated by whether or not the patient had DLT in the prior cycle. If re-treatment must be held for more than 2 weeks the investigator should be notified. If a patient develops another DLT at the reduced dose or if they experience a life-threatening toxicity at any time, they will be removed from study. If the single delayed toxicity preventing the start of a new cycle is ANC persisting more than 2 weeks, the use of G-CSF for achieving treating parameters is permitted, at the discretion of the investigator, and the same carboplatin dose may be used for the following cycle if prophylactic G-CSF is utilized.

For treatment or dose modification related questions, please contact the Lead PI, Mark Gilbert, MD 240-760-6023, mark.gilbert@nih.gov

3.3 QUESTIONNAIRES

The MDASI-BT or SP (Appendix **13.2** or **13.3**) will be utilized for this portion of the study. Full instruments are provided in the appendix. In addition, information regarding demographics and treatment history will be collected as part of the larger study and used in this analysis.

The MDASI-BT or SP consists of 23 symptoms rated on an 11-point scale (0 to 10) to indicate the presence and severity of the symptom, with 0 being "not present" and 10 being "as bad as you can imagine." Each symptom is rated at its worst in the last 24 hours. Symptoms included on the instrument include those commonly associated with cancer therapies, those associated with increased intracranial

pressure, and those related to focal deficits. The questionnaire also includes ratings of how much symptoms interfered with different aspects of a patient's life in the last 24 hours. These interference items include: general activity, mood, work (includes both work outside the home and housework), relations with other people, walking, and enjoyment of life. The interference items are also measured on 0 - 10 scales. The average time to complete these instruments is 5 minutes. The MDASI-BT or SP has been translated into 18 languages [18, 20].

3.4 STUDY CALENDAR

STUDIES TO BE OBTAINED	**Pre-Study (within 14 days of study registration Step 2)**	**Course 1-6 (± 3 days)**	**Greater than Course 6**	**Discontinuation or Completion of Therapy**
Consent	X			
History	X	X[3]		X[8]
Physical Exam (Ht, Wt, BSA, VS)	X	X[3]		X[8]
KPS Performance Status	X	X[3]		X[8]
Neurologic Exam	X	X[3]		X[8]
CBC, differential, platelets	X[7]	X[7]	X[9]	X
Serum Pregnancy Test (β-HCG)[1]	X		X [9]	X
PT, PTT, INR	X			
Serum Creatinine, Calculated Creatinine Clearance, Urine protein/ creatinine ratio (or urinalysis)	X	X[2]	X[9]	X
SGOT (AST), Total Bilirubin	X	X[2]	X[9]	X
MRI Head and/or Spine (including diffusion, perfusion and spectroscopy)/ or CT	X	X[3]		X [6]
MDASI Symptom Assessment	X	X[3]		X [8]
Adverse Events Notation and relevant information		X[5]		X[5]
Off Treatment Follow-up Assessment				X[4]
Tissue to establish tumor diagnosis (15 unstained slides at a minimum)	X			

[1] Serum pregnancy test (β-HCG) for women of childbearing potential.

[2] To be performed every 4 weeks prior to each cycle.

[3] To be performed every other cycle. MDASI (BT or SP, depending on tumor location) to be completed +/- 1 week from date of MRI (every 8 weeks) as long as clinical therapy is being administered.

[4] Patients who discontinue treatment due to progression will be followed for survival every 3 months. Patients who come off therapy for reasons other than progression should be followed until progression or institution of new anti-tumor therapy.

[5] Patients will be evaluated for adverse events at the end of each cycle. All relevant information regarding drug doses, concomitant medications, laboratory examinations and treatment related toxicities.

[6] Patients who discontinued treatment for toxicity or maximum number of cycles was reached remain on study and should be followed with MRI every 8 weeks (+/- 30 days) until progression.

[7] To be performed every 2 weeks during treatment

[8] To be performed every 8 weeks (+/- 30 days) at same time as MRI

[9] At discretion of treating physician, as necessary for treatment management

3.5 ON STUDY EVALUATION

CBC, differential, and platelets will be performed every two weeks during treatment. Creatinine, calculated creatinine clearance, bilirubin, SGOT, urine protein/ creatinine ratio (or urinalysis) will be performed every four weeks and prior to each cycle.

A brain MRI/CT will be done prior to every other cycle, following the parameters specified in Appendix **13.4.**

All relevant information regarding drug doses, concomitant medications, and doses, measurable lesions with measurements, tumor response, laboratory examinations, and treatment-related toxicities shall be documented in the patient's medical record and flow sheets.

A complete Neurologic exam (to include documentation of the patients Karnofsky Performance Status) will be performed prior to every other cycle.

All patients will be followed for overall survival, when possible.

a) Patients who discontinue treatment due to progression will be followed for survival every 3 months (+/- 30 days). Each patient will be followed for survival for as long as the study is open "or" for a maximum of 5 years.

b) Patients who come off therapy for reasons other than progression should be followed until progression or institution of new anti-tumor therapy. They should then be followed for survival.

Patients will be evaluated for adverse events at the end of each cycle. In addition, all serious adverse events will be reported to the NCI and the lead PI as directed in Section **7.3.**

The patient will complete the MDASI-BT or MDASI-SP (Appendix **13.2** or **13.3**) at the time of clinical evaluation with MRI as long as the clinical therapy is being administered, unless clinical deterioration makes self-report not possible before that time. The time when patients are unable to complete the self

report questionnaires will be used as part of the study analysis. The MDASI-BT or MDASI-SP will be completed only by the patient, unless changes in vision or weakness make this difficult. If this occurs, then the caregiver or research assistant may read the questions to the patient or assist with marking the severity number or score as described by the patient. A patient caregiver may complete the questionnaires as a patient-preference proxy if the patient's deficits preclude self-report.

3.6 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

3.6.1 Criteria for Removal from Protocol Therapy

3.6.1.1 Progression of disease (as defined in Section **6.3.1**)

Patients must be followed by the same type of brain scan, as was used for baseline tumor measurements, and will be removed from study if progression is documented after any cycle of treatment. Patients with stable disease, partial or complete response will continue on therapy.

3.6.1.2 Unacceptable toxicity (as defined by the investigator).

Note: A maximum of 6 cycles of carboplatin will be administered. If carboplatin is discontinued due to either toxicity or maximum number of treatment is reached, patients may continue to receive single-agent bevacizumab until disease progression. Patients who discontinued treatment for toxicity or maximum number of cycles was reached remain on study and should be followed with MRI every 8 weeks (+/- 30 days) and undergo study assessments as outlined in Section **3.4.**

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

3.6.1.4 Medical or psychiatric illness which in the investigator's judgment renders the patient incapable of further therapy.

3.6.1.5 Treatment delay due to toxicity greater than 60 days measured from the start of the preceding cycle.

All reasons for discontinuation of treatment must be documented.

3.6.2 Off Study Criteria

3.6.2.1 Participant requests to be withdrawn from study

3.6.2.2 Screen failure

3.6.2.3 Investigator discretion

3.6.2.4 Death

3.6.3 Off Protocol Therapy and Off-Study Procedure:

3.6.3.1 At NCI

N/A

3.6.3.2 For participating sites:

The Participant Status Update Form will be supplied by the Research Nurse. This form must be completed for each patient taken off treatment as well as when the patient is taken off study. Participating sites will send a completed form with supporting source documentation to NCI RN via encrypted email at nci_bttc@mail.nih.gov . The source document should be redacted ("black out" any patient identifiers) and must confirm the date and reason why the patient is no longer on study. For

questions, please contact the Coordinating Center. The Participants Status Update Form will be forwarded to the CRO by the Coordinating Center.

4 CONCOMITANT MEDICATIONS/MEASURES

4.1 G-CSF ADMINISTRATION

Prophylactic use of G-CSF is not permitted prior or during cycle 1. After cycle 1, the prophylactic use of G-CSF will be left at the discretion of the treating physician. Therapeutic use of G-CSF for the management of febrile neutropenia is permitted during any cycle, including cycle 1.

4.2 SUPPORTIVE CARE

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

4.2.2 Febrile neutropenia may be managed according to the local institution's Infectious Disease guidelines. Measures may include appropriate laboratory testing, including blood and urine cultures and the institution of broad-spectrum antibiotics. If a source for the fever is not identified, or the fever resolves when the neutrophil count recovers, antibiotics may be discontinued and the patient observed. Use of G-CSF is permitted at the discretion of the treating physician.

4.2.3 Anti-emetics

The use of anti-emetics will be left to the investigators' discretion and/or institutional guidelines.

The following is an example of prophylactic anti-emetic therapy for carboplatin:

Pre-treatment antiemetic therapy:

Ondansetron 20mg PO/Granisetron 1mg IV

Dexamethasone 12mg PO/IV

Aprepitant 125 mg PO

Post-treatment:

Dexamethasone 12mg PO daily on days 2&3

Aprepitant 80mg PO daily on days 2&3

PRN anti-emetic:

Metoclopromide 10mg PO/IV every 4 hours prn

(Chemotherapy can be given immediately after pre-treatment with oral ondansetron and/or oral dexamethasone; patients who fail ondansetron should receive granisetron 1 mg IV prior to chemotherapy; Patients who are unable to swallow should receive: Dexamethasone 12 mg IV, Ondansetron 24 mg ODT or granisetron 1 mg IV; patients receiving dexamethasone for hypersensitivity prophylaxis or for the brain tumor do not need additional oral dexamethasone).

4.2.4 Other Concomitant Medications

Therapies considered necessary for the well-being of the patient may be given at the discretion of the investigator. Other concomitant medications should be avoided except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems. All concomitant medications must be recorded.

4.2.5 Other Anticancer or Experimental Therapies

No other anticancer therapy (including chemotherapy, radiation, hormonal treatment or immunotherapy) of any kind is permitted during the study period. No other drug under investigation may be used concomitantly with the study drug.

4.2.6 Surgery

If neurosurgical management is required for reasons not due to tumor progression, these procedures must be documented, including the indications for surgery, the surgical operative note and pathology report. Please refer to section **3.2.3**for instruction on holding study drugs.

5 BIOSPECIMEN COLLECTION

5.1 PATHOLOGY REVIEW

Following step 1 registration, slides from the most recent pre-registration biopsy must be submitted for review. The purpose of this review is to verify the histologic diagnosis before step 2 registration.

The materials are to be submitted after registration step 1 to Dr. Ken Aldape:

Ken Aldape, MD

Laboratory of Pathology

Center for Cancer Research

National Cancer Institute

Building 10, Room 2S235

Bethesda, MD 20892-1500

Ph: 301-480-5010

kenneth.aldape@nih.gov

A Tissue Collection Shipping form Section **13.9** must be submitted to Dr. Aldape and the NCI Research Nurse each time specimen submissions are made. If the patient's slides have been reviewed on a previous CERN study and there has been no interim surgery or biopsy, the slides do not need to be re-submitted. The site must submit a copy of the previous review results to the NCI Research Nurse, via encrypted email as documentation for the new study.

Pathology Materials Required for Review:

1. One to two representative H&E stained slides from a pre-registration biopsy demonstrating lesion.
2. A copy of the pathology report and the operative report.
3. The Tissue Collection Shipping form, (Section **13.9**)

4. The submitting institution is responsible for the costs of shipping and handling.

5.2 LABORATORY CORRELATES

5.2.1 Baseline tumor expression of hypoxia-related factors:

In this study, paraffin embedded tissue or frozen tissue (or 15 unstained slides at a minimum) will be collected from all patients, for evaluation of expression of hypoxia-related and angiogenesis factors such as VEGF, VEGFR-2/KDR, CD31, CA9, HIF-2α and others, utilizing immunohistochemistry, RT-qPCR and gene expression studies. Tissue evaluation will be required for every case before study registration Step 2. Send pathology material by overnight mail directly to Dr. Ken Aldape.

Ken Aldape, M.D.

Laboratory of Pathology

Center for Cancer Research

National Cancer Institute

Building 10, Room 2S235

Bethesda, MD 20892-1500

Ph: 301-480-5010

Kenneth.aldape@nih.gov

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D) and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All Adverse Events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Patients will be followed for adverse events for 30 days after removal from study treatment or until off-study, whichever comes first.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.

- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form are recorded on the Baseline Evaluations Adverse Events Case Report Form. Abnormal laboratory values or test results as characterized in the bulleted list above are recorded on the Adverse Events Case Report Form.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

Data on this study will be entered into C3D within 2 weeks of completion of each cycle of treatment. Designated research staff from the registering institution will enter the data via remote electronic data entry. The protocol specific electronic forms are to be used by the participating sites. All investigators will utilize these forms for Baseline, Treatment, Tumor Evaluation, Off Treatment, Survival, and Off-study data.

6.1.1 Confidentiality

All documents, investigative reports, or information relating to the patient are strictly confidential. Any patient specific reports (i.e., Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the NCI must have the patient's full name & social security number "blacked out" and the assigned patient ID number, protocol accession number, and protocol number written in. Patient initials may be included or retained for cross verification of identification.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

I will share human data generated in this research for future research as follows (check all that apply):

_x__ Coded, linked data in an NIH-funded or approved public repository.

_x__ Coded, linked data in another public repository.

_x__ Coded, linked data in BTRIS (automatic for activities in the Clinical Center)

__x_ Identified or coded, linked data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through*:*

_x__ An NIH-funded or approved public repository. Insert name or names:_ clinicaltrials.gov

___ Another public repository. Insert name or names:

_x__ BTRIS (automatic for activities in the Clinical Center)

__x_ Approved outside collaborators under appropriate individual agreements.

__x_ Publication and/or public presentations.

When will the data be shared?

_x__ Before publication.

_x__ At the time of publication or shortly thereafter.

6.3 RESPONSE CRITERIA

The primary efficacy endpoint for this study is PFS at one year. Progression free survival will be calculated from patient registration. However, objective response status should be measured and recorded. For this and all other time to event analyses that use registration date, if a patient is registered on the pre-operative portion of the study, the start date for calculation of time to event will be the date of first post-operative study drug administration.

RECIST criteria: Criteria permitting uni-dimensional response measurement have been adopted and published by an international consensus committee, Response Evaluation Criteria In Solid Tumors Group (RECIST). In order to ensure comparability of data from this trial with data from earlier trials, this trial will retain the traditional evaluation definition in Section **6.3.1.** However, RECIST criteria that can be collected will be used for secondary evaluation. Concordance with the traditional approach will be summarized.

6.3.1 Definitions

6.3.1.1 Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment.

6.3.1.2 Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for objective response. These patients will have their response classified according to the definitions stated below. However, all patients regardless of the presence or absence of measurable disease will be evaluated for the secondary endpoint of overall survival. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

6.3.1.3 Measurable Disease: Bidimensionally measurable lesions with clearly defined margins by CT or MRI scan.

6.3.1.4 Evaluable Disease: Unidimensionally measurable lesions, masses with margins not clearly defined.

6.3.1.5 Non-Evaluable Disease: Not Applicable for response evaluation

6.3.1.6 Objective Status, To Be Recorded at Each Evaluation: If there are too many measurable lesions to measure at each evaluation, choose the largest two to be followed before a patient is entered on study. The remaining lesions will be considered evaluable for the purpose of objective status determination. Unless progression is observed, objective status can only be determined when ALL measurable and evaluable sites and lesions are assessed.

6.3.1.6.1 Complete Response (CR): Complete disappearance of all measurable and evaluable disease. No new lesions. No evidence of non-evaluable disease. All measurable, evaluable and non-

evaluable lesions and sites must be assessed using the same techniques as baseline. Patients must not be on steroids.

6.3.1.6.2 Partial Response (PR): Greater than or equal to 50% decrease under baseline in the sum of products of perpendicular diameters of all measurable lesions. No progression of evaluable disease. No new lesions. All measurable and evaluable lesions and sites must be assessed using the same techniques as baseline. The steroid dose at the time of the scan evaluation should be no greater than the maximum dose used in the first 8 weeks from initiation of therapy.

6.3.1.6.3 Partial Response, Non-Measurable (PRNM): Not applicable.

6.3.1.6.4 Stable/No Response: Does not qualify for CR, PR, or progression. All measurable and evaluable sites must be assessed using the same techniques as baseline. The steroid dose at the time of the scan evaluation should be no greater than the maximum dose used in the first 8 weeks from initiation of therapy.

6.3.1.6.5 Progression: 25% increase in the sum of products of all measurable lesions over smallest sum observed (over baseline if no decrease) using the same techniques as baseline, OR clear worsening of any evaluable disease, OR appearance of any new lesion/site, OR clear clinical worsening or failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer).

6.3.1.6.6 Unknown: Progression has not been documented and one or more measurable or evaluable sites have not been assessed.

6.3.2 Best Response: This will be calculated from the sequence of objective statuses.

For patients with all disease sites assessed at every evaluation period, the best response will be defined as the best objective status as measured according to Section **6.3.1.6.** If the response does not persist at the next regular scheduled MRI, the response will still be recorded based on the prior scan, but will be designated as a non-sustained response. If the response is sustained, e. g., still present on the subsequent MRI, it will be recorded as a sustained response, lasting until the time of tumor progression. Best response is unknown if the patient does not qualify for a best response or increasing disease and if all objective status determinations before progression are unknown.

6.3.3 Neurological Exam: Although not used for determining response, it is useful to evaluate improvement in the neurologic exam, (as compared to the baseline assessment), that should coincide with objective measurement of tumor size.

+2	Definitely better
+1	Possibly better
0	Unchanged
-1	Possibly worse
-2	Definitely worse

6.3.4 Performance Status: Patients will be graded according to Karnofsky Performance Status (see Appendix B).

6.3.5 Time to Treatment Failure: From date of registration step 2 to the date of first observation of progressive disease (as defined in Section **6.3.1.6.5**), non-reversible neurologic progression or permanently increased steroid requirement (applies to stable disease only), death due to any

cause, or early discontinuation of treatment. If a patient is registered on the pre-operative portion of the study, the start date for calculation of time to event will be the date of first post-operative study drug administration.

6.3.6 Time to Death: From date of registration to date of death due to any cause.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.2.1 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.3 NCI GUIDANCE FOR REPORTING EXPEDITED ADVERSE EVENTS FOR MULTI-CENTER TRIALS

Report events to the Reviewing IRB as per its policy. Please also notify the coordinating center PI and study coordinator of your submission at the time you make it.

8 SAFETY REPORTING TO COORDINATING CENTER

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

8.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

8.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

8.1.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

8.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

8.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

8.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

8.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.2 ASSESSING CAUSALITY

Investigators are required to assess whether there is a reasonable possibility that the study agent/s caused or contributed to an adverse event. The following general guidance may be used.

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

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

8.2.1 Reporting Pregnancy

Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

The site PI must report to the lead PI within 5 **working** days from the time the **research team** becomes aware of event.

8.3 DATA AND SAFETY MONITORING PLAN

8.3.1 Principal Investigator/Research Team

The clinical research team will have a teleconference on a regular basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the NIH Intramural IRB.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8.3.2 NCI Coordinating Center Monitoring Plan

As the CCR is the coordinating center for this multi-site study, the CCR will maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary study endpoints; adherence to the protocol, regulations, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

This trial will be monitored by personnel employed by an NCI contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

8.3.3 Safety Monitoring Committee

This protocol will require oversight from the Safety Monitoring Committee (SMC). Initial review will occur as soon as possible after the annual NIH Intramural IRB continuing review date. Subsequently, each protocol will be reviewed as close to annually as the quarterly meeting schedule permits or more frequently as may be required by the SMC. For initial and subsequent reviews, protocols will not be reviewed if there is no accrual within the review period. Written outcome letters will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

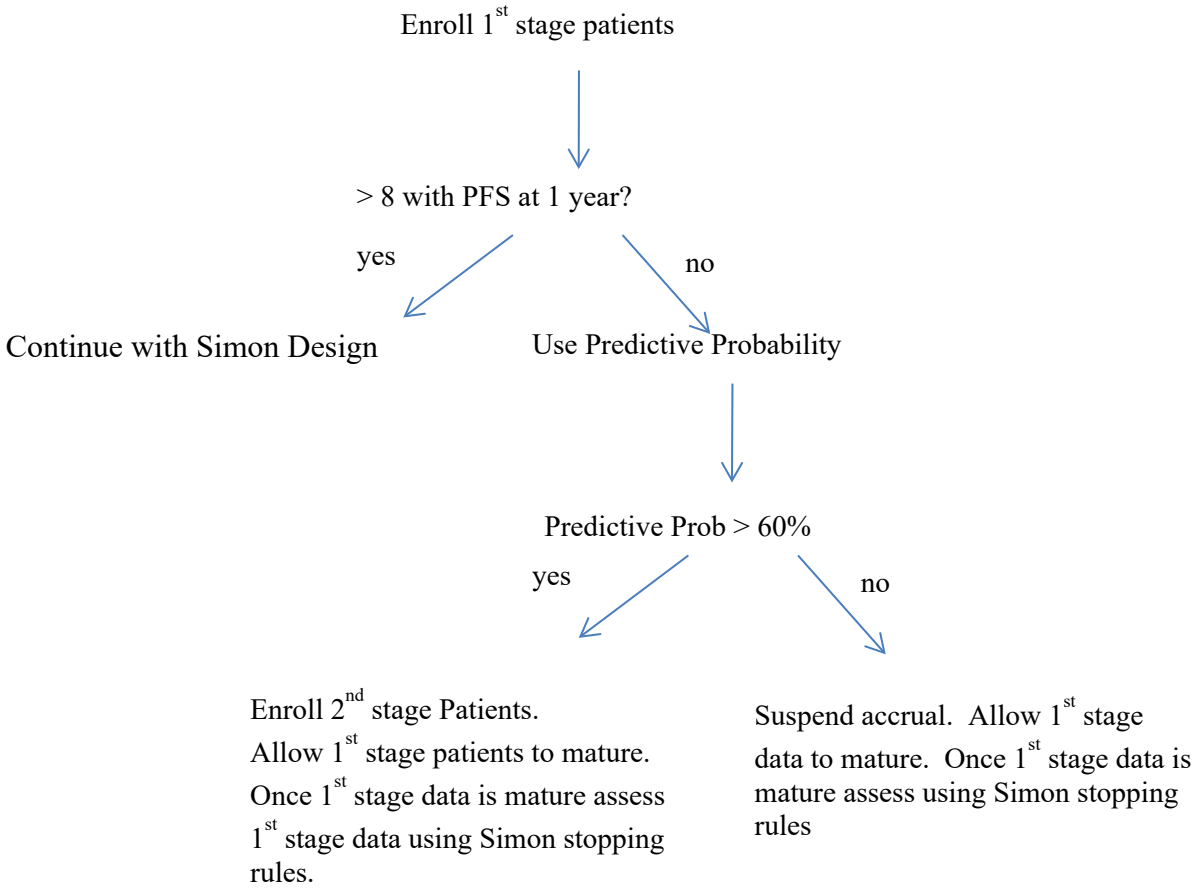
9 STATISTICAL CONSIDERATIONS

This is a phase II study to evaluate the efficacy of carboplatin and bevacizumab for the treatment of recurrent low grade or anaplastic ependymoma.

The primary endpoint of this study is PFS rate at one year. A review of the MSKCC experience (N=12) has shown that the median PFS in this population is approximately 5 months after start of second line of chemotherapy, and the 1y- PFS was approximately 30% (Omuro et al, personal data). This was confirmed by analysis of the CERN database, which found a median PFS of 6 months (N=14) in patients at second recurrence (Armstrong et al, personal communication).

In this trial, we will utilize a Simon optimal two-stage design in which a 30% one-year progression-free rate is considered not promising, a 50% one-year recurrence free rate is considered promising, and the probabilities of a type I error (falsely accepting a non-promising therapy) and type II error (falsely rejecting a promising therapy) are set at 0.1 and 0.1, respectively. In the first stage of this design, 22 patients will be accrued. If at least 8 patients are progression-free at one year among these 22 patients,

then an additional 24 patients will be accrued to the second stage. At the end of the trial, if 18 or more patients are progression-free at one year, the regimen will be declared worthy of further study. This design yields at least a 0.90 probability of a positive result if the true progression-free rate is at least 50% and yields a 0.90 probability of a negative result if the true recurrence free rate is 30%. At the interim time-point some patients will have been followed for less than 1 year. We will implement the following strategy to deal with this situation: We will calculate the predictive probability of observing at least 8 progression free patients by the end of 1 year. This predictive probability will be calculated based on a discrete time survival model (Albert and Chib, 2001). If the predictive probability is greater than 60% we will continue to enroll patients and evaluate the 1st stage data once it is mature. If it is less than 60% we will suspend accrual and wait for the first stage data to mature. A schematic of these rules is presented below:



We do not expect patients to drop out of the trial once they initiate therapy. If patients do dropout we will use appropriate methods to account for this fact. Options will include: 1) treating these patients as failures; 2) Using a time to response model and treating the dropped out patients as censored observations. 3) A sensitivity analysis for patient withdrawals. In this approach, we will jointly model time to response and time to dropout to account for the possibility that dropouts are informative in the sense that patients with longer survival time may be more/less likely to drop out the study. We will compare the results of this approach to option 2, which treats dropout as independent censored events.

9.1.1 Secondary objectives (not including patient-reported outcomes)

Secondary objectives include overall survival, response rates and toxicity profile. Kaplan Meier methodology will be utilized for calculation of overall survival estimates. The crude incidence rates of treatment responses (PR + CR) and toxicities will be calculated, and reported along with 95% confidence intervals.

9.1.2 Patient-reported outcomes

Received MDASI-BT or SP forms will be checked versus the timing schedule and considered as valid if they fall within ten days of the scheduled assessment. Compliance rates will be calculated as the number of received valid forms over the number of expected forms. Differences between groups in compliance will be tested by use of Fisher's exact test at every time point.

We will use descriptive statistics to describe how patients rate symptom severity and interference with function at each time point. Error bar graphs for each of the symptoms will be constructed at each time point. The proportion of patients rating their symptoms to be 7 or greater (on a 0-10 scale) will also be reported. We will construct individual patient profiles for each of the selected symptoms to describe the individual patients' patterns of change over time. We will calculate the mean core symptom severity, mean severity of the MDASI-BT or SP and mean symptom interference at the time of clinical evaluation. Estimates of differences in the mean symptom severity and mean symptom interference between responders and non-responders will be estimated in the intent to treat population. All patients with at least one valid questionnaire will be included in the analyses. Questionnaires completed at study registration will be considered baseline. All questionnaire data received after randomization will be used in the primary analyses.

Differences of at least 2 points will be classified as the minimum clinically meaningful change in the symptom severity and symptom interference measures. For example, an increase of 2 points or more would mean a moderate improvement, whereas a decrease of 2 points or more would be interpreted as moderate worsening. For individual symptoms, a rise in a symptom score means deterioration, whereas a reduced score means improvement of the specific symptom.

9.1.3 Exploratory objectives will include

- Evaluation of PFS, overall survival, response rates and toxicities according to anatomical location (supratentorial, posterior fossa and spinal cord). Evaluate treatment effects of this combination on advanced MRI of the brain. Perfusion and diffusion-based MRI parameters including but not restricted to blood volume, mean and median ADC and structural volumes will be analyzed. Results will be summarized, and mean and median values at different time points will be tabulated. Changes in such parameters will be checked for statistical significance and correlated with the disease status.
- Evaluation of plasma levels of angiogenesis-related factors. Percent changes in levels of each protein will be correlated with responses to treatment. Additionally, means and medians of all patients together will be calculated and tabulated for each time point, with depiction of standard deviations. A Wilcoxon test will be used to determine p value of changes in mean values of YKL-40 and HES1, with a p value of less than 0.05 considered statistically significant.

10 COLLABORATIVE AGREEMENTS

This study was transferred from MDACC to NCI, under the executed Data Transfer Agreement (12472-16).

10.1 MULTI-INSTITUTIONAL GUIDELINES

10.1.1 IRB Approvals

The PI will provide the NIH Intramural IRB and Central Registration Office with a copy of the participating institution's approved yearly continuing review. Registration will be halted at any participating institution in which a current continuing approval is not on file at the NIH Intramural IRB.

10.2 PROTOCOL THERAPY ADMINISTRATION AT A NON-PARTICIPATING SITE

We expect the majority of patients to be treated at a participating site. However, this study allows protocol therapy to be administered at a venue other than the participating site. An example of this venue would be the patient's community/local oncologist's facility. This is particularly applicable to patients whose residence is at a significant distance away from the participating institution. The community or local oncologist must strictly follow instructions and requirements as mandated by the protocol.

10.2.1 Participating Site Responsibilities

10.2.1.1 The local oncologist must be given instructions by the registering Investigator on the proper conduct of the study. This will include (but is not limited to);

- The treatment plan.
- Study agent dosing or dose modification as applicable, Carboplatin dose calculation is per Calvert Formula, **calculations must be verified by the registering Investigator or his/her designee**.
- Required laboratory work up and submission of lab results to the site.
- Documentation of visits which may include AE reporting and the patient's general status.

10.2.1.2 Protocol oversight at the community/local oncologists level will be the responsibility of the registering Investigator. This scope of responsibility includes:

- **Protocol Orientation/Education:** Educating the local physician about the protocol specifics, AE, and source document submission requirements.
- **Source Documentation:** Collecting and retaining of all of the patients source documentation from the local physician.
- **AEs and SAEs:** Monitoring and tracking of all of the patients adverse events, and reporting all SAEs as required by the protocol.
- **Patient Assessments:** Patients must return to the registering Institution for protocol assessments that are used to make decisions on patient's retention on the trial.
- **Monitoring and Auditing:** because the Site PI is responsible for all of the above, the NCI monitors will not travel to the local Physicians facilities to audit the local physician's records. These records must be present at the participating site, then flagged and made available to the monitors by the site Investigator's designee's.

10.2.1.3 Protocol compliance with study requirements is a necessity for all patients participating in this study. If the community/local oncologist is unable to provide the care as mandated by the protocol, and/or is unable to comply with the required documentation, the patient must agree to return to the registering investigator's institution to continue on with the study. The patient's protocol participation may also be reconsidered.

10.2.2 Responsibilities of Local Physicians

The local physician will receive a copy of this protocol to reference for guidance on drug administration It is the responsibility of the local physician to administer drug per protocol and to collect laboratory and research data. The local physician should complete and return the Local Physician Agreement found in Appendix **15.6** to affirm these delegated responsibilities.

10.2.2.1 Reliance Agreement

A reliance agreement (Appendix **13.5**) as well as a letter of agreement between the registering Investigator and the community/local oncologist (Appendix **15.6**) must be signed.

10.2.2.2 Drug Accountability

Carboplatin and Bevacizumab are commercially available and will be provided by treating physicians.

Progress notes should include the date, drug, dose, route, and start time and end time of the administration. Please document all concomitant medications to include the date, drug, dose, route, and time given. Documentation should be sent via facsimile report to the participating site. within three business days of drug administration.

10.2.2.3 Laboratory Testing

Documentation of required values should be sent via facsimile report to the participating site.within three business days of drug administration:

10.2.2.4 Adverse Event Reporting

See Section **7**, Safety Reporting Requirements/Monitoring Plan for further guidance on adverse events.

11 HUMAN SUBJECTS PROTECTIONS

11.1 RATIONALE FOR SUBJECT SELECTION

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. Males and females will be recruited with no preference tosex. No exclusion to this study will be based on race. Minorities will actively be recruited to participate.

11.2 PARTICIPATION OF CHILDREN

As there are no data on the combination of Carboplatin and Bevacizumab in children, they are not included in this protocol.

11.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT (CERN SITES)

Each institution will follow their own procedure for re-consenting subjects unable to re-consent and will notify the Coordinating Center at time of continuing review of these occurrences.

11.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

11.4.1 Potential Risks/ Discomforts

Carboplatin and Bevacizumab may each cause low blood cell counts (red blood cells, platelets, and/or white blood cells): A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. A low platelet count increases the risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding).

A low white blood cell count increases the risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

Using the study drugs together may cause side effects that are not seen when each is given alone. The study drug combination may also increase the frequency and/or severity of the side effects listed above.

Blood draws may cause pain, bleeding, and/or bruising. Fainting and/or development of an infection with redness and irritation of the vein at the site where blood is drawn may occur. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Questionnaires may contain questions that are sensitive in nature. This study may involve unpredictable risks to the participants.

Taking part in this study can result in risks to an unborn or breastfeeding baby, and participants should not become pregnant, breastfeed a baby, or father a child while on this study. Participants must use birth control during the study if sexually active and for 1 month after the last dose of study drug(s). Medically acceptable birth control types include approved hormonal birth control (such as birth control pills, Depo-Provera, or Lupron Depot), barrier methods (such as a condom or diaphragm) with spermicide, or intrauterine device (IUD). Talk to the study doctor about acceptable methods of birth control.

11.4.2 Potential Benefits

The study drugs may help to control the disease. Future patients may benefit from what is learned. There may be no benefits for participants in this study.

11.5 RISKS/BENEFITS ANALYSIS

This study is for patients who have relapsed from standard therapies for ependymoma. Currently, no standard therapy at recurrence has been established, and the impact of chemotherapy at recurrence has been limited. Participants may obtain better response with the combination of carboplatin and bevacizumab.

11.6 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

The investigational nature and objectives of this trial, the procedures and treatments involved and their attendant risks and discomforts, and the potential benefits will be carefully explained to the patient or the patient's advocate. This process will include a general description of the disease process, as well as a description of the patient's expected clinical course. Alternative therapies will be carefully explained,

and outlined in the consent document. The patient will be asked to read the consent at his/her convenience and will be encouraged to ask questions.

Enrollment for treatment on this study will only occur if the patient meets all eligibility criteria, is judged by the investigator to potentially benefit from the therapy, is able and willing to provide full consent, and has signed the consent document.

The treatment consent must be signed in person prior to protocol treatment.

11.6.1 For reconsent only (NCI)

Not applicable. As of Amendment C (Version Date 04/24/2017), participants will not be enrolled at the Clinical Center, NIH.

12 REGULATORY AND OPERATIONAL CONSIDERATIONS

12.1 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

12.2 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NCI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

12.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No

information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NCI CCR

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

13 PHARMACEUTICAL INFORMATION

13.1 RATIONALE FOR IND EXEMPTION

This investigation of Bevacizumab and Carboplatin, both marketed drugs are exempt from the IND requirements because all the criteria for an exemption in § 312.2(b) are met:

- The drug products are lawfully marketed in the United States.
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).
- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).

The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

13.2 **DRUG NAME: BEVACIZUMAB**

13.2.1 **Appearance**: Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution for intravenous (IV) infusion.

13.2.2 **How supplied**: Bevacizumab may be supplied 20-cc (400-mg) glass vials containing 16 ml bevacizumab, at 25 mg/ml).

13.2.3 Formulation: 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.

13.2.4 Storage and Stability: Upon receipt of the study drug, vials are to be refrigerated at 2°C– 8°C (36°F–46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. Vials should be protected from light.

Opened vials must be used within 8 hours. VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 subject may not be used for any other subject. Once a study drug has been added to a bag of sterile saline, the solution must be administered within 8 hours.

13.2.5 Mechanism of Action: Bevacizumab is a recombinant, humanized monoclonal antibody which binds to, and neutralizes, VEGF, preventing its association with endothelial receptors, Flt-1 and KDR. VEGF binding initiates angiogenesis (endothelial proliferation and the formation of new blood vessels). The inhibition of microvascular growth is believed to retard the growth of all tissues.

13.2.6 Human Toxicity:

Likely (occurring in more than 10% of patients)

Cardiovascular: Hypertension (23% to 67%; grades 3/4: 5% to 18%), thromboembolic event (≤21%; grades 3/4: 15%; venous thrombus/embolus: 8%; grades 3/4: 5% to 7%; arterial thrombosis 6%; grades 3/4: 3%), hypotension (7% to 15%)

Central nervous system: Pain (31% to 62%), headache (24% to 37%; grades 3/4: 2% to 4%), dizziness (19% to 26%), fatigue (≤45%; grades 3/4: 4% to 19%), sensory neuropathy (grades 3/4: 1% to 17%; in combination with paclitaxel: 24%)

Dermatologic: Alopecia (6% to 32%), dry skin (7% to 20%), exfoliative dermatitis (3% to 19%), skin discoloration (2% to 16%)

Endocrine & metabolic: Hypokalemia (12% to 16%)

Gastrointestinal: Abdominal pain (50% to 61%; grades 3/4: 8%), vomiting (47% to 52%; grades 3/4: 6% to 11%), anorexia (35% to 43%), constipation (29% to 40%), diarrhea (grades 3/4: 1% to 34%), stomatitis (25% to 32%), gastrointestinal hemorrhage (19% to 24%), dyspepsia (17% to 24%), taste disorder (14% to 21%), flatulence (11% to 19%), weight loss (9% to 20%), nausea (grades 3/4: 4% to 12%)

Hematologic: Hemorrhage (≤40%; grades 3/4: 1% to 5%), leukopenia (grades 3/4: 37%), neutropenia (grade 4: 6% to 27%)

Neuromuscular & skeletal: Weakness (57% to 74%), myalgia (8% to 19%), back pain (≤12%)

Ocular: Tearing increased (6% to 18%)

Renal: Proteinuria (4% to 36%; grades 3/4: ≤7%; median onset: 5.6 months; median time to resolution: 6.1 months)

Respiratory: Upper respiratory infection (40% to 47%), epistaxis (16% to 35%), dyspnea (25% to 26%), rhinitis

Miscellaneous: Infection (≤55%; serious: 9% to 14%; pneumonia, catheter, or wound infections)

Common (occurring in 1 – 10% of Patients)

Cardiovascular: DVT (6% to 9%; grades 3/4: 9%), syncope (grades 3/4: 3%), intra-abdominal venous thrombosis (grades 3/4: 3%), cardio-/cerebrovascular arterial thrombotic event (2% to 4%), CHF (with prior anthracycline therapy: 4%; grades 3/4: 2%), left ventricular dysfunction (grades 3/4: 1%)

Central nervous system: Confusion (1% to 6%), abnormal gait (1% to 5%); CNS hemorrhage (1% to 5%; grades 3/4: 1%), reversible posterior leukoencephalopathy syndrome ([RPLS] ≤1%)

Dermatologic: Nail disorder (2% to 8%), skin ulcer (≤6%), rash desquamation (grades 3/4: 3%), wound dehiscence (1% to 6%), acne (≤1%)

Endocrine & metabolic: Dehydration (grades 3/4: 3% to 10%), hyponatremia (grades 3/4: 4%)

Gastrointestinal: Xerostomia (4% to 7%), colitis (1% to 6%), ileus (grades 3/4: 4% to 5%), gingival bleeding (2% to 4%), fistula (1%), gastrointestinal perforation (≤4%), gastroesophageal reflux (≤2%), gingivitis (≤2%), mouth ulceration (≤2%), tooth abscess (≤2%), intra-abdominal abscess (1%), gastritis (≤1%), gingival pain (≤1%)

Genitourinary: Polyuria/urgency (3% to 6%), vaginal hemorrhage (4%)

Hematologic: Neutropenic fever/infection (5%; grades 3 and/or 4: 4% to 5%), thrombocytopenia (5%)

Hepatic: Bilirubinemia (1% to 6%)

Neuromuscular & skeletal: Bone pain (grades 3/4: 4%), neuropathy (other than sensory: grades 3/4: 1% to 5%)

Ocular: Blurred vision (≤2%)

Otic: Tinnitus (≤2%), deafness (≤1%)

Respiratory: Voice alteration (5% to 9%), pneumonitis/pulmonary infiltrates (grades 3/4: 5%), hemoptysis (nonsquamous histology 2%), pulmonary embolism (≤1%)

Miscellaneous: Infusion reactions (<3%)

Rare but Serious (occurring in fewer than 1% of patients)

Anaphylaxis, anastomotic ulceration, angina, cerebral infarction; fistula (biliary, bladder, bronchopleural, duodenal, endophthalmitis, enterocutaneous, esophageal, eye inflammation, gastrointestinal, rectal, renal, tracheoesophageal [TE] and vaginal); hemorrhagic stroke, hypersensitivity, hypertensive crises, hypertensive encephalopathy, intestinal necrosis, intestinal obstruction, mesenteric venous occlusion, microangiopathic hemolytic anemia (when used in combination with sunitinib), MI, nasal septum perforation, nephrotic syndrome, pancytopenia, polyserositis, pulmonary hemorrhage,

pulmonary hypertension, renal failure, renal thrombotic microangiopathy, sepsis, subarachnoid hemorrhage, toxic anterior segment syndrome (TASS), transient ischemic attack, ureteral stricture wound healing complications.

13.2.7 Clinical Pharmacokinetic Properties:

Distribution: V_d: 46 mL/kg

Half-life elimination: ~20 days (range: 11-50 days)

Excretion: Clearance: 2.75-5 mL/kg/day

13.2.8 Administration:

Bevacizumab will be diluted in a total volume of 100mL of 0.9% Sodium Chloride Injection, USP or as per institutional guidelines. 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, it is recommended that all subsequent doses 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.

13.2.9 Supplier:

Bevacizumab and Carboplatin are commercially available agents. Both agents will be dispensed by the participating site's pharmacy and will be charged to the patient's medical insurance carrier.

13.3 **DRUG NAME: CARBOPLATIN**

13.3.1 **Appearance:** Carboplatin is available as a sterile lyophilized powder.

13.3.2 **How supplied**: Carboplatin is commercially supplied as a sterile lyophilized powder in single-dose vials containing 50 mg, 150 mg, or 450 mg of the drug, in equal parts by weight with mannitol.

13.3.3 **Formulation**: Immediately prior to use, each vial of carboplatin should be reconstituted with either sterile water for injection, D5W, or sodium chloride injection, in sufficient volume to produce a carboplatin concentration of 10 mg/ml.

13.3.4 **Storage and Stability**: Carboplatin in unopened vials is stable for as long as three years when stored at temperatures of 15-30 C and when protected from light.

13.3.5 **Mechanism of Action**: Carboplatin is an alkylating agent which covalently binds to DNA; possible cross-linking and interference with the function of DNA.

13.3.6 **Human Toxicity**: The following side effects have been reported with carboplatin:

Likely (occurring in more than 10% of patients)

Central nervous system: Pain (23%)

Endocrine & metabolic: Hyponatremia (29% to 47%), hypomagnesemia (29% to 43%), hypocalcemia (22% to 31%), hypokalemia (20% to 28%)

Gastrointestinal: Vomiting (65% to 81%), abdominal pain (17%), nausea (10% to 15%)

Hematologic: Myelosuppression (dose related and dose limiting; nadir at ~21 days; recovery by ~28 days), leukopenia (85%; grades 3/4: 15% to 26%), anemia (71% to 90%; grades 3/4: 21%), neutropenia (67%; grades 3/4: 16% to 21%), thrombocytopenia (62%; grades 3/4: 25% to 35%)

Hepatic: Alkaline phosphatase increased (24% to 37%), AST increased (15% t19%)

Neuromuscular & skeletal: Weakness (11%)

Renal: Creatinine clearance decreased (27%), BUN increased (14% to 22%)

Common (occurring in 1-10% of patients)

Central nervous system: Neurotoxicity (5%)

Dermatologic: Alopecia (2% to 3%)

Gastrointestinal: Constipation (5%), diarrhea (6%), stomatitis/mucositis (1%), taste dysgeusia (1%)

Hematologic: Hemorrhagic complications (5%)

Hepatic: Bilirubin increased (5%)

Local: Pain at injection site

Neuromuscular & skeletal: Peripheral neuropathy (4% to 6%; up to 10% in older and/or previously-treated patients)

Ocular: Visual disturbance (1%)

Otic: Ototoxicity (1%)

Renal: Creatinine increased (6% to 10%)

Miscellaneous: Infection (5%), hypersensitivity (2%)

Rare but serious (occurring in fewer than 1% of patients)

Anaphylaxis, anorexia, bronchospasm, cardiac failure, cerebrovascular accident, embolism, erythema, fever, hemolytic uremic syndrome (HUS), hyper-/hypotension, malaise, necrosis (associated with extravasation), nephrotoxicity, neurotoxicity, pruritus, rash, secondary malignancies, urticaria, loss of vision.

Clinical Pharmacokinetic Properties:

Distribution: V_d: 16 L/kg; into liver, kidney, skin, and tumor tissue

Protein binding: 0%; platinum is 30% irreversibly bound

Metabolism: Minimally hepatic to aquated and hydroxylated compound

Half-life elimination: Terminal: 22-40 hours; Cl_{cr} >60 mL/minute: 2.5-5.9 hours

Excretion: Urine (~60% to 90%) within 24 hours

13.3.7 **Administration**: Immediately prior to use, each vial of carboplatin should be reconstituted with either sterile water for injection, D5W, or sodium chloride injection, in sufficient volume to produce a carboplatin concentration of 10 mg/ml, or as per institutional guidelines. IV infusion over 30 minutes: Do not use aluminum products in the mixing or administration of carboplatin because aluminum may react with it and cause potential loss of potency.

13.3.8 **Supplier**: Bevacizumab and Carboplatin are commercially available agents. Both agents will be dispensed by the participating site's pharmacy and will be charged to the patient's medical insurance carrier.

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15 APPENDICES

15.1 KARNOFSKY PERFORMANCE STATUS AND NEUROLOGICAL FUNCTION

Patient's performance status and Neurologic Functions will be graded according to the following scales:

Karnofsky Performance Status

KPS 100	Normal; no complaints; no evidence of disease
KPS 90	Able to carry on normal activity; minor signs or symptoms of disease
KPS 80	Normal activity with effort; some sign or symptoms of disease
KPS 70	Cares for self; unable to carry on normal activity or do active work
KPS 60	Requires occasional assistance, but is able to care for most personal needs
KPS 50	Requires considerable assistance and frequent medical care
KPS 40	Disabled; requires special care and assistance
KPS 30	Severely disabled; hospitalization is indicated, although death no imminent
KPS 20	Very sick; hospitalization necessary; active support treatment is necessary
KPS 10	Moribund; fatal processes progressing rapidly
KPS 0	Dead

Neurologic Function

☐	+2	Definitely Better
☐	+1	Possibly Better
☐	0	Unchanged
☐	-1	Possibly Worse
☐	-2	Definitely Worse
☐	B	Baseline

15.2 MD ANDERSON SYMPTOM INVENTORY FOR BRAIN TUMORS (MDASI-BT)

Date: _____ **Institution:** _____

Participant Initials: _____ **Hospital Chart #:** _____

Participant Number: _____

MD Anderson Symptom Inventory - Brain Tumor (MDASI - BT)

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please select a number from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	**As Bad As You Can Imagine** 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your **weakness** on one side of the body at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your difficulty **understanding** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your difficulty **speaking (finding the words)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Date: _____ **Institution:** _____

Participant Initials: _____ **Hospital Chart #:** _____

Participant Number: _____

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
17. Your **seizures** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your difficulty **concentrating** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your **vision** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your change in **appearance** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your change in **bowel pattern (diarrhea or constipation)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your **irritability** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms **interfered** with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items ***in the last 24 hours***? Please select a number from 0 (symptoms have not interfered) to 10 (symptoms interfered completely) for each item.

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
23. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
24. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
25. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
26. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
27. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
28. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

15.3 MD ANDERSON SYMPTOM INVENTORY FOR SPINE TUMORS (MDASI-SP)

Date: _____ **Institution:** _____

Participant Initials: _____ **Hospital Chart #:** _____

Participant Number: _____

M. D. Anderson Symptom Inventory - Spine Tumor (MDASI-SP)

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours***. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

CORE Items	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feeling of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Date: _____ **Institution:**_____

Participant Initials: _____ **Hospital Chart #:**_____

Participant Number: _____

SPINE Tumor Specific Items	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
14. Your **radiating spine pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your **weakness in the arms and/or legs** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your **loss of control of bowel and/or bladder** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
17. Your **change in bowel pattern (diarrhea/constipation)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your **sexual function** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms **interfered** with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items **in the last 24 hours**:

	Did not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
19. General activity?	○	○	○	○	○	○	○	○	○	○	○
20. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
21. **Work** (including work around the house)?	○	○	○	○	○	○	○	○	○	○	○
22. **Relations** with other people?	○	○	○	○	○	○	○	○	○	○	○
23. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
24. **Enjoyment** of life?	○	○	○	○	○	○	○	○	○	○	○

15.4 MRI ACQUISITION PROTOCOL (OPTIONAL PROCEDURE)

Acquisition protocol	
• Auto-align scout	(2 min)
• Pre-contrast T1	(2 min)
• High resolution T2 Volume	(5 min)
• FLAIR	(3 min)
• BOLD/ASL (*optional*)	(14 min)
• Pre-contrast variable flip angle T1 maps	(1 min)
• Permeability (T1 dynamic)	(6 min)
• Post-contrast variable flip angle T1 maps	(1 min)
• Diffusion Tensor Imaging	(7 min)
• Perfusion (T2/T2*)	(3 min)
• 3D Post-contrast	(5 min)
• Post-contrast T1	(2 min)
• MR Spectroscopy (optional)	(8 min)

Our proposed acquisition protocol is described in the box, and consists of approximately 65 minutes of imaging time (typically 90 to 120 minutes of time that the subject is in the magnet, counting setup and scan delays). Each of these datasets will be analyzed using tools that are published and well known in the neuroradiologic community. A brief outline of our analysis techniques follows:

Dynamic Contrast Enhanced – Magnetic Resonance Imaging (DCE-MRI)

DCE-MRI will be used to monitor the effects on tumor vasculature through parameters reflecting both tumor perfusion and permeability. This sequence uses a bolus injection of 0.1 mmol/kg of Gd-DTPA. Data will be analyzed using the standard Tofts/Kermode model with the typical approach of Patlak et al [21].

T2-weighted contrast-enhanced MRI or perfusion weighted imaging (PWI)

A second dose of Gd-DTPA (typically 0.1-0.2 mmol/kg) is administered for first-pass T2/T2-weighted imaging. We use a combination gradient-echo/spin echo approach to allow estimation of tumor vascular size based on the equations in the box. As shown in our earlier work [22], this can be used to estimate average vessel diameter, which we believe may change with effective anti-angiogenic therapy. This approach also provides estimates of cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT), and perfusion efficiency (1/MTT).

Diffusion Tensor Imaging (DTI)

We will measure the full water self-diffusion tensor before and after treatment in this patient population. The tensor fractional anisotropy (FA) will be calculated and can be used to define white matter tract directions and tumor invasion. Apparent diffusion coefficient (ADC) maps will also be calculated.

Simultaneous Blood Oxygenation Level Dependent (BOLD) and Arterial Spin Labeling (ASL) Imaging (Optional)

Combined BOLD/ASL imaging is a non-contrast approach to simultaneously measuring cerebral blood flow (ASL) and cerebral metabolic rate of oxygen consumption (BOLD) (Wong EC, NMR Biomed,

1997, 10:237). Our standard approach for this is to use a pulsed ASL sequence followed by a single-shot, gradient echo (GE) echo planar imaging acquisition. Two echoes are acquired, short echo (TE = 11 ms) for ASL (CBF maps) and longer echo (TE = 40 ms) for BOLD. Patients are administered room air and 100% oxygen at varying time points throughout the scan. The gas paradigm is as follows: baseline room air (8 min) – 100% O_2 (4 min) – washout room air (2 min) at a constant ~35 L/min flow rate. Blood oxygen levels are continuously monitored throughout the scan with a pulse oximeter.

MRS (Magnetic resonance spectroscopy) - Optional Procedure

Chemical shift imaging (CSI) is performed to obtain spatial distribution of metabolites (NAA, choline, creatine, lactate, myoinositol, mobile lipids) in tumors and normal brain tissue. An adiabatic LASER sequence (Andronesi et al., 2009) with improved localization and excitation profile is used. Typical parameters include TR = 1.5 s, TE = 45 ms, weighted phase encoding, TA = 5 min, and a final voxel size of 5x5x15 mm^3. Optimization of shimming and water suppression is performed prior of CSI which needs 3 min, making the total time 8 min. Metabolite maps are calculated using LCModel fitting software (Provencher et al., 1993).

15.5 **RELIANCE AGREEMENT**

Agreement between

Institution Name

and

THE NATIONAL INSTITUTES OF HEALTH

To Rely on an NIH IRB

Pursuant to 45 C.F.R. 46.114, the National Institutes of Health (NIH) and *Institution Name* are entering into this agreement for NIH to conduct Institutional Review Board (IRB) review of the research protocol or activities identified below, which are jointly conducted by NIH and *Institution B.*

Name of Institution Providing IRB Review (Institution A): National Institutes of Health

Federal Wide Assurance (FWA) # 00005897, expiration date 08/28/2018

IRB Number: IRB00000001

Name of Institution Relying on the Designated IRB (Institution B): *Institution Name*

FWA #_____, expiration date _____

Institution B will rely on the designated NIH IRB for review and continuing oversight of its human subjects research described below. This agreement is limited to the following specific protocol(s) or research activity:

Name of Research Project/Activity: **Phase II trial of Carboplatin and Bevacizumab for the Treatment of Recurrent Low-grade and Anaplastic Supratentorial, Infratentorial and Spinal Cord Ependymoma in Adults: A Multi- Center Trial**

Protocol Number(s):

Name of Principal Investigator (NIH): Mark Gilbert, MD

Name of Investigator(s) (Institution B): *PI Name*

Name of NIH Principal Investigator's Institute or Center: National Cancer Institute

The review performed by the NIH IRB will meet the human subject protection requirements of Institution B's OHRP-approved FWA. The protocol(s) reviewed by the NIH IRB must include a description of the

research to be conducted by Institution B. The NIH IRB will follow written procedures for reporting its findings and actions to appropriate officials at Institution B. Relevant minutes of IRB meetings will be made available to Institution B upon request. Institution B remains responsible for ensuring compliance with the IRB's determinations and with the terms of its OHRP-approved FWA and for providing local context.

Both Institutions will maintain current copies of the IRB approved protocol. NIH will conduct its portion of this joint research in accord with the terms and conditions of its OHRP-approved FWA. Institution B will conduct its portion of this joint research in accord with the terms and conditions of its OHRP-approved FWA. This Agreement will be kept on file at both Institutions and will be available to OHRP upon request.

The NIH IRB retains responsibility for compliance with regulatory requirements under 45 C.F.R. Part 46 and 21 C.F.R. 56 (as applicable) related to the administration and operation of the IRB. These include, for example, following written procedures and maintaining records in accord with 45 C.F.R. parts 46.103 and 115, respectively. Institution B agrees that the NIH IRB may suspend or terminate approval of research that is not conducted in accordance with the NIH IRB's requirements or that is associated with unexpected serious harm to subjects pursuant to 45 C.F.R. 46.113. The NIH IRB will notify Institution B of any non-compliance, or suspensions, or terminations of this research in a timely manner.

Institution B will ensure that before implementing a change to an NIH IRB-approved protocol its investigator will obtain NIH IRB approval for the change (unless the change is designed to eliminate an apparent immediate hazard to subjects), pursuant to 45 C.F.R. 46.103. Institution B retains responsibility, pursuant to 45 C.F.R. Part 46, including subsections103 and 113, to promptly report to the NIH IRB, appropriate institutional officials, and the HHS or NIH agency head any unanticipated risks to subjects or others, and any serious or continuing noncompliance with 45 C.F.R. Part 46 or the IRB's requirements or determinations. The NIH IRB may also make these reports, but doing so does not relieve Institution B of the obligation to report to institutional officials and HHS or NIH officials.

This Agreement is effective on the date that the last official signs and may be terminated by either party at any time. If the Agreement is terminated prior to the completion of the research, Institution B will need to obtain alternative IRB review.

Signatory Officials:

X_____

Institution Name

Name: _____

Title: _____

Address: _____

_____

_____

Phone: _____

Fax: _____

E-mail: _____

Date: _____

Deputy Director, Office of Human Subjects Research, National Institutes of Health
10 Center Drive, Room 2C146
Bethesda, Maryland 20892, MSC 1154
Phone: 301-402-3444
Fax: 301-402-3443
E-mail: HoldenC@od.nih.gov

Date: _____

X_____

National Institutes of Health

Charlotte Holden, JD

15.6 LOCAL PHYSICIAN AGREEMENT

I am a licensed physician in the state of _____. I am credentialed in the facility _____(*list name and address of facility*) where I practice medicine to prescribe chemotherapeutic agents.

I agree to administer the therapy as written in the protocol and follow other protocol guidance.

I understand that my role in the study is limited to standard medical care practices such as: prescribing and administering therapy, performing physical exams, obtaining blood work as outlined in the protocol, obtaining research specimens as outlined in the protocol, and sending all documentation of drug administration and other related medical record documents to the *(Enrolling Site Name*) in a timely manner.

I agree to maintain the privacy and confidentiality of all information received or developed in connection with this protocol.

Protocol Title:

Phase II trial of Carboplatin and Bevacizumab for the Treatment of Recurrent Low-grade and Anaplastic Supratentorial, Infratentorial and Spinal Cord Ependymoma in Adults: A Multi-Center Trial

_____ _____

Signature of Physician Date

_____

Name of Physician (printed or typed)

15.7 LOCAL PHYSICIAN INFORMATION

Physician Name	Facility Name	Facility Address	Facility Contact Number
Alissa Thomas, MD	University of Vermont Medical Center	111 Colchester Ave, Burlington, VT 05401	802-847-8400

15.8 CCR PROBLEM REPORT FORM

NCI Protocol #:	Protocol Title:
	Report version: *(select one)* ____Initial Report ____Revised Report ____Follow-up
Site Principal Investigator:	
Date of problem:	Location of problem: *(e.g., patient's home, doctor's office)*
Who identified the problem? *(provide role (not name of person): nurse, investigator, monitor, etc…)*	
Brief Description of Subject *(if applicable)* (*Do NOT include personal identifiers)*	Sex: ___ Male ___ Female Age: ___ Not applicable (more than subject one is involved)
Diagnosis under study:	
Name the problem: *(select all that apply)* [ ] Adverse drug reaction [ ] Abnormal lab value [ ] Death [ ] Cardiac Arrest/ code [ ] Anaphylaxis [ ] Sepsis/Infection [ ] Blood product reaction [ ] Unanticipated surgery/procedure [ ] Change in status (e.g. increased level of care required) [ ] Allergy (non-medication) [ ] Fall [ ] Injury/Accident (not fall) [ ] Specimen collection issue [ ] Informed consent issue [ ] Ineligible for enrollment [ ] Breach of PII [ ] Tests/procedures not performed on schedule [ ] Other, brief 1-2 word description: _____ Detailed Description of the problem: (*Include any relevant treatment, outcomes or pertinent history*):	
*Is this problem unexpected? *(see the definition of unexpected in the protocol))* __YES __NO Please explain:	

*Is this problem related or possibly related to participation in the research? __YES __NO Please explain:
*Does the problem <u>suggest</u> the research places subjects or others at a greater risk of harm than was previously known or recognized? __YES __NO Please explain:
Is this problem? (*select all that apply*) [ ] An Unanticipated Problem* that is: [ ] Serious [ ] Not Serious [ ] A Protocol Deviation that is: [ ] Serious [ ] Not Serious [ ] Non-compliance **Note if the 3 criteria starred above are answered, "YES", then this event is also a UP.*
Is the problem also *(select one)* [ ] AE [ ] Non-AE
Have similar problems occurred on this protocol at your site? __YES __NO If "Yes", how many? ____ Please describe:
Describe what steps you have already taken as a result of this problem:
In addition to the NIH IRB, this problem is also being reported to: (*select all that apply*) [ ] Local IRB [ ] Study Sponsor [ ] Manufacturer : _____ [ ] Institutional Biosafety Committee [ ] Data Safety Monitoring Board [ ] Other: _____ [ ] None of the above, not applicable

INVESTIGATOR'S SIGNATURE:	DATE:

15.9 TISSUE COLLECTION SHIPPING FORM

A Tissue Collection Shipping Form (below) listing pathology materials being submitted for Tissue Evaluation completed by the local pathologist must be included in the pathology submission. These forms must include the protocol number, patient case number, and the patient's initials.

Tissue evaluation is highly recommended for every case. Send pathology material by overnight mail directly to Dr. Ken Aldape:

Ken Aldape, MD

Laboratory of Pathology

Center for Cancer Research

National Cancer Institute

Building 10, Room 2S235

Bethesda, MD 20892-1500

Ph: 301-480-5010

kenneth.aldape@nih.gov

- Include on the form the name, telephone number, and fax number of the person to notify with the results of the tissue evaluation.
- Shipments must be made Monday through Thursday.
- Notify Dr. Aldape by email on or before the day of submission: (1) that a case is being submitted for review; (2) the name of the contact person; (3) when to expect the sample; and (4) the overnight shipping carrier and tracking number.
- Dr. Aldape will email the appropriate contact person from the submitting institution with the results and will fax a copy of the completed form to the institution.

When Dr. Aldape has completed testing of the tumor tissue, the remaining tissue will be sent back to the submitting institution.

Submission of frozen tissue is strongly encouraged in order to maximize the information gained from this trial. When available, frozen tissue should be sent in dry ice to Dr. Aldape at the above address.

Upon receipt, the specimen is labeled with the protocol number and the patient's case number only.

The specimens will be stored for an indefinite period of time. If at any time the patient withdraws consent to store and use the specimens, the material will be returned to the institution that submitted it.

Tissue Collection Shipping Form **PLEASE USE ONE FORM PER PATIENT**

CC 16C0009 (Prior CERN09-02): Phase II trial of Carboplatin and Bevacizumab for the Treatment of Recurrent Low-grade and Anaplastic Supratentorial, Infratentorial and Spinal Cord Ependymoma in Adults: A Multi- Center Trial

DATE SHIPPED:

SITE NAME:

INVESTIGATOR'S NAME:

PATIENT'S INITIALS:

PATIENT'S ID NUMBER:

Tissue sample:

Collection Date:

Number of paraffin blocks:

Number of unstained slides (15 slides preferred if block is not available):

Please remember all samples for a patient must be shipped within 28 days of collection and to label samples as instructed in the protocol.

Name of person completing this form:

Telephone number:

Signature:

Date:

SHIP TO:
Ken Aldape, M.D.

Laboratory of Pathology

Center for Cancer Research

National Cancer Institute

Building 10, Room 2S235

Bethesda, MD 20892-1500

Ph: 301-480-5010

**Note: Prior to shipping the samples, please contact Dr. Aldape by email on or before the day of to ensure appropriate tracking and receipt of the sample. Shipment must be made Mondays through Thursdays by overnight shipment to ensure timely arrival of samples during working days.