Phase I/II Trial Of Super-Selective Intraarterial Infusion Of Erbitux (Cetuximab) And Avastin (Bevacizumab) For Treatment Of Relapsed/Refractory Intracranial Glioma In Patients Under 22 Years Of Age

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PROTOCOL TITLE: PHASE I/II TRIAL OF SUPER-SELECTIVE INTRAARTERIAL INFUSION OF ERBITUX (CETUXIMAB) AND AVASTIN (BEVACIZUMAB) FOR TREATMENT OF RELAPSED/REFRACTORY INTRACRANIAL GLIOMA IN PATIENTS UNDER 22 YEARS OF AGE

WMC PROTOCOL NUMBER: 1202012214

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IN THE EVENT OF EMERGENCY

Any death, serious* adverse experience, or unexpected (and severe) adverse experience undergone by the patient while receiving or within 30 days of receiving treatment under this research protocol, even though the event may not appear to be drug-related, must be promptly reported (within 24 hours) by telephone or telefax to the Sponsor or designee. Reports should be made to:

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525 East 68th Street
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Contact at (212) 746-1996 may be made after business hours, weekends, and on holidays. Leave a message and a return call will be placed.

*A serious adverse experience is one which constitutes a definite hazard or handicap to the patient, including, but not limited to an event which:

- is fatal
- is life-threatening
- requires or prolongs hospitalization
- is persistently or significantly disabling/incapacitating
- is a congenital anomaly/birth defect
- necessitates either surgical or medical intervention to prevent the following outcomes: allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

PATIENT ENROLLMENT ON STUDY

Investigators must notify the Clinical Research Coordinator in advance to pre-qualify a patient for enrollment. Once a patient is identified as meeting the study entry criteria, the investigator or his/her designee will contact the Principal Investigator or designee (one of the individuals listed above) for final approval for patient enrollment.

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Test Materials:	Mannitol (hexan-1,2,3,4,5,6-hexol ($C_6H_8(OH)_6$) Cetuximab (Erbitux, Genentech Pharmaceuticals) Bevacizumab (Avastin, Genentech Pharmaceuticals)
Dosage Levels:	Mannitol 25% 3-10ml/s for 30s (total dose, 90-300ml) for blood brain barrier (BBB) disruption Cetuximab intra-arterial 200mg/m^2 Bevacizumab intra-arterial 15mg/kg
Route of Administration:	Intracranial Superselective Intra-arterial

STUDY SYNOPSIS

This is an open-label, non-randomized, single-arm, Phase I and II research study of intracranial superselective intra-arterial Erbitux (Cetuximab) and Avastin (Bevacizumab) for treatment of relapsed/refractory or unresectable glial neoplasms of the brain in children and young adults under the age of 22.

Overview and Background: Central nervous system (CNS) malignancies are the second most common malignancy and the most common solid tumor of childhood, including adolescence. Annually in the United States, approximately 2,200 children are diagnosed with CNS malignancy and rates appear to be increasing. CNS tumors are the leading cause of death from solid tumors in children. Over 90% of CNS tumors are located in the brain, and approximately 25% of CNS tumors are supratentorial. Of CNS malignancies in those under 20, 52% are astrocytomas of various grades, 21% PNETs, 15% other gliomas, and 9% ependymomas, though the frequency of these tumors varies further depending on age within this population. Pilocytic (WHO grade I) astrocytomas can have relatively good prognosis with 5 year survival as high as 95% after gross total resection, but higher grade gliomas, anaplastic astrocytoma (AA) (WHO grade III) and glioblastoma multiforme (GBM) (WHO Grade IV), have 5 year survivals of approximately 50% and 19.5% respectively. Ependymomas and primitive neuroectodermal tumors (PNETs) have similarly poor prognosis with 5 years survival of 56.9% and 56.8%. Overall, for all grades of malignant brain tumor, 5 year survival is 64.6% for those 0-14 and 66% for those 0-20. In addition to the poor prognosis from patient's tumors, the effect of adjuvant therapy, especially radiation, on the developing brain can pose a major obstacle in the treatment of pediatric patients and lead to developmental, endocrinologic, behavioral, and cognitive problems in the children who do survive their initial tumor.

High-grade malignant brain tumors, glioblastoma multiforme (GBM) and anaplastic astrocytoma (AA) exhibit the most aggressive behavior, resulting in median overall adult survival durations of only 9-12 months for GBM, and 3-4 years for AA, from initial diagnosis, despite multimodal treatment approaches. Survival duration after diagnosis in children is highly variable depending in part on age at diagnosis, location of tumor, and extent of resection; however, most children with high grade glioma die within 3 years of diagnosis. Infants often have more aggressive disease while juvenile GBM may more closely mirror the adult course. Initial therapy consists of surgical resection for most pediatric brain tumors, with the exception of diffuse pontine glioma whose location frequently precludes surgical intervention aside from biopsy. The timing and combinations of adjuvant or concomitant chemotherapy and radiation in the initial treatment of pediatric low and high-grade gliomas is much less well defined than in adult glioma therapy and significant variations exists between major pediatric cancer centers. Many children with fully or partially resectable high grade tumors experience a recurrence after first-line therapy, therefore improvements in both first-line and salvage therapy are critical to enhancing quality-of-life and prolonging survival.

Besides other chemotherapeutic drugs Erbitux (Cetuximab) is currently used to treat recurring GBM after failure of standard radiation and chemotherapy with temozolomide. Because of the blood brain barrier (BBB) where IV drugs do not penetrate the blood vessel walls well to get into the brain, no one knows for sure if these IV drugs actually get into the brain after infusion. We have recently completed a Phase I clinical trial that has shown that SIACI of Cetuximab is safe and effective in adult patients at 200 mg/kg with recurrent malignant glioma. Avastin(Bevacizumab) has been shown to be active in a range of tumors including GBM and anaplastic astrocytoma.(Bokstein et al.

2008; Kang et al. 2008; Narayana et al. 2008; Vredenburgh et al. 2008; Zuniga et al. 2008). We have recently completed a Phase I clinical trial demonstrating the safety of SIACI of avastin at 15 mg/kg in adults. Therefore, this phase I and II clinical research trial will test the hypothesis that Bevacizumab and Cetuximab can be safely and effectively used by direct intracranial superselective intra-arterial infusion in patients <22 years of age with relapsed/refractory intracranial glioma.

Therefore the experimental aspects of this treatment plan will include:

1. Subjects will first be treated with Mannitol prior to chemotherapy infusion (Mannitol 25%; 3-10 mL/s for 30seconds) in order to disrupt the blood brain barrier. This technique has been used in several thousand patients in previous studies for the IA delivery of chemotherapy for malignant glioma. We have used this without complication in our Phase I protocols as well.
2. To treat patients with intra-arterial delivery (SIACI) of Erbitux and Avastin for patients with recurring or relapsing glioma.
3. With the implementation of Protocol Version December 6, 2019, the dosing of Bevacizumab and Cetuximab changed from a single dosing, to monthly dosing. Dosing will continue until patients demonstrate radiographic progression.

Inclusion criteria: Males or females, <22 years of age, with documented histologic diagnosis of relapsed or refractory glioblastoma multiforme (GBM), anaplastic astrocytoma (AA), fibrillary astrocytomas (FA), pilomyxoid astrocytoma, PXA, oligodendroglioma, or anaplastic mixed oligoastrocytoma (AOA) or patients with radiographic pontine glioma.

Anti-tumor response: Response will be evaluated after one cycle of chemotherapy via an MRI with the injection of contrast performed on post procedure day 0, 1 month post procedure, and every month thereafter.

Study Agents: Mannitol, Erbitux, and Avastin are registered agents.

Safety/Toxicity Monitoring: Patients will be treated with a previously tested, dose and schedule of Mannitol prior to chemotherapy infusion (Mannitol 25%; 3-10 mL/s for 30 seconds) in order to disrupt the blood brain barrier. Following blood brain barrier disruption the patient will receive an intracranial superselective intra-arterial catheterization and infusion with Erbitux (Cetuximab) at a dose of 200mg/m^2 over 30 minutes and Avastin (Bevacizumab) at a dose of 15mg/kg over 30 minutes. Both hematologic and non-hematologic adverse events will be determined and scored according to the NCI Common Toxicity Criteria (version 4.0). Hemorrhagic, Dermatologic, gastrointestinal, respiratory and nervous system disorders are expected to be the primary toxicity in patients receiving this treatment regimen. Patients may at any point during the phase I/II study receive supportive care, including growth factors, blood cell transfusions, as clinically indicated.

INTRODUCTION

Each year approximately 2200 children less than age 20 are diagnosed with malignant central nervous system tumors. These brain tumors are typically treated by surgery, radiation therapy and chemotherapy, either individually or in combination. Present therapies are inadequate, as evidenced

by the low 5-year survival rate for brain cancer patients, 66% for all types of pediatric CNS tumors and significantly lower for more aggressive tumor types. Glioma is the most common form of primary brain cancer, afflicting approximately 7,000 patients in the United States each year. Over 50% of pediatric CNS tumors are gliomas. High grade astrocytomas are relatively uncommon (<10% of CNS tumors); however these tumors have devastating consequences with most affected children surviving less than 3 years from diagnosis despite surgical and adjuvant intervention. These highly malignant cancers remain a significant unmet clinical need in oncology. GBM (the highest grade of glioma) often has a high expression of EFGR (Epidermal Growth Factor Receptor). The importance of EGFR is well established in adult glioblastoma. Pediatric glioblastoma was previously thought to have lower expression levels, but recent evidence suggests that expression may play an important role in pediatric tumors as well. In contrast, normal human brain does not express EGFR, making this an exciting target in the treatment of brain tumors. Several methods of inhibiting this receptor have been tested, including monoclonal antibodies, vaccines, and tyrosine kinase inhibitors. GBM also has a high expression of vascular endothelial growth factor (VEGF), a protein that is produced by both tumor cells and stromal cells, including inflammatory cells.(Buie and Valgus 2008; Chamberlain 2006; de Groot and Yung 2008; Poulsen et al. 2008; Sathornsumetee and Rich 2007; Vredenburgh et al. 2007) In human GBM specimens, the expression of VEGF is associated with a poor prognosis.(Desjardins et al. 2008; Zuniga et al. 2008) Conversely, in a xenograft model, antibodies to VEGF have inhibited the growth of GBM.(Buie and Valgus 2008; Kang et al. 2008; Vredenburgh et al. 2008) Avastin and Irinotecan intravenous chemotherapy has become the standard of care for recurring relapsing GBM (de Groot and Yung 2008). Intra-arterial delivery of chemotherapy with Avastin has become widely used in other solid tumors including Hepatocellular and Pancreatic Carcinoma.

Cetuximab (Erbitux, IMC-C225) is a recombinant human (IgG1)/mouse (Fv regions) chimeric monoclonal antibody which binds specifically to the epidermal growth factor receptors (EGFR) and competitively inhibits the binding of EGFR and other ligands. Cetuximab-binding also results in internalization of the antibody-receptor complex, which causes a down-regulation of EGFR expression on the cell surface. Consequently, signal transduction through this pathway is blocked, which inhibits tumor growth and ultimately leads to cell death. Studies have suggested that cetuximab also decreases angiogenesis, mediates antibody-dependent cell-mediated cytoxicity, and positively increases the activity with radiotherapy and chemotherapy. Data from a recent stratified phase II trial, in which cetuximab was administered intravenously to 55 patients with recurrent high-grade gliomas, 28 who were EGFR Positive and 27 who were EGFR Negative. The primary end point for this study was the response rate in both study arms separately. 5.5% had a partial response and 29.6% had stable disease. We recently showed in our Phase I trial that intra-arterial Cetuximab is safe for the treatment of recurrent GBM patients >18 years of age.

Bevacizumab(Avastin) is a humanized immunoglobulin (Ig) G1 monoclonal antibody that binds to and inhibits the activity of VEGF. Bevacizumab is synergistic with chemotherapy in colorectal, lung, brain and breast carcinomas. As a single agent, Bevacizumab prolonged the time to progression for patients with metastatic renal cell carcinoma compared with that for patients receiving placebo (Vredenburgh et al. 2007). Monoclonal antibodies to VEGF have inhibited the growth of GBM in vitro and in vivo (Sathornsumetee and Rich 2007). In fact, Avastin and Irinotecan intravenous chemotherapy has become the standard of care for recurring relapsing GBM in adult patients. A preliminary report of the combination of bevacizumab and irinotecan for patients with malignant gliomas demonstrated an encouraging response rate of 43%.(Vredenburgh et al. 2007) In addition, the 6-month overall survival with bevacizumab and irinotecan was

improved compared with temozolomide: 77% versus 60% respectively. Comparison of Avastin and CPT-11 show a 6-month Progression Free Survival (PFS) and median PFS in patients with GBM of 43% and 24 weeks, compared with previous results of 15% and 9 weeks, respectively, in patients with GBM.(Vredenburgh et al. 2007) The 1-year overall survival with bevacizumab and Irinotecan was superior to historical controls: 37% versus 21%, respectively. We recently showed in our Phase I trial that intra-arterial delivery of Avastin is safe for the treatment of recurrent GBM in patients >18 years of age. This study is a follow up study to assess the effects of intra-arterial Cetuximab and Avastin in patients <22 years of age.

Clinical Experience with the Individual Chemotherapy Agents

Mannitol: Intraarterial infusion of Mannitol (25%; 3-10ml/s for 30seconds) in order to achieve osmotic disruption of the cerebral circulation has been well described. Neuwelt et al performed 3498 BBB disruption procedures of the internal carotid artery using the same dose in conjunction with alkylating agent chemotherapy infusions in 405 patients. There was no associated risk of intracerebral hemorrhage, seizure or stroke. We have shown in our experience that there was no adverse effect of SIACI of Mannitol.

Erbitux: The currently used intravenous dose of Erbitux chemotherapy is 400mg/m^2 IV. In our recently completed Phase I clinical trial an intra-arterial dose of 200 mg/m^2 was safe for the treatment of GBM and no adverse effects were detected in the treated patients.

Avastin: The currently used intravenous dose of Avastin chemotherapy is 10mg/kg IV. In our recently completed Phase I clinical trial an intra-arterial dose of 15 mg/m^2 was safe for the treatment of GBM and no adverse effects were detected in the treated patients.

Rationale for the dosing schedule: The proposed research trial design utilizes the addition of intracranial superselective intraarterial chemotherapy infusion of Cetuximab and Avastin. With the implementation of protocol version 6 December 2019, infusion frequency was changed from a single, one time dosing to monthly dosing due to favorable early results for this trial. 12 patients were treated on the initial one time dosing schedule – of that, 4 patients exhibited subjective symptom improvement that allowed 2 of them to return to school. At a 1 month timepoint used to determine response, 5 had responses (2 had stable disease, 2 had a PR, and 1 had a CR). Response was determined by comparison of linear and volumetric criteria as demonstrated by Shah et al 2005. Thus, it is the belief that increasing to monthly dosing will improve patient responses.

Choice of Starting the Dose Used in this Study Regimen: In our Phase I trials, we have determined that Erbitux and Avastin are safely delivered intraarterialy at doses of 200 mg/m^2 and 15 mg/kg respectively in patients >18 years of age. Since these doses are body surface area and weight based, we will use the same dosages in this study for patients <22 years of age. Three patients will receive these doses to confirm safety in patients <22 years of age and additional patients will then be treated with these dosages to assess efficacy.

Cerebral Angiography: The basic concept of cerebral angiography involves the navigation of a catheter up through the vasculature to the aortic arch. The major vessels that supply the cerebral circulation either originate from the arch directly or from major tributaries that arise from the arch. These vessels include the Inominate Artery and Subclavian Arteries. Angiography begins with arterial access. By convention this usually involves the puncture and cannulation of the right

femoral artery using the Seldinger technique. Local anesthetic is applied to the femoral skin and a single wall puncture needle is used to access the artery. Once the artery is entered then a wire is passed through the puncture needle into the artery and the needle is exchanged for an introducer sheath. The original wire is then removed. The introducer sheath is connected to a continuous heparinized saline flush. This introducer sheath then becomes the portal of entry for the diagnostic catheter. Under direct visualization of fluoroscopy, the diagnostic angiography catheter is then passed through the introducer sheath up the femoral artery, iliac artery and into the descending aorta with the use of a guide wire. This guide wire is later used to access the cerebral vasculature. The catheter and wire are then advanced together from the descending aorta to the thoracic aorta and into the aortic arch. Once in the arch the catheter wire combination are used to cannulate the Inominate artery. The Inominate artery gives rise to the right Common Carotid artery and the right Subclavian artery. The right vertebral artery usually has its origin from the proximal right Subclavian artery. The guide wire is advanced into the right Common Carotid artery and diagnostic catheter is then advanced over it. The wire is then removed and an angiographic image is obtained of the carotid bifurcation. The wire is then re-introduced and either the external or internal carotid artery is then accessed. For the intracranial circulation a roadmap, an image generated by injecting contrast and allowing software to subtract out bone, is generated and the guide wire is advanced into the internal carotid artery. With the catheter in the internal carotid artery, a cerebral angiogram is performed over the cranium in AP and Lateral views. The same procedure is repeated on the left side of the cerebral circulation, with the catheter first being placed in the internal carotid artery and then the internal carotid artery. The vertebral arteries are also selectively cannulated and images of the posterior cerebral circulation are obtained**.**

Super-selective Angiography: Most endovascular interventions begin with super-selective catheterization of a specific vessel. Prior to this the patient is given a Heparin bolus to obtain an automated coagulation time of approximately three times baseline (Usually 50 units/kg). Next, the diagnostic catheter is exchanged for a guiding catheter. A guiding catheter is stiffer and will provide more support to a micro catheter necessary for super selective catheterization. A new roadmap image is generated and now the micro catheter is introduced with a micro-guide wire. The specific vessel leading to the specific pathology is identified and the micro-guide wire is advanced into this vessel. The micro-catheter is then subsequently advanced over this micro-guide wire and the guide wire is removed. A super-selective angiogram is then performed by injecting contrast through the micro catheter to confirm that it is in the desired vessel, in this case the vessel supplying the territory containing the brain tumor. Even more super selective catheterization can be performed in order to localize the lesion more specifically. Once the desired catheter position has been achieved the infusion of Mannitol and Cetuximab/Avastin will be performed over the specified time course. On the completion of the infusion the micro catheter is removed and an angiogram is performed from the guiding catheter to check the cerebral circulation before the catheter and introducer sheath are removed. The guiding catheter is removed and homeostasis is achieved at the femoral artery with either manual compression or the use of an arterial closure device.

RISK/BENEFIT OF THE STUDY

Data generated from clinical trials using IV Erbitux and Avastin indicate both safety and efficacy of these drugs. Available preclinical and clinical data demonstrate the safety and activity of intra-arterial Erbitux and Avastin in other solid cancer models. Our data in adults also indicates safety of IA Erbitux and Avastin. We will be able to follow prospectively patients who receive IA Erbitux

and Avastin to better understand the safety and ultimate efficacy of this regimen in patients <22 years of age with recurrent/refractory glioma.

Intravenous Erbitux use is most likely to result in the following toxicities: skin toxicity, thrombocytopenia, confusion, lymphopenia, infusion related allergic reaction, intratumoral hemorrhage, diarrhea and fatigue. We have not reported any toxicities with superselective intra-arterial Erbitux infusion.

Intravenous Avastin use is most likely to result in the following toxicities: CNS hemorrhage (3%) thromboemboloic (11%), proteinuria (6%), and fatigue (11%). There have been to date no detailed (observed or documented) toxicities reported with superselective intra-arterial Avastin infusion.(Vredenburgh et al. 2008)

This treatment could be harmful to a gestating embryo or fetus, if pregnancy were to occur. Females of childbearing potential and fertile males should be informed as to the potential risk of procreation while participating in this research trial and will be advised that they must use effective contraception during the treatment period. A pregnancy test should be performed on each postpubertal female of childbearing potential immediately prior to entry into the research study.

There may be unknown or unanticipated discomforts or risks in addition to those specified above. CNS hemorrhage may lead to death. Because some of these procedures are relatively new and are attempts to advance medical knowledge, however, every precaution should be taken to assure the patients' personal safety and to minimize discomfort. In addition, risks of carotid and cerebral angiography apply to these patients. These include but are not limited to infection, bleeding, stroke, death, vessel injury, groin hematoma and retroperitoneal hematoma. Recent data indicates that the risk of cerebral angiography is less than 1 %.

Individual patients may benefit by having a decreased risk of recurrence of brain tumor. They may also live longer. Alternatively, there may be no benefit to the patient's participation in this research study. Society will benefit if an effective therapy is identified for an illness, which attacks children and which is almost uniformly fatal in a short time frame.

I. OBJECTIVES/ENDPOINTS

1. PRIMARY ENDPOINTS

- The safety of intra-arterial delivery of previously determined doses of intra-arterial Avastin and Cetuximab in pediatric patients is a primary endpoint of the study (see statistics below). The descriptive frequency of subjects experiencing toxicities will also be tabulated. Toxicities will be assessed and graded according to the NCI Common Toxicity Criteria, version 4.0. Exact 95% confidence intervals around the toxicity proportions will be calculated to assess the precision of the obtained estimates. We will assess if patients are stable disease at 3 months post initial injection.

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- Composite overall response rate at 6 months: The composite overall response rate (CORR) at 6 months will be examined. The overall response proportion along with

a 95% confidence interval will be estimated via binomial proportions. We will define "evaluable" patients as patients who met eligibility requirements and have initiated therapy.

- Increased progression-free survival (PFS) and overall survival (OS) will be assessed by Kaplan-Meier survival analysis, assuming adequate follow-up time. PFS will be measured from the date of the first dose of SIACI Cetuximab/Avastin to the date of progression. OS will be measured from the date of diagnosis to the date of death. Subjects will be followed for one year after their last dose of study treatment, or until death.

2. SECONDARY ENDPOINTS

- Assessment of symptom improvement

II. PATIENT SELECTION

A. Criteria for Inclusion:

- Male or female patients, <22 years of age, with a documented histologic diagnosis of relapsed or refractory glioblastoma multiforme (GBM), anaplastic astrocytoma (AA), fibrillary astrocytomas (FA), pilomyxoid astrocytoma (PXA), oligodendroglioma, or anaplastic mixed oligoastrocytoma (AOA), or radiologically diagnosed brainstem glioma

- Patients must have at least one confirmed and evaluable tumor site.*
  *A confirmed tumor site is one in which is biopsy-proven with the exception of brainstem glioma which will be eligible with radiographic diagnosis. NOTE: Radiographic procedures (*e.g.*, Gd-enhanced MRI or CT scans) documenting existing lesions must have been performed within **three** weeks of treatment on this research study.

- Patients must have a Karnofsky or Lansky performance status ≥60%. Karnofsky is used for patients ≥16 years and Lansky for those <16. (see **Appendix A**; Performance Status Evaluation) and an expected survival ≥ three months.

- No chemotherapy for three weeks prior to treatment under this research protocol and no external beam radiation for eight weeks prior to treatment under this research protocol.

- Patients must have adequate hematologic reserve with absolute neutrophils≥1000/m^{m3} and platelets ≥100,000/ mm^3.

- Pre-enrollment chemistry parameters must show: bilirubin<1.5X the institutional upper limit of normal (IUNL); AST or ALT<2.5X IUNL and creatinine<1.5X IUNL.

- Pre-enrollment coagulation parameters (PT and PTT) must be ≤1.5X the IUNL.

- Concomitant Medications:

  - Growth factor(s): Must not have received within 1 week of entry onto this study.

  - Steroids: Systemic corticosteroid therapy is permissible in patients with CNS tumors for treatment of increased intracranial pressure or symptomatic tumor edema. Patients with CNS tumors who are receiving dexamethasone must be on a stable or decreasing dose for at least 1 week prior to study entry.

- Patients of reproductive age must agree to use a medically effective method of contraception during and for a period of three months after the treatment period. A pregnancy test will be performed on each premenopausal female of childbearing potential immediately prior to entry into the research study.

- Patients or their parents/guardians must be able to understand and give written informed consent. Informed consent must be obtained at the time of patient screening.

- Because of known concerns with Avastin and wound healing, craniotomy patients are eligible for the treatment if they have had a craniotomy greater than two weeks prior to IA therapy. Craniotomy or major procedure after SIACI Avastin therapy should wait 4 weeks. Minor surgeries may be performed after two weeks.

B. Criteria for Exclusion

- Females who are pregnant or lactating.

- Females of childbearing potential and fertile men will be informed as to the potential risk of procreation while participating in this research trial and will be advised that they must use effective contraception during and for a period of three months after the treatment period. If they do not agree, they will be ineligible for the study.

- Patients with significant concurrent medical or psychiatric conditions that would place them at increased risk or affect their ability to receive or comply with treatment or post-treatment clinical monitoring.

III. TEST AGENT PREPARATION AND ADMINISTRATION

A. Supplies of research study agents

Erbitux (Pharmacy)

Avastin (Pharmacy)

B. Preparation of the research study agents

1. Erbitux

Chemical name: Cetuximab

Storage: Store vials at 2 degrees to 8 degrees C.
Stability: Protect from light, do not freeze or shake.

Half life: 4.75 days
Excretion: 2.75-5ml/kg/day

2. Avastin

Chemical name: Bevacizumab
Storage: Store vials at 2 degrees to 8 degrees C.
Stability: Protect from light, do not freeze or shake.

Half life: 20 days (range: 11-50days)
Excretion: 2.75-5ml/kg/day

C. Doses of Research study Drugs:

Erbitux®: The dose for IA Erbitux will be 200mg/m^2.
Avastin®: The dose for IA Avastin will be 15 mg/kg.

D. Route of Administration

- Erbitux® and Avastin® will be given intracerebrally by superselective intraarterial infusion

E. Dosing Procedure

The doses and schedule of treatment for all of the drugs to be used in the research study are given above. This is an outpatient regimen, in which the drug is administered via IA delivery. Treatment will be administered monthly. Tumor response will be assessed with baseline MRI on post procedure day 1, MRI one and three month post procedure.

1. Dose Interruption or Discontinuation:
   If an unacceptable toxicity is experienced during any portion of a patient's infusion, the investigator will follow the procedures outlined (see Section **VII.B**; Management of Toxicity; Dose Interruption or Discontinuation).

IV. EXPERIMENTAL PLAN

A. Control Methods

There may be multiple research study sites, but no activation of additional sites may occur until there is IRB approval at those sites and either institutional agreements are obtained between The New York Presbyterian Hospital-Weill Medical College of Cornell University and these sites or until site-specific agreements with the drug suppliers are executed.

This is an open-label research trial, non-randomized phase I/II clinical research trial.

B. Duration of this Research Trial

To complete the trial approximately 40 patients will be required. The New York Presbyterian Hospital-Weill Medical College of Cornell University and the University of Miami will be employed for this research study. Overall, it is anticipated that accrual to complete the study will be 6 years.

C. Trial Design/Sample Size and Statistical Considerations:

The primary endpoint will be the 6 month composite overall response rate (CORR). We will define "evaluable" patients as patients who met eligibility requirements, have initiated therapy, and were not removed from the study for non-compliance or patient withdrawal within the first 6 months.

Sample size:

Intra-arterial Cetuximab and Bevacizumab (single arm study):

The 6-month CORR for patients treated with Cetuximab has been estimated to be 20%; therefore, the target 6-month CORR for the intra-arterial Cetuximab and Bevacizumab arm will be ≥18%. Sample size recommendations for the phase II design are determined according to Simon's two-stage optimum design. We project a CORR at 6 months of 5%, below which the regimen will be unacceptable, and a CORR at 6 months of 18%, above which the regimen will be considered worthy of further exploration. The null hypothesis that the 6-month CORR is less than or equal to 5% will be tested against the alternative hypothesis that the 6-month CORR is greater than or equal to 18%.

The sample size computations were performed assuming a 5% level of significance and 80% power. Patients will be continuously accrued throughout the study up to a maximum of 44 patients. If 1 or fewer patients out of the first 17 evaluable patients respond after 6 months of follow-up, the study will be terminated and the regimen will be declared to have a negative result. If 2 or more patients out of the first 17 evaluable patients respond after 6 months of follow-up, ongoing accrual will proceed to the target sample size of 44 patients (i.e., if all 44 patients have not been accrued at this point). The treatment will be declared effective and worthy of further testing if 5 or more patients respond after 6 months of follow-up among the 44 patients entered in the study. This two-stage design yields a ≥0.80 probability of a positive result if the true 6-month CORR is ≥18%. It yields a ≥0.95 probability of a negative result if the true 6-month CORR is ≤5%. A 95% confidence interval constructed around the expected 6-month CORR of 18% can be estimated to be within ± 11.4% of the observed CORR.

Numbers of observed patients with CORR after
6 months of follow-up required to accept or reject H_0 at each stage.
Under this design, H_0 will not be rejected at Stage 1.

	N	Accept H_0	Reject H_0
Stage 1	17	≤ 1	---
Stage 2	44	≤ 4	≥ 5

Analysis Plan for Endpoints:

Primary Endpoints:

The primary endpoint in both treatment arms is the 6-month CORR. A ninety-five percent confidence interval will be estimated for the 6-month CORR via binomial proportions.

Secondary Clinical Endpoints:

Secondary endpoints include median PFS and OS in both treatment arms. Median PFS and OS, including survival curves, will be estimated using Kaplan-Meier methodology. Greenwood's formula will be used to calculate 95% confidence intervals for the Kaplan-Meier estimates.

The frequency of subjects experiencing toxicities will be tabulated. Toxicities will be assessed and graded according to CTCAE v. 4.0 terminology. Exact 95% confidence intervals around the toxicity proportions will be calculated to assess the precision of the obtained estimates.

All p-values will be two-sided with statistical significance evaluated at the 0.05 alpha level. Ninety-five percent confidence intervals will be calculated to assess the precision of the obtained estimates. All analyses will be performed in SAS Version 9.2 (SAS Institute, Inc., Cary, North Carolina) and STATA Version 12.0 (StataCorp, College Station, Texas).

Sample Size/Accrual Rate

The planned sample size is 47 patients (3 for initial safety and 44 for determination of efficacy). Assuming that 10% of patients are unevaluable/ineligible at the efficacy phase, we anticipate that a total of 50 patients will be enrolled in the efficacy phase of the study. Total sample size will therefore be 53 patients (3 for initial safety and 50 for efficacy phase). Accrual is expected at a rate of 2-3 subjects per month.

D. Patient Entry and Time on Research Study

1. Enrollment Process

Patients will be centrally registered with Weill Cornell Medicine, Joint Clinical Trials Office, Cancer Clinical Trials Operations. To register a patient, the following documents must be email to the Joint Clinical Trials Office's central regulatory mailbox - CancerCTRegistrar@med.cornell.edu.

- WCMC Patient Registration Form
- First and last page of the fully executed informed consent form, plus additional pages if with subject's markings
- Fully executed HIPAA research authorization form (if separate from the consent document)
- Eligibility checklist signed and dated by investigator and second study team member
- Documentation of any eligibility waivers granted

2. Assignment of Patient Identification

   Patients meeting the research study entry criteria will be assigned patient identification code as they enter the research study. Patient identification numbers will be assigned in chronological order. Research study center designations will be assigned to other centers, who are selected to participate in this research trial.

   Information regarding patient identification, as well as the number of vials of test medication utilized for the patient and the dose administered to the patient, will be recorded on the Drug Dispensing Log (to be provided by the Sponsor), as well as in the CRFs.

3. Inpatient / Outpatient Requirements

   Patients will be treated on an outpatient basis.

   Patients may be followed routinely by their private physician when necessary. Follow up procedures which are standard of care and do not involve study treatment, may be conducted at external sites if this is more feasible for the subject. In this case, relevant medical records will be requested by WCM for data collection.

4. End of Research study

   All patients will be monitored for tumor response (by MRI scanning) and toxicity (by physical examination and blood tests) for the duration of study therapy.

5. Follow-up Monitoring for Response and Safety

   Patients in the phase I/II study, will be closely monitored for dermatologic and respiratory toxicity. The primary observation period after IA therapy will be 28 days. After the 28 day period, the patient will start treatment as recommended by patient's neurooncologist. Thereafter, toxicities will be monitored by history,

physical examination and blood tests, chest xray as outlined in Table 1 below. Tumor response assessment by MRI will be performed on post procedure day 1, at 1 month and 3 months post procedure.

E. Treatment Plan

Superselective intra-arterial Dose of Erbitux® and Avastin® will be given at a dose of 200mg/m^2 IA and 15 mg/kg respectively, on a monthly basis.

F. Supportive products/concomitant medications:

All medications within four weeks prior to administration of research study drug, and all concomitant therapy administration during the research study with the reasons for therapy use will be recorded in the data collection form. Surgery will also be recorded. For all subsequent visits, all concomitant therapy, which is continuing or has been **added**, **discontinued** or **had a dosage change** since the previous visit must be recorded. All patients should be maintained on the same medications throughout the research study period, as medically feasible.

1. Antiemetic medications: The specific post-treatment antiemetic therapy will be left to the investigators discretion. Dose and frequency of usage for antiemetic therapy administered to treat patients receiving the research study drug will be recorded in the data collection form. For all subsequent visits, all concomitant therapy, which is continuing or has been added, discontinued or had dosage changed since the previous visit must be recorded.

2. Platelets: Platelet transfusions should be given to all patients if platelets are below 25,000/mm^3. Platelets may be given if counts are >25,000/mm^3, at the investigators discretion if any signs of bleeding occur.

3. Use of hematopoietic growth factors: The use of hematopoietic growth factors is permitted at the clinician's discretion.

4. Corticosteroids: A reasonable dose of corticosteroid (*e.g*., dexamethasone) will be determined on clinical grounds for each patient if needed to alleviate increased intracranial pressure. An effort will be made to keep the patient on this steroid dose until the next scan is obtained. Changing steroid doses may complicate the interpretation of tumor response. Corticosteroid doses can be tapered as clinically indicated if the patient appears to be responding to therapy (as judged by serial scans) and neurological examination.

V. PARAMETERS TO BE MEASURED

All patients enrolled in this will be evaluated according to the procedures described in Sections A and B and below. All screening studies are to be performed ≤4 weeks

prior to research study entry and, as noted below, some tests will be repeated 1-4 days prior to initiation of treatment. Patients will be assessed for the presence of measurable disease and tumor response by MRI scan. An MRI will be performed on post procedure day 1, at one and three month post procedure.

A. Safety Assessments

All evaluations should be performed on or about the indicated research study day.

1. Assessment of Patient Eligibility and Signing of Informed Consent
   - Screening/Baseline: All patients must meet all inclusion criteria and not have any exclusion criteria to be eligible for the research study. All patients or their parent/guardian must sign an informed consent prior to enrollment, and prior to submitting to any research protocol-related procedure, unless such testing was performed as part of the routine clinical diagnosis or management of the patient.

2. Medical History (complete history at screening, including primary and secondary diagnoses; updates at the indicated times thereafter)

3. Disease Confirmation
   - Screening/Baseline: This needs to include a pathology report as well as reports from imaging studies (particularly MRI scans) to confirm that there is at least one measurable target or index lesion. If there is only one target lesion, it will be required that it show progression or be documented by biopsy with the exception of radiographically diagnosed brainstem glioma. Biopsy tissue will be sent to neuropathology for evaluation of tumor mutations such as VEGF over expression.

4. Performance Status Evaluation, Karnofsky or Lansky (see **Appendix A**)
   - Screening/Baseline: Prior to the start of research protocol treatment (within 1-4 days)
   - Cycle 1 Day 2Day 1 of each subsequent cycle
   - End of Treatment Visit

5. Vital Signs (to include: body temperature, pulse rate, blood pressure, and respiration rate)
   - Screening/Baseline
   - Day 1 of each cycle
   - Cycle 1 Day 2
   - End of Treatment Visit

6. Physical Examination (complete at screening, including height and weight; thereafter complete excluding height)
   - Screening/Baseline: This will be performed within 1-4 days of initiation of treatment.
   - Day 1 of Each Cycle
   - Cycle 1 Day 2

- End of Treatment Visit

7. Hematology (to include CBC with differential and platelet count)
   - Screening/Baseline: This will be performed within 1-4 days of initiation of treatment.
   - Cycle 1 Day 1 (post initial treatment)
   - Day 1 of each cycle
   - End of Treatment Visit

8. Serum Chemistries (to include: Na, K, Cl, bicarbonate, BUN, creatinine, glucose, bilirubin, AST, ALT, alkaline phosphatase, LDH, creatinine, Ca, Mg, phosphorus, albumin, total protein, uric acid)
   - Screening/Baseline: This must be within 2 weeks of enrollment on research study.
   - Day 1 of Each Cycle
   - Cycle 1 Day 2
   - End of Treatment Visit

9. PT and PTT
   - Screening/Baseline: This will be performed within 1-4 days of initiation of treatment.
   - Day 1 of Each Cycle
   - Cycle 1 Day 2
   - End of Treatment Visit

10. Urinalysis
    - Screening/Baseline: This will be performed within 1-4 days of initiation of treatment.
    - Thereafter, as clinically indicated.

11. Pregnancy Test (urine or serum; in postpubertal females)
    - Screening/Baseline (negative result must be documented on CRF)
    - As clinically indicated

12. Imaging and Tumor Assessment
    - MRI Head and Tumor Assessment using RANO criteria to be obtained
    - Screening/Baseline: This will be performed within 1-4 days of initiation of treatment.
    - Day 1 of Each Cycle
    - Cycle 1 Day 2

13. Survival Follow Up
    - After discontinuing treatment, phone calls will be made for survival follow up every 6 months until death or up to one year whichever comes first.

B. Disease/Tumor Assessment

1. MRI (contrast-enhanced) for Lesion Measurements (*i.e.*, brain)

- Screening/Baseline (within 3 weeks prior to research study entry).

- Response will be assessed with a contrast-enhanced MRI on post procedure day one after intra-arterial treatment, at one month post procedure, and then repeated every month thereafter until disease progression.

  Contrast-enhanced MRI will be considered the standard method for evaluating tumor involvement. The location and dimensions of "target" (or "index") lesions, as well as other measurable lesions, will be documented on the patient's CRF. Lesion dimensions will also be recorded. MRI imaging must use the same "cuts" for all follow-up imaging studies to assure accuracy of the data collected. For all objective responses the duration of the response will be determined, from the day the initial response is observed (using baseline images for comparison) to the time that progression is observed. If disease progression is documented at any time after treatment, no further imaging will be required.

  The criteria for progression is based on the Response Assessment in Neuro-Oncology (RANO). The criteria for imaging response is based on volumetric segmentation of enhancing and T2 FLAIR positive tumor (Shah et al 2005).

  Imaging which is conducted at an external institution will be re-read by a radiologist at Weill Cornell Medicine.

VI. OVERVIEW OF SCHEDULED PROCEDURES

	Baseline (within 4 days of C1D1)	Cycle 1 Day 1 (Tx Day)	Cycle 1 Day 2 (Post Tx)[a]	Cycle X Day 1	Cycle X Day 2)[a]	End Of Treatment Visit	Follow-Up
Tests & Observations							
History	X						
Physical Exam and Vital Signs	X	X	X	X		X	
Performance Status	X		X	X		X	
Tumor Measurement	X		X	X			
Toxicity Evaluation	X	X	X	X			
Documentation of dexamethasone dose	X		X				
Laboratory							
CBC, diff, platelets	X		X	X	X	X	
PT, PTT	X			X	X	X	

Chemistries (including electrolytes)	X		X	X	X	X	
Urinalysis	X	As clinically indicated					
Pregnancy Test (urine or serum, in postpubertal females)	X	As clinically indicated					
Imaging							
MRI Head	X		X	X[d]			
Survival Follow-Up							
Phone Call							X[c]
Treatment							
		X		X			

a Occur approximately 24 hours post-op.
b To occur once every 30
c phone calls for survival follow up are required every 6 months until death or 1 year whichever occurs first.
d to occur within 3 days of treatment, and to be resulted prior to treatment

VII. TOXICITY OF INVESTIGATIONAL DRUG

All screening studies are to be performed ≤4 weeks prior to research study entry (imaging study must be completed within three weeks of study procedure) and, as noted below, some tests will be repeated 1-4 days prior to initiation of treatment. Patients will be assessed for the presence of measurable disease and tumor response by MRI of the brain with and without contrast. A tumor response assessment (MRI) will be performed on post procedure day one, at one month post procedure, and every month thereafter.

To date, at least 5,000 cancer patients have received Erbitux. Erbitux is approved by the Food and Drug Administration to treat squamous cell carcinoma of the head and neck and colorectal cancer. We have treated patients with SIACI Mannitol/Erbitux for the treatment of malignant brain tumors and did not observed any dose limiting toxicity from the drug up to a dose of 200 mg/m^2. Hemorrhagic, Dermatologic, gastrointestinal, respiratory and nervous system disorders may occur as primary toxicity in patients receiving this treatment regimen.

To date, at least 10,000 cancer patients have received Avastin at a dose ranging from 3mg/kg up to 20mg/kg IV every two weeks in previous clinical trials. Avastin is used in Colorectal, head and neck, brain, prostate, and renal cancer. We have treated patients with SIACI Mannitol/Avastin for the treatment of malignant brain tumors and did not observed any dose limiting toxicity from the

drug up to a dose of 200 mg/m^2. Adverse events associated with IV Avastin administration reported in two recent clinical trials include hypertension, pain, headache, dizziness, alopecia, nausea/vomiting, stomatitis, fatigue and thromboembolism.

VIII. MANAGEMENT OF TOXICITY

Careful assessment of toxicity experienced by the patient will be carried out throughout the course of this research study. Grades of toxicity (Modified NCI Common Toxicity Criteria 4.0) will be utilized as the criteria to determine appropriate management of the patient.

All clinical adverse experiences, whether observed by the investigator, or observed or experienced by the patient, will be reported. Any significant change from baseline in a laboratory parameter will be reported to the Sponsor and will be documented. All treatment-emergent clinical and laboratory adverse events must be carefully evaluated for severity (see **Appendix B**; mild, moderate, severe, life-threatening), duration, and relationship to research protocol treatment (see **Appendix C**; unrelated, remote, possible, probable, related). Such information will be documented on the appropriate page of the patient's CRF.

The investigator, subinvestigator, or designated health professional must be present at the time of scheduled patient visits for follow-up monitoring and should also to evaluate whether compliance with the research protocol is being maintained. If, at any point during the research study, significant changes occur in either the patient's clinical status or laboratory parameters, such changes will be followed until the parameter either returns to baseline or is adequately explained.

Clinical experience, thus far, indicates that adverse experiences (AEs) related to the use of Erbitux® and Avastin® are mostly cardiovascular (hypertension), and GI (acute nausea and vomiting). Other AEs that may occur but are less common in association with the administration of this agent is: neurotoxicity (including headache), diarrhea, anorexia and fatigue. These AEs are generally mild to moderate, reversible and/or manageable with symptomatic treatment, dose delays or reductions. In our experience with IA Cetuximab and Bevacizumab, we have not seen any significant AE's related to the route of administration.

A) Dose Modification: Set doses of Erbitux or Avastin will be delivered to patients as determined by safe dosages in the Phase I adult trials conducted to date. Dose modification is not planned.

B) Dose Interruption: Any sign of acute allergic reaction to Erbitux or Avastin will, depending upon the severity, necessitate temporary interruption or permanent discontinuation of the offending agent during infusion.

C) Removing Patients from Study: Every effort will be made to keep the patient on research study; however, in the event that a patient is withdrawn from the research study, the investigator should document the reasons for withdrawal as thoroughly as possible and notify the PI. This evaluation should include final observations, as required by the research protocol at the time of the patient's withdrawal. The reason(s) for early termination must be

clearly documented on the appropriate page of the patient's case report form (CRF). A CRF must be completed for any patient who receives ANY amount of treatment on this research study.

Patients will be taken off study if their disease progresses, or if they have a grade 4 or higher adverse event.

D) Replacements: Should a patient withdraw or need to be withdrawn from the research study, a replacement subject will be sought using the stipulated research protocol entry criteria. Patients who have completed toxicity and tumor response assessments, but have shown disease progression, will be not be eligible to receive additional treatment under this research protocol, but will be considered evaluable and will not be replaced by additional patients.

IX. ADVERSE EXPERIENCES

A. Adverse Experience Definition: An **adverse experience** (AE) is any undesirable, noxious, or pathological change, compared to pre-existing conditions, that occurs to a subject during a clinical research study or the follow-up period, whether or not it is considered to be related to the test drug. Adverse experiences include:

- Suspected adverse drug reactions.
- Reactions from drug overdose, abuse, withdrawal, sensitivity, or toxicity.
- Significant changes or abnormalities, when compared to baseline, in structure (sign), function (symptom), clinical laboratory results, or physiological testing. This includes any worsening of a pre-existing condition temporally associated with the use of research study medication.
- Other medical events, regardless of their relationship to the test drug, such as injury, surgery, accidents, extensions of symptomatology, or apparently unrelated illnesses.

B. Evaluating Adverse Experiences: The investigator will determine the seriousness, intensity, and causality of an adverse event based on the grading definitions found in the CTCAE version 4.0 or higher.

The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE, the following grading system should be used to assess severity:

Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures

Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
Grade 5 (Death related to AE) – experiences which result in subject death

Serious Adverse Experiences (notify Sponsor if adverse experience is both **serious and unexpected** within 24 hours [see below]; document on CRF)

THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE) IS ANY OF THE FOLLOWING WHICH OCCURS WHILE THE SUBJECT IS ACTIVELY ENROLLED IN THE STUDY OR WITHIN 30 DAYS OF COMPLETING THE STUDY TREATMENT:

- DEATH
- IMMEDIATELY LIFE-THREATENING ADVERSE EVENT
- REQUIRES INPATIENT HOSPITALIZATION
- PROLONGATION OF AN EXISTING HOSPITALIZATION
- CONGENITAL ANOMALY/BIRTH DEFECT
- MEDICALLY IMPORTANT EVENT*
- DISABILITY/INCAPACITY (PERSISTENT OR SIGNIFICANT)

*Medically important events that may not result in death, be live-threatening or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the experience may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

C. Documenting Adverse Experiences: All adverse experiences (including SAEs) are to be accurately recorded on the Adverse Experience page of the patient's CRF. Each experience will be graded on a four-point scale (see **Appendix D**; mild, moderate, severe, life-threatening) as to severity. The date of onset as well as the duration of the experience will be recorded. In addition, the method used to treat the adverse experience and the outcome of the adverse experience will also be noted. The investigator will attempt to assess the relationship of the experience (unrelated, remote, possible, probable, related) to the test drug(s) (see **Appendix E**; Clinical Adverse Experiences: Determining Relationship to Test Drug).

D. Reporting SAEs, Unexpected Adverse Experiences, and Patient Deaths

1. Time-frame for Reporting: Any death or **serious and unexpected** adverse experience of any patient during treatment or within 30 days of completing treatment under this research protocol must be promptly reported **(within 24 hours)** by telephone or telefax to the Sponsor or designee.

2. Procedure for Reporting All Serious Adverse Events For A Non-IND Study:

To report a SAE:

- Notify Drug Safety Surveillance (DSS) within 2 working days of the event. (DEATHS, REGARDLESS OF CAUSE, OR IMMEDIATELY LIFE THREATENING EVENTS POSSIBLY RELATED TO STUDY DRUG MUST BE REPORTED WITHIN 24 HOURS.)

- We will notify our IRB of the event promptly per IRB requirements.

We will also notify the above if the following occurs:

- PREGNANCY (IN PATIENT OR PARTNER) - we acknowledge that these are not serious unless a serious outcome is seen (*e.g.*, miscarriage, congenital anomaly)
- OVERDOSE - we acknowledge that these are not serious unless a serious outcome occurs

3. Information to be Provided by the Investigator

Initial Information: At the time of the initial contact(s), the investigator must transmit information to the Sponsor or designee for completion of a Safety Report. The Sponsor or designee will require that all of the following information about the patient and the adverse experience:

- Patient identification code, sex, age or date of birth
- Height, weight or body surface area (where required for dose calculation)
- Underlying diagnosis and extent of disease
- Dose and frequency of test medications administered
- Dates of test medication administration
- Description of event, including date of onset and duration
- Date of death (if applicable)
- Intervention(s) required
- Concomitant therapy (including regimen(s) and indication)
- Pertinent laboratory data/diagnostic test (including dates)
- Pertinent medical history
- Test medication status (dose interrupted, discontinued)
- Did event abate after interruption of test medication administration (if applicable)?
- Did event recur after test medication was reintroduced (if applicable)?

In addition to the above information, the Sponsor will require the investigator's assessment of the following:

- Severity of the adverse experience
- Relationship of the adverse experience to research study treatment
- Outcome of the adverse experience

E. Follow-up Information on an SAE: Appropriate diagnostic tests should be performed and therapeutic measures, if indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has resolved or is otherwise explained. Follow-up data concerning the SAE (*e.g.*, diagnostic test reports, physician's summaries, etc.) must also be submitted to the Sponsor, as they become available, preferably by telefax.

F. Review of an SAE: The PI will review each serious and unexpected adverse experience report and further evaluate the relationship of this adverse experience to test medications and to the patient's underlying disease. Based on this assessment, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of other patients participating in the clinical research study. If the discovery of a new adverse experience related to test medication raises concern over the safety of its continued administration to patients, the PI will take immediate steps to notify the IRB and all investigators participating in clinical studies of the test drugs used in this research protocol

Further action required may include any of the following:

- Modification of the research protocol.
- Discontinuation or suspension of the research study.
- Alteration of the informed consent process by modification of the existing consent form and informing current research study participants of new findings.
- Modification of previously identified expected adverse experiences lists to include adverse experiences newly identified as test medication-related.

X. PRECAUTIONS

A. Precautions Regarding Procreation: Females of childbearing potential and fertile men will be informed as to the potential risk of procreation while participating in this research trial and will be advised that they must use effective contraception during the treatment period. A pregnancy test will be performed on each postpubertal, female of childbearing potential immediately prior to entry into the research study. A negative pregnancy test must be documented on the CRF prior to administration of the test material.

B. Additional Precautions: Information regarding precautions and adverse experiences associated with this test medication can be found in the Scientific Background section of this document and in the package inserts for the individual research study medications.

XI. REGULATORY CONSIDERATIONS

A. Conditions for Modifying or Terminating the Research Study

1. Modifications

In the event that modifications in the experimental design, dosages, parameters, patient selection, etc., are indicated or required, such changes will only be instituted following consultation between the Sponsor and investigator and will be accomplished through formal amendments to this research protocol and approval by the appropriate review committees, except where necessary to eliminate apparent hazards to patients.

A modification to the research protocol will not be made without the express written approval of the Sponsor. Any amendment prepared by the Sponsor will be implemented according to the Sponsor's standard operation procedures and will be reported to the appropriate IRB(s), and made a formal component of the research protocol document.

2. Termination

Should the Sponsor and/or the investigator(s) discover conditions, during the course of the research study, that indicate it should be discontinued, an appropriate procedure for termination will be instituted. The principal investigator is responsible for assuring continuing review and approval of the clinical research study. The investigator must also promptly report all changes in the research activity and all unanticipated problems involving risk to the patients or others to his/her IRB. If the research study remains in progress for more than one year, the investigator must obtain annual renewal and reapproval from the IRB. Documentation of renewal must be submitted to the Sponsor.

B. Informed Consent

A copy of the IRB-approved consent form document to be utilized during this research study must be submitted to the Sponsor for review prior to research study initiation.

Prior to entry into this research study, the purpose and nature of the research study and possible adverse effects must be explained to each patient in the presence of a witness. It is the responsibility of the investigator to obtain written informed consent from each patient. A copy of the signed informed consent document should then be given to the patient. The original executed version must remain in the patient's file and must be available for verification by a representative of the Sponsor.

C. Documents to be Submitted to the Sponsor Prior to Research study Initiation

The following documents must be submitted to the Sponsor prior to research study initiation:

- Curriculum vitae of the principal investigator and each sub-investigator. Physician CVs should include medical license numbers.

- Written, signed notification of IRB approval of the research protocol (copy).

- Written, signed notification of the approval of the informed consent document to be utilized during the research study (copy).

- The stamped/signed by IRB informed consent document to be utilized during the research study (copy).

- Signed and dated Investigator Agreement; agreement appears as final page of the research protocol (original).

XII. MONITORING PLAN

A. Institutional Review Board: Weill Cornell Medicine (WCM) requires that all research approved by the WCM IRB include an appropriate plan for the monitoring of data to ensure the safety of human subjects. Research supported by Federal agencies will be monitored according to all regulations and guidelines of the relevant Federal agency.

B. Data and Safety Monitoring Board: The WCM DSMB will review the IRB approved protocol, informed consent documents, and data safety monitoring plan (DSMP) prior to study initiation. During the course of the study, the DSMB will perform a review of cumulative data annually to evaluate safety, efficacy, study conduct, and scientific validity and integrity of the trial. The WCM DSMB will also review all SAEs occurring on the study using the same reporting policy as the WCM IRB (http://researchintegrity.weill.cornell.edu/institutional_review_board/irb_adv.html). The WCM DSMB may also convene as need if stopping criteria are met or other safety issues arise that the Principal Investigator and/or IRB would like the WCM DSMB to address. The study Principal Investigator is responsible for submitting all written DSMB recommendations to the IRB upon receipt.

C. Efficacy: Additionally, if no subjects out of the first 13 subjects respond after 6 months of follow-up, the study will be terminated for lack of treatment efficacy.

D. After Amendment dated 30 March 2020 – the study will be terminated for the following reasons:

i. If no subjects out of the first 10 subjects respond within the first 6 months of therapy, the study will be terminated for lack of treatment efficacy

ii. If the there are more than 2 grade IV (or higher) toxicities seen in the same subject (out of the first 10 subjects), the study will be terminated for excessive toxicity

XIII. INVESTIGATOR RESPONSIBILITIES

A. Medical Supervision: Medical supervision for the conduct of this research protocol is the responsibility of the Principal Investigator. The Principal Investigator may delegate certain day-to-day activities to a subinvestigator, but retains overall responsibility for ensuring that the research study is conducted properly and in accordance with the design and intent herein. The Principal Investigator is responsible for ensuring that drugs and devices are available for treating possible medical emergencies. The Principal Investigator is responsible for ensuring that the research study is conducted according to sound medical practices.

B. Confidentiality: The PI affirms that all research study results and information furnished by acquired by the Sponsor during the course of the research study will be maintained in strict confidence. Such information, as well as data generated from this research study, may need to be communicated to the PI's or subinvestigators' review committees, under an appropriate understanding of confidentiality.

C. Record Retention- Records from the *Drug Dispensing Log:* Research study center personnel will maintain adequate records of the receipt and disposition of all test medications used in the research study. Records should include dates, quantities received, quantities dispensed, and the identification code of the patient who received the test medications. The investigator agrees to administer the research study medications only to patients under his/her personal supervision.

D. Patient Exclusion Log: A record listing all patients considered for entry into the research study and subsequently excluded must be maintained by the PI. Patients excluded form the research study will have the reason for exclusion recorded on the Patient Exclusion Log, which will be provided by the Sponsor.

E. Recording and Processing of Data: Individual CRFs must be completed in black ink. All data must be carefully completed to permit meaningful interpretation. CRFs are designed for computer processing and analysis. Corrections to entered data may be made by drawing a single line through the information to be corrected. All such corrections must be initialed and dated. No correction fluid or obscuring tape may be utilized. A completed CRF is required for every patient who received any amount of test medication. CRFs must be signed by either the PI or his designee.

F. Record Retention: Records from the research study must be retained by subinvestigators until they can be retrieved by the PI or designee once the data from individual research study patients has been collected and CRFs completed.

G. Laboratory Reports: Prior to initiation of this research study, the investigator must supply the PI or designee with the normal laboratory values for the laboratories to be utilized. The corresponding laboratory certification number must also be noted. Laboratory safety evaluations must be performed at the intervals specified. If unexplained laboratory abnormalities occur, corroborative tests will be performed until the laboratory parameter has returned to normal and/or adequate explanation of

the abnormality has been provided. Copies of any additional records pertinent to the research study (*e.g.* laboratory data, radiological reports, patient chart summaries, autopsy reports) must be made available to the PI, if requested, with due precaution taken to ensure patient confidentiality.

H. Monitoring: This research study will be monitored by representatives of the PI and Sponsor (The New York Presbyterian Hospital-Weill Medical College of Cornell University) throughout its duration. Monitoring will be in the form of personal visits with the investigator and his/her staff as well as any appropriate communications by telephone, telefax, or mail. Every effort will be made to maintain the anonymity and confidentiality of patients during this clinical research study.

XIV. PROTOCOL DEVIATIONS

Departures from either the research protocol entry criteria or the experimental plan, as outlined herein, will be determined as allowable on a case-by-case basis. The investigator must contact the PI or designee as soon as possible to discuss the associated circumstances. The PI will then decide as to the patient's continued research protocol eligibility status. All research protocol deviations and the reasons for such deviations must be noted on the appropriate page of the patient's CRF.

XV. ANALYSIS OF DATA

Data Review During this Research study: All research study data are to be reviewed at regular meetings of the principal participants to monitor the progress of the project.

APPENDIX A

Performance Status Evaluation

Karnofsky Scale (recipient age ≥ 16 years)		Lansky Scale (recipient age <16 years)	
Able to carry on normal activity; no special care is needed		**Able to carry on normal activity; no special care is needed**	
100	Normal, no complaints, no evidence of disease	100	Fully active
90	Able to carry on normal activity	90	Minor restriction in physically strenuous play
80	Normal activity with effort	80	Restricted in strenuous play, tires more easily, otherwise active
Unable to work, able to live at home cares for most personal needs, a varying amount of assistance is needed		**Mild to moderate restriction**	
70	Cares for self, unable to carry on normal activity or to do active work	70	Both greater restrictions of, and less time spent in active play
60	Requires occasional assistance but is able to care for most needs	60	Ambulatory up to 50% of time, limited active play with assistance/supervision
50	Requires considerable assistance and frequent medical care	50	Considerable assistance required for any active play, fully able to engage in quiet play
Unable to care for self, requires equivalent of institutional or hospital care, disease may be progressing rapidly		**Moderate to severe restriction**	
40	Disabled, requires special care and assistance	40	Able to initiate quite activities
30	Severely disabled, hospitalization indicated, although death not imminent	30	Needs considerable assistance for quiet activity
20	Very sick, hospitalization necessary	20	Limited to very passive activity initiated by others (e.g., TV)
10	Moribund, fatal process progressing rapidly	10	Completely disabled, not even passive play

APPENDIX B

Clinical Symptomatology and Adverse Experience Grading Scale

- Mild: Awareness of symptom, but, easily tolerated. Usually transient requiring no special treatment; does not interfere with usual status or activities
- Moderate: May be ameliorated by simple therapeutic measures; may interfere with usual activities
- Severe: Incapacitating; unable to perform usual activities
- Life-threatening: Requires immediate intervention; need for emergency treatment

APPENDIX C
Clinical Adverse Experiences: Determining Relationship to Test Drug

Unrelated

This category applies to those adverse experiences which, after careful medical consideration, are clearly felt to be due to extraneous causes (disease, environment, etc.) that are unrelated to the administration of test drug.

Remote (must have first two)

This category applies to those adverse experiences which, after careful medical consideration, are felt unlikely to be related to the administration of the test drug. The relationship of an adverse experience to the test drug can be considered remote if:

- It does not follow a reasonable temporal sequence from administration of the drug.
- It could readily have been a result of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- It does not follow a known response pattern to the suspected drug.
- It does not reappear or worsen when the drug is readministered.

Possible (must have first two)

This category applies to those adverse experiences which, after careful medical consideration, are felt unlikely to be related to the administration of the test drug, but the possibility cannot be ruled out with certainty. The relationship of an adverse experience to the test drug can be considered possible if:

- It follows a reasonable temporal sequence from administration of the drug.
- It could readily have been a result of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- It follows a known response pattern to the suspected drug.

Probable (must have first three)

This category applies to those adverse experiences which, after careful medical consideration, are felt with a high degree of certainty to be related to the administration of

the test. The relationship of an adverse experience to the test drug can be considered probable if:

- It follows a reasonable temporal sequence from administration of the drug.
- It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- It disappears or decreases upon cessation of drug or reduction in dose*.
- It follows a known response pattern to the suspected drug.

Related (must have first three)

This category applies to those adverse experiences, which, after careful medical consideration, are felt to be related to the administration of the test. The relationship of an adverse experience to the test drug can be considered related if:

- It follows a reasonable temporal sequence from administration of the drug or drug levels have been established in body fluids or tissues.
- It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- It disappears or decreases upon cessation of drug or reduction on dose and appears upon rechallenge*.
- It follows a known response pattern to the suspected drug.

*There are exceptions when an adverse experience does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists; *e.g.*, 1) tardive dyskinesia, 2) fixed drug eruptions.