# CLINICAL PROTOCOL

<table>
<thead>
<tr>
<th>Title:</th>
<th>A PHASE 2 EVALUATION OF TRC105 IN THE TREATMENT OF RECURRENT OR PROGRESSIVE GLIOBLASTOMA AFTER PRIOR ANTIANGIOGENIC THERAPY (INCLUDING ANTI-VEGF THERAPY)</th>
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</thead>
<tbody>
<tr>
<td>Protocol Number:</td>
<td>105GM201/Case1312</td>
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</tbody>
</table>
| Study Sponsor: | Cleveland Clinic  
9500 Euclid Avenue  
Cleveland, OH 44195  
Phone: (216) 636-0007 |
| Secondary Study Sponsor: | TRACON Pharmaceuticals, Inc.  
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| Signature & Date: | Signed: [Signature]  
Dated: 5/03/12 |
| Version Date: | Original version: January 26, 2012  
Amendment #1: May 22, 2012 |
1. **SYNOPSIS**

<table>
<thead>
<tr>
<th><strong>Name of Sponsor/Company:</strong></th>
<th>TRACON Pharmaceuticals, Inc.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name of Investigational Product:</strong></td>
<td>TRC105</td>
</tr>
<tr>
<td><strong>Name of Active Ingredient:</strong></td>
<td>TRC105</td>
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<tr>
<td><strong>Title of Study:</strong></td>
<td>A PHASE 2 EVALUATION OF TRC105 IN THE TREATMENT OF RECURRENT OR PROGRESSIVE GLIOBLASTOMA AFTER PRIOR ANTIANGIOGENIC THERAPY (INCLUDING ANTI-VEGF THERAPY)</td>
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<tr>
<td><strong>Study Centers:</strong></td>
<td>Cleveland Clinic (The study will be conducted at the main campus) and Case Western University.</td>
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<tr>
<td><strong>Principal Investigator:</strong></td>
<td>Manmeet S. Ahluwalia, MD</td>
</tr>
<tr>
<td><strong>Studied period (years):</strong></td>
<td>Date first patient enrolled: May 2012</td>
</tr>
<tr>
<td></td>
<td>Estimated date endpoint obtained: October 2012</td>
</tr>
<tr>
<td></td>
<td>Estimated date last patient completed: February 2013</td>
</tr>
<tr>
<td><strong>Phase of development:</strong></td>
<td>2</td>
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**Rationale:**

Angiogenesis plays a central role in the progression of solid cancer. TRC105 is an antibody to CD105, an important non-VEGF angiogenic target on vascular endothelial cells. TRC105 inhibits angiogenesis, tumor growth and metastases in preclinical models. In a phase 1 study of advanced solid tumors, TRC105 therapy caused a global reduction in angiogenic biomarkers and reduced tumor burden at doses that were well-tolerated. We hypothesize that TRC105 will have single-agent activity in glioblastoma (GBM). By targeting a non-VEGF pathway, TRC105 has the potential to complement VEGF inhibitors which could represent a major advance in GBM therapy.

**Objectives:**

**Primary:**

- Determine median time to progression in patients with recurrent or progressive GBM who have progressed on anti-angiogenic therapy (including anti-VEGF therapy).

**Secondary:**
• Assess safety and tolerability of TRC105 by CTCAE version 4.0.
• Determine objective response rate (ORR) by modified RANO criteria.
• Determine the rate of progression free survival at 6 months (PFS-6).
• Determine median overall survival (OS).
• Explore associations between clinical outcome and VEGF-A, VEGF-C, VEGF-D, PlGF, PDGF-AA, PDGF-BB, HGF, ANG-2, IGFBP-1, IGFBP-3, PEDF, sVEGF-R1, sVEGF-R2, sTie-2, MMP2, MMP9, TGF-β1, TGF-β2, osteopontin, TSP-1, TSP-2, TGF-β R3, tissue factor, PAI-1, CRP, d-dimer, von Willebrand factor, Gro-α, P-selectin, E-selectin, ICAM-1, VCAM-1, MCP-1, E-cadherin, sCD105, SDF-1α, II-6, IL-8 and FGF at baseline, during treatment, and time of progression.

Methodology:

This is an open label single arm phase 2 trial. TRC105 will be administered at a dose of 10 mg/kg weekly on days 1, 8, 15 and 22 of each 28-day cycle.

Number of Patients:

Approximately 14 patients with recurrent GBM will be enrolled. An additional 3 patients may be enrolled to replace ineligible patients or patients who withdraw consent prior to receiving study treatment. Approximately 125-150 patients with recurrent GBM are seen each year at Cleveland Clinic and Case Western University. It is estimated that 2-3 patients will be enrolled per month and that the study will complete enrollment over a 6-12 month time frame.

Eligibility Criteria:

Inclusion criteria:

1. Patients with histologically confirmed glioblastoma or other grade IV malignant glioma (i.e. gliosarcoma, small cell glioblastoma, etc.), recurrent after prior external-beam fractionated radiotherapy and temozolomide chemotherapy.
2. Patients who have received prior anti-angiogenic therapy for treatment of malignant glioma (e.g. bevacizumab, cediranib, cilengitide, etc.).
3. Patients with any number of recurrences are allowed.
4. Karnofsky performance status ≥ 60%.
5. Age ≥ 18 years old.
6. Patients must have the following laboratory values:
   • Absolute neutrophil count (ANC) ≥ 1.5 x 10⁹/L
   • Platelets ≥ 100 x 10⁹/L
   • Hemoglobin (Hgb) > 9 g/dL
   • Serum total bilirubin: ≤ 1.5 x ULN
   • ALT and AST ≤ 3.0 x ULN
   • Serum creatinine ≤ 1.5 x ULN
   • Blood coagulation parameters: INR ≤ 1.5
7. Minimum interval since completion of radiation treatment is 12 weeks
8. Minimum interval since last drug therapy:
• 3 weeks since last non-cytotoxic therapy
• 3 weeks must have elapsed since the completion of a non-nitrosourea-containing chemotherapy regimen
• 6 weeks since the completion of a nitrosourea-containing chemotherapy regimen.

9. Patients must have signed an approved informed consent and authorization permitting release of personal health information.

10. Patients with the potential for pregnancy or impregnating their partner must agree to follow acceptable birth control methods to avoid conception. The anti-proliferative activity of this experimental drug may be harmful to the developing fetus or nursing infant. Female patients of child-bearing potential must have a negative pregnancy test.

11. Patients must have no concurrent malignancy except curatively treated basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix and breast, adequately treated stage I or II cancer from which the patient is in complete remission. Patients with other prior malignancies must be disease-free for ≥ three years.

12. Patients must be maintained on a stable or decreasing corticosteroid regimen from the time of their baseline scan until the start of treatment and/or for at least 5 days before starting treatment.

13. Patients must have a Mini Mental State Exam score ≥ 15.

Exclusion criteria:

1. Patients who have had previous treatment with TRC105.

2. Patients who have undergone major surgery (e.g. intra-thoracic, intra-abdominal or intra-pelvic), open biopsy or significant traumatic injury ≤ 4 weeks prior to starting study drug, or patients who have had minor procedures, percutaneous biopsies or placement of vascular access device ≤ 1 week prior to starting study drug, or who have not recovered from side effects of such procedure or injury.

3. Patients with impaired cardiac function or clinically significant cardiac diseases, including any of the following:
   • History or presence of serious uncontrolled ventricular arrhythmias
   • Clinically significant resting bradycardia
   • Any of the following within 6 months prior to starting study drug: myocardial infarction (MI), severe/unstable angina, Coronary Artery Bypass Graft (CABG), Congestive Heart Failure (CHF), Cerebrovascular Accident (CVA), Transient Ischemic Attack (TIA), Pulmonary Embolism (PE)
   • Uncontrolled hypertension (defined by a SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg while on anti-hypertensive medications)

4. Patients with cirrhosis, or active viral or nonviral hepatitis.

5. Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory)

6. Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. active or uncontrolled infection, uncontrolled diabetes) that could cause unacceptable safety risks or compromise compliance with the protocol.

7. Pregnant or breast-feeding women

8. Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human, chimeric, or humanized antibodies.
9. Patients with active bleeding or pathologic conditions that carry a high risk of bleeding, (i.e. hereditary hemorrhagic telangiectasia).
10. Patients who are currently receiving anticoagulation treatment
11. Patients unwilling or unable to comply with the protocol

**TRC105 Dose and Route of Administration:**

Following the appropriate premedication regimen, TRC105 is to be administered intravenously at a dose of 10 mg/kg over 1 to 4 hours on days 1, 8, 15 and 22 of each 28 day cycle.

**Duration of Treatment:**

Patients are eligible for treatment with TRC105 until disease progression or unacceptable toxicity. A patient should be withdrawn from study treatment if, in the opinion of the Investigator, it is medically necessary, or if it is the wish of the patient. In addition, patients will be withdrawn from treatment in the case of:

1. Modified RANO criteria defined disease progression. In cases where RECIST cannot be applied, progression should be based on unequivocal evidence of progressive disease sufficient to require a change in therapy.
2. A need for surgery, radiation, or for other anticancer therapy not specified in the protocol.
3. Lost to follow-up or noncompliant.
4. Any TRC105 dose delay > 6 weeks.
5. Pregnancy. Pregnant patients should be followed for the duration of the pregnancy and the outcome of the pregnancy should be documented.
6. Arterial thrombosis of any grade (including cerebrovascular ischemia, cardiac ischemia/infarction, or peripheral or visceral arterial ischemia) or grade 3 or 4 venous thrombosis (including pulmonary embolism).

**Parameters to be Assessed:**

**Safety:**

Safety assessments will include physical exams, performance status, laboratory results (complete blood counts and serum chemistry) and 12-lead ECG’s (in patients who develop arrhythmia), and additional studies as clinically indicated. A formally chartered in-house TRACON Safety Review Team will review safety data. In addition, recurring teleconferences will be held with Investigators at all clinical sites.

**Pharmacokinetics:**

Serum TRC105 concentrations will be measured using validated methods at time points specified in the schedule of events.

**Immunogenicity:**

Serum TRC105 concentrations will be measured using validated methods at time points specified in the schedule of events.

**Exploratory Biomarkers:**
Serum concentrations of a panel of angiogenic protein biomarkers will be measured at baseline, during treatment, and at the time of progression to explore TRC105 pharmacodynamics.

**Efficacy:**

Modified RANO criteria will be applied to assess response and progression.

**Funding, Regulatory, and Feasibility Issues:**

TRC105 study drug will be provided by TRACON. Up to 17 patients will be enrolled for a total of 14 evaluable patients. Every year 125-150 patients with recurrent GBM are seen at Cleveland Clinic and at Case Western Reserve University. Approximately 2-3 patients per month will be entered onto the study and accrual will be completed in 6-12 months. All patients will be followed until progression.

**Patient Acceptability/Ethics and Consent Issues:**

There are no effective therapies for patients with recurrent GBM that progress on antiangiogenic therapy. TRC105 has shown early evidence of clinical activity in patients with other cancers that have progressed on antiangiogenic therapy and therefore deserves study in patients with refractory GBM.
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<th>Explanation</th>
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<td>ADCC</td>
<td>Antibody-Dependent Cell-mediated Cytotoxicity</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AFP</td>
<td>Alpha Fetoprotein</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immunodeficiency Syndrome</td>
</tr>
<tr>
<td>ALKs</td>
<td>Activin receptor-Like Kinases</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine Aminotransferase</td>
</tr>
<tr>
<td>ANC</td>
<td>Absolute Neutrophil Count</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate Aminotransferase</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
</tr>
<tr>
<td>AUC_last</td>
<td>Time of Last Measurable Concentration of Area Under the Curve</td>
</tr>
<tr>
<td>BALB/c mice</td>
<td>Mouse Strain</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood Urea Nitrogen</td>
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<tr>
<td>CA-125</td>
<td>Cancer Antigen-125</td>
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<tr>
<td>CABG</td>
<td>Coronary Artery Bypass Graft</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete Blood Count</td>
</tr>
<tr>
<td>CEA</td>
<td>Carcinoembryonic Antigen</td>
</tr>
<tr>
<td>CHOP</td>
<td>Cyclophosphamide Hydroxydaunomycin Oncovin® Prednisone</td>
</tr>
<tr>
<td>CL</td>
<td>Clearance</td>
</tr>
<tr>
<td>(C_{\text{max}})</td>
<td>Maximum Serum Concentration</td>
</tr>
<tr>
<td>CPA</td>
<td>Cyclophosphamide</td>
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<tr>
<td>CR</td>
<td>Complete Response</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>CTC</td>
<td>Common Terminology Criteria</td>
</tr>
<tr>
<td>dL</td>
<td>Deciliter</td>
</tr>
<tr>
<td>DLT</td>
<td>Dose Limiting Toxicity</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep Vein Thrombosis</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ECM</td>
<td>Extracellular Matrix</td>
</tr>
<tr>
<td>EGFR</td>
<td>Epidermal Growth Factor Receptor</td>
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<tr>
<td>ELISA</td>
<td>Enzyme-Linked ImmunoSorbent Assay</td>
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<tr>
<td>EOS</td>
<td>End of Study</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>g</td>
<td>Gram</td>
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<tr>
<td>GOG</td>
<td>Gynecologic Oncology Group</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>HACA</td>
<td>Human Anti-Chimeric Antibodies</td>
</tr>
<tr>
<td>HAMA</td>
<td>Human Anti-Murine Antibodies</td>
</tr>
<tr>
<td>Her-2</td>
<td>Human epidermal growth factor receptor 2</td>
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<tr>
<td>HHT-1</td>
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<tr>
<td>HIF-1-α</td>
<td>Hypoxia-Inducible Factor-1-α</td>
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<td>HIPAA</td>
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<tr>
<td>HIV</td>
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</tr>
<tr>
<td>HRA</td>
<td>Health Regulatory Authority</td>
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<tr>
<td>Abbreviation or specialist term</td>
<td>Explanation</td>
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<td>--------------------------------</td>
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</tr>
<tr>
<td>HUVECs</td>
<td>Human Umbilical Vein Endothelial Cells</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>ID</td>
<td>Identification</td>
</tr>
<tr>
<td>IEC</td>
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<tr>
<td>IgG</td>
<td>Immunoglobulin G</td>
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<tr>
<td>IgM</td>
<td>Immunoglobulin M</td>
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<tr>
<td>INR</td>
<td>International Normalized Ratio</td>
</tr>
<tr>
<td>IP</td>
<td>Intraperitoneal</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>i.v.</td>
<td>Intravenous</td>
</tr>
<tr>
<td>$K_d$</td>
<td>Avidity Binding Constant</td>
</tr>
<tr>
<td>kg</td>
<td>Kilogram</td>
</tr>
<tr>
<td>L</td>
<td>Liter</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate Dehydrogenase</td>
</tr>
<tr>
<td>LOQ</td>
<td>Limit of Quantification</td>
</tr>
<tr>
<td>$\mu$L</td>
<td>Microliter</td>
</tr>
<tr>
<td>Mg</td>
<td>Milligram</td>
</tr>
<tr>
<td>mL</td>
<td>Milliliter</td>
</tr>
<tr>
<td>MACA</td>
<td>Monkey Anti-Chimeric Antibody</td>
</tr>
<tr>
<td>MAMA</td>
<td>Monkey Anti-Murine Antibody</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td>mm</td>
<td>Millimeter</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MTD</td>
<td>Maximum Tolerated Dose</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>NCIC</td>
<td>National Cancer Institute of Canada</td>
</tr>
<tr>
<td>ng</td>
<td>Nanogram</td>
</tr>
<tr>
<td>NHP</td>
<td>Nonhuman Primate</td>
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<tr>
<td>NOAEL</td>
<td>No Adverse Effect Level</td>
</tr>
<tr>
<td>PBS</td>
<td>Phosphate-Buffered Saline</td>
</tr>
<tr>
<td>PD</td>
<td>Progressive Disease</td>
</tr>
<tr>
<td>PDGF</td>
<td>Platelet Derived Growth Factor</td>
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<tr>
<td>PlGF</td>
<td>Placental Growth Factor</td>
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<td>Picomolar</td>
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<td>Partial Response</td>
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<td>Percutaneous Transluminal Coronary Angioplasty</td>
</tr>
<tr>
<td>PTT</td>
<td>Partial Thromboplastin Time</td>
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<td>Response Evaluation Criteria in Solid Tumors</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>sCD105</td>
<td>Soluble CD105/endoglin</td>
</tr>
<tr>
<td>SCID</td>
<td>Severe Combined Immunodeficient</td>
</tr>
<tr>
<td>SD</td>
<td>Stable Disease</td>
</tr>
<tr>
<td>SGOT</td>
<td>Serum Glutamic Oxaloacetic Transaminase</td>
</tr>
<tr>
<td>SGPT</td>
<td>Serum Glutamic Pyruvic Transaminase</td>
</tr>
<tr>
<td>Abbreviation or specialist term</td>
<td>Explanation</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>SN6j</td>
<td>Murine parent antibody of TRC105</td>
</tr>
<tr>
<td>sVEGFR2</td>
<td>Soluble VEGF Receptor 2</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Transforming Growth Factor</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid Stimulating Hormone</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper Limit of Normal</td>
</tr>
<tr>
<td>US</td>
<td>United States of America</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular Endothelial Growth Factor</td>
</tr>
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</table>
3. INTRODUCTION

3.1. Background

3.1.1. Glioblastoma Multiforme

Up until the early 2000's, the standard of care for glioblastoma (GBM) was surgical resection followed by radiation therapy. In 2005, Stupp et al. demonstrated that by adding temozolomide during and after radiation therapy, the median survival of patients with GBM improved from 12.1 months to 14.6 months [1]. Furthermore, chemoradiation with temozolomide increased the two-year survival rate from 10.4 to 26.5%. As a result, temozolomide with radiation became the standard of care for the treatment of GBM. Despite this significant improvement, nearly all patients with GBM recur with a median time to progression of approximately 6 months [1]. Treatment options for recurrent GBM include re-resection, BCNU wafer implantation, stereotactic radiosurgery, and/or systemic therapy; all of which show modest activity at best.

3.1.2. Angiogenesis and Cancer

Angiogenesis is required for the survival and growth of solid cancers [2, 3]. It is generally accepted that solid cancers have two phases, an avascular phase and a vascular phase [3]. During the initial avascular phase, tumors exist as small aggregates of malignant cells supported by simple diffusion of oxygen and nutrients. The progressive growth of solid cancers beyond clinically occult sizes requires the continuous formation of new blood vessels, a process known as tumor angiogenesis. Tumor growth and metastasis require angiogenesis. Therefore, inhibition of tumor angiogenesis and selective inhibition of the tumor vasculature represent potentially effective strategies for the prevention and treatment of solid cancers.

Therapies directed against targets implicated in the development of tumor angiogenesis are attractive for many reasons. First, except for female reproduction and wound healing, angiogenesis in adults is generally part of a pathologic process such as tumor growth or choroidal neovascularization. Second, treatments that interrupt tumor angiogenesis should apply broadly to all solid cancers. Third, angiogenic targets are present in the plasma or on endothelial cells themselves. These targets are readily accessible to antibody treatments, in contrast to targets expressed within tumors that are more difficult for antibodies to access. Fourth, angiogenic targets on vascular endothelial cells are less prone to genetic mutation than targets expressed by genetically unstable cancer cells. As a result, development of resistance may be more predictable for agents that target endothelial cell functions than for those targeting cancer cells.

Indeed, agents that target pathways required for tumor angiogenesis have an important role in the therapy of cancer patients. The monoclonal antibody bevacizumab, which binds to the angiogenic cytokine VEGF, significantly prolongs overall survival for patients with advanced colorectal cancer or non-small cell lung cancer when added to standard chemotherapy regimens [4, 5]. Bevacizumab is also effective therapy for renal cell cancer, breast cancer and malignant glioma [6-8]. Orally available small molecule VEGF inhibitors include sunitinib, sorafenib,
pazopanib and axitinib, all of which have been shown to prolong survival in patients with metastatic renal cell cancer and/or hepatocellular cancer [8-11].

### 3.1.2.1. Angiogenesis and Glioblastoma

Antiangiogenic strategies are of interest in treating GBM due to the highly vascular nature of these tumors. Preclinical data have demonstrated the dependence of glioma growth on generation of tumor-associated blood vessels [12, 13]. The malignant cells of GBM express high levels of vascular endothelial growth factor (VEGF) in situ, and inhibition of VEGF signaling delays the growth of glioma xenografts in immunodeficient mice [14]. Bevacizumab is a humanized monoclonal antibody that targets VEGF and has clinical activity in a number of human tumors, including colorectal cancer and non–small-cell lung cancer [5, 15]. Bevacizumab has limited single-agent activity in these cancer types and is generally given in combination with cytotoxic agents. The FDA recently approved bevacizumab in patients with recurrent GBM based on single-agent response rates of 19.6% and 25.9% in two clinical trials [16]. While bevacizumab has activity in recurrent GBM, patients still uniformly develop progressive disease. In addition, patients who progress after bevacizumab have dismal outcome, median progression-free survival in these patients is 1-1.5 months [17]; thus, there still remains a great need for more effective agents. We hypothesize that anti-angiogenic approaches directed against non-VEGF endothelial targets will inhibit angiogenesis, even after the GBM has developed resistance to therapies directed against VEGF and its receptors.

### 3.1.3. CD105 and Angiogenesis

CD105 (endoglin) is a homodimeric cell membrane glycoprotein that was initially identified as a human leukemia-associated antigen [18] and later also found on endothelial cells [19, 20]. The expression of CD105 is relatively restricted in adult humans, and high levels of membrane CD105 in adult humans is limited to proliferating endothelial cells and red blood cell precursors known as proerythroblasts [21]. CD105 is a TGF-β coreceptor that is essential for angiogenesis [22, 23] and CD105 is strongly expressed on the proliferating vascular endothelium of solid tumors [24, 25]. All of these properties make CD105 an attractive target for the antiangiogenic therapy of cancer [26].

Vascular targeted therapy may more effectively address large established tumors than conventional antiangiogenic therapies that target receptor ligands such as anti-VEGF therapy [27]. In animal models, CD105 targeted therapy has demonstrated both vascular targeting effects and antiangiogenic effects, as it induces regression of established tumors, prevents new tumor formation, and inhibits the expansion of existing tumors [25, 28-31]. Therefore, CD105 is a novel alternative target relative to currently available angiogenesis inhibitors, all of which target the VEGF pathway.

CD105 alters downstream signaling of multiple kinase receptor complexes of the TGF-β superfamily, including TGF-β receptors, activin receptor-like kinases (ALKs) and activin receptors [32]. In the absence of CD105, activation of TGF-β receptors results in phosphorylation of SMAD proteins that inhibit endothelial cell growth. In the presence of CD105, activation of TGF-β receptors results in phosphorylation of SMAD proteins that promote endothelial cell growth. Moreover, anti-CD105 antibody therapy acts synergistically with TGF-β to inhibit endothelial cell proliferation and angiogenesis [33].
CD105 expression is required for endothelial cell proliferation, and CD105 is upregulated in the setting of hypoxia through the induction of hypoxia-inducible factor-1-α (HIF-1-α) [34]. CD105 has also been shown to protect hypoxic cells from apoptosis [35]. Targeted inactivation (knockout) of murine CD105 results in defective vascular development. Mice lacking CD105 die in utero from defective vascular development by gestational day 11 [23].

CD105 is critical for normal human blood vessel development [36]. CD105 haplotype insufficiency causes a well-described syndrome known as hereditary hemorrhagic telangiectasia type 1 (HHT-1 or Rendu-Osler-Weber Syndrome). HHT-1 is a rare autosomal dominant genetic disorder characterized by localized angiodysplasia involving the nasal, buccal, gastrointestinal mucosa and skin microvasculature. Angiodysplasia also occurs in vessels from internal organs including the lungs, liver and brain [37]. The genotype is manifested in utero, but the phenotype does not become apparent for many years following birth. Affected patients commonly present with epistaxis in the second decade of life. The phenotype of this disorder is limited to vascular effects, indicating the specific role of CD105 in the vasculature [38].

CD105 is highly expressed on the proliferating endothelial cells of tumor vessels including brain, lung, breast, colorectal, gastric, liver, endometrial, renal cell, head and neck, and ovarian cancers. In adults, CD105 expression is limited to vascular endothelial cells and proerythroblasts, a red blood cell precursor [21].

Importantly, CD105 expression is upregulated in tumor endothelial cells following inhibition of the VEGF pathway. CD105 expression increased more than 2-fold in human pancreatic cancers grown in mice treated with an antibody that binds VEGF [39]. As well, treatment of human bladder cancers grown in mice with an antibody that blocks activation of the VEGF receptor increased CD105 expression within the core tumor vasculature [40].

CD105 expression is a prognostic factor in solid tumor patients. In studies from the United States and Europe, high CD105 microvessel density was shown to be an independent marker for worse survival in patients with malignant glioma [41]. In addition, high microvessel density by CD105 has been correlated with poor prognosis in clinical studies of breast cancer [42, 43], ovarian cancer [44, 45], lung cancer [46], prostate cancer [47, 48], colorectal cancer [49, 50], gastric cancer [51], endometrial cancer [52], hepatocellular carcinoma [52, 53], esophageal adenocarcinoma [54], and head and neck cancer [55, 56].

Plasma CD105 levels measured by sandwich ELISA are prognostic in retrospective studies of cancer patients. In one study, the mean plasma CD105 concentration in 76 patients with colorectal cancer was 4-fold higher than the mean value in 40 healthy subjects without cancer [49]. In the study, a positive correlation was observed between CD105 concentration and stage of disease. In another study, the mean sCD105 concentration in 59 patients with advanced metastatic solid cancer was 63.8 ng/mL versus 41.0 ng/mL in cancer patients without metastases, and 28.3 ng/mL in patients without a cancer diagnosis [57]. In a study of breast cancer patients receiving hormonal therapy, the upper limit of normal for soluble CD105 was determined to be 8.70 ng/mL, and patients with elevated CD105 had shorter overall survival than those who did not [43].
3.1.4. **TRC105 Background**

TRC105 is a genetically engineered human/murine chimeric monoclonal antibody directed against human CD105 [58], a growth proliferation receptor found on the surface of normal and proliferating endothelial cells [25, 28, 59].

The antibody is an IgG1 kappa immunoglobulin containing murine variable region sequences and human constant region sequences [58]. TRC105 has an approximate molecular weight of 148 kDa. TRC105 has a binding avidity for human CD105 of approximately 5 pM. TRC105 is formulated as a phosphate-buffered saline (PBS) solution at a concentration of 5 mg/mL or 7 mg/mL.

SN6j, the murine parent antibody of TRC105, binds to human umbilical vein endothelial cells (HUVECs) with nearly identical avidity as TRC105. SN6j has been shown to bind the tumor vasculature of malignant tissues including breast, colon, rectum, kidney and lung cancers. Reactivity with tumor tissues is restricted to the tumor endothelium, as CD105 is not generally expressed on tumor cells [28]. TRC105 induces ADCC on proliferating HUVECs at low concentrations and induces apoptosis and growth inhibition at higher concentrations.

Of note, TRC105 enhanced the antiangiogenic effect of bevacizumab *in vitro* using two HUVEC-based models of human angiogenesis. Both TRC105 and bevacizumab have single-agent activity in these models, and the combination achieved near complete inhibition. In one model, TRC105 enhanced the activity of bevacizumab to inhibit VEGF-induced HUVEC sprout formation (Figure 1). In a related model, TRC105 and bevacizumab worked synergistically to inhibit HUVEC tubular network formation *in vitro*. These findings add evidence to support the combination of TRC105 and bevacizumab as a way to enhance efficacy.
3.1.4.1. Phase 1 Monotherapy Study Design for Solid Cancers

Several studies with TRC105 are underway or have completed. An open-label, phase 1, multicenter study of TRC105 (Study 105ST101) is complete. Fifty patients were treated until disease progression with TRC105 at 0.01-15 mg/kg/q2wk or 10-15 mg/kg/wk. Ongoing studies include a phase 1b study of TRC105 in combination with bevacizumab, a phase 1b study of TRC105 in combination with capecitabine, a phase 1b study of TRC105 in combination with sorafenib and phase 2 monotherapy studies in ovarian, bladder, prostate and liver cancer.

3.1.4.1.1. Phase 1 Pharmacokinetics

In Study 105ST101, TRC105 pharmacokinetics were assessed on patients enrolled at doses up to 15 mg/kg weekly. Circulating TRC105 was not measurable above the lower limit of quantitation of the assay (78 ng/mL) in patients receiving doses below 0.3 mg/kg. TRC105 was measurable above the target concentration based on preclinical data (200 ng/mL) for 4 hours at 0.3 mg/kg, 1 day at 1 mg/kg, 5 days at 3 mg/kg, and 7 days at 10 mg/kg TRC105 dosed every two weeks. Serum concentrations expected to saturate CD105 binding sites (≥ 200 ng/mL) were achieved continuously at 15 mg/kg q2wk and 10 mg/kg weekly, and TRC105 accumulated at 15 mg/kg weekly (Figure 2).
3.1.4.1.2. Phase 1 Immunogenicity

In Study 105ST101, serum samples for evaluation of TRC105 immunogenicity, including HAMA and HACA, were collected predose on day 1 of each 28 day cycle, at the end of study, and then at 4 and 12 weeks after the end of study visit.

HAMA and HACA data are available from the phase 1 monotherapy TRC105 trial. Neither HAMA nor HACA were detected in patients treated with CHO-produced TRC105, which will be used for all future clinical trials, including this study.

3.1.4.1.3. Phase 1 Safety

A total of 50 patients were treated on Study 105ST101 with escalating doses of TRC105 at 0.01, 0.03, 0.1, 0.3, 1, 3, 10 and 15 mg/kg every two weeks and then 10 and 15 mg/kg weekly. Infusion reactions, anemia, fatigue, epistaxis and headache were the most frequently observed adverse events considered related to TRC105, as summarized in Table 2 below.

Table 2: 105ST101 Phase 1 Frequency of Adverse Events (N=50)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Frequency (%)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion Reaction</td>
<td>18%</td>
<td>Nine of 50 patients experienced infusion reactions. The majority were grade 2; three of the infusion reactions were grade 3. None of the grade 3 infusion reactions occurred in patients receiving the prescribed pre-medication regimen. One patient participating in an ongoing study who received the required pre-medication regimen developed grade 4 vasovagal syncope. He recovered after i.v. fluids and oxygen. Infusion reactions generally consisted of one or more of the following: pyrexia, rigors, change in blood pressure, change in heart rate, irregular heart rate, dyspnea, or urticaria. The frequency and severity of infusion reactions were reduced by extending the duration of the first infusion from one to four hours and requiring premedications (including dexamethasone) prior to the TRC105 infusion.</td>
</tr>
</tbody>
</table>
Anemia

One of three patients at 15 mg/kg every 2 weeks developed grade 3 anemia; one of three patients at 10 mg/kg weekly developed grade 2 anemia (this patient had grade 2 anemia prior to starting study therapy). Three of three patients at 15 mg/kg weekly (above the MTD) developed dose-limiting grade 3 anemia and required blood transfusions by cycle 2. One of the patients at 15 mg/kg weekly progressed to grade 4 anemia in cycle 3 and recovered when TRC105 was discontinued.

Laboratory and clinical evaluations suggest that the anemia does not appear to be caused by blood loss, hemolysis, plasma volume expansion, iron deficiency, B-12/folate deficiency, or low erythropoietin levels. The anemia is associated with TRC105 accumulation in blood and is believed to result from TRC105 binding to and inhibiting proerythroblasts which are red blood cell precursor in the marrow known to express CD105.

Fatigue

14% Grade 1 & grade 2

Epistaxis

10% Grade 1 & grade 2 at the higher dose levels. The bleeding was not enough to explain the degree of anemia.

Headache

10% Grade 1 & grade 2

Telangiectasia

6% Grade 1

Constipation

4% Grade 1 & grade 2

Diarrhea

4% Grade 1

Pyrexia

4% Grade 1

Flushing

4% Grade 1

Nausea

4% Grade 1

Vomiting

4% Grade 1

Telangiectasia

6% Grade 1

Constipation

4% Grade 1 & grade 2

Diarrhea

4% Grade 1

Pyrexia

4% Grade 1

Flushing

4% Grade 1

Nausea

4% Grade 1

Vomiting

4% Grade 1

Telangiectasia

6% Grade 1

Constipation

4% Grade 1 & grade 2

Diarrhea

4% Grade 1

Pyrexia

4% Grade 1

Flushing

4% Grade 1

Nausea

4% Grade 1

Vomiting

4% Grade 1

Gastrointestinal hemorrhage

2% One patient with peptic ulcer disease was enrolled at 0.1 mg/kg every 2 weeks developed grade 4 hemorrhage from a gastric ulcer 4 days after the first dose of TRC105. He was transfused two units of packed red blood cells and the bleeding resolved with nonsurgical management by the time of upper endoscopy. No other serious bleeding has been observed.

Gingival bleeding

2% Grade 1

Infusion reactions experienced on Study 105ST101 are summarized in Table 3. The risk of infusion reactions was reduced with a dexamethasone premedication regimen was instituted at higher doses.

Table 3: 105ST101 Phase 1 Summary of Infusion Reactions (N=50)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Study Day</th>
<th>Premedication</th>
<th>Grade</th>
<th>Subsequent Infusion Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg/kg q2 wks (NS0-produced TRC105)</td>
<td>C1D1</td>
<td>No</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>1 mg/kg q2 wks (NS0-produced TRC105)</td>
<td>C1D15</td>
<td>No</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>0.3 mg/kg q2 wks (CHO-produced TRC105)</td>
<td>C1D1</td>
<td>No</td>
<td>2</td>
<td>No</td>
</tr>
</tbody>
</table>
Adverse events considered possibly related to TRC105 from the Phase 1 first-in-human study are listed in the table below. These events have been limited to grade 1 or 2, with the exception of one grade 4 gastrointestinal hemorrhage, three grade 3 infusion reactions, and grade 3/4 anemia.

Table 4: 105ST101 Phase 1 Possibly Related Adverse Events (N=50)

<table>
<thead>
<tr>
<th>TRC105 Dose</th>
<th>Preferred Term</th>
<th>Gr 1</th>
<th>Gr 2</th>
<th>Gr 3</th>
<th>Gr 4</th>
<th>Gr 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01 mg/kg q2 weeks (NS0, n=3)</td>
<td>Vaginal hemorrhage</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.03 mg/kg q2 weeks (NS0, n=3)</td>
<td>Fatigue</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dysgeusia</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1 mg/kg q2 weeks (NS0, n=6)</td>
<td>Gi hemorrhage</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proteinuria</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flushing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>0.3 mg/kg q2 weeks (NS0, n=3)</td>
<td>Diarrhea</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>1 mg/kg q2 weeks (NS0, n=6)</td>
<td>Infusion related reaction</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperuricemia</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td></td>
<td></td>
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<tr>
<td>0.3 mg/kg q2 weeks (CHO, n=6)</td>
<td>Infusion related reaction</td>
<td>2</td>
<td>1</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>TRC105 Dose</td>
<td>Preferred Term</td>
<td>Gr 1</td>
<td>Gr 2</td>
<td>Gr 3</td>
<td>Gr 4</td>
<td>Gr 5</td>
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<tr>
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<tr>
<td>1 mg/kg q2 weeks (CHO, n=6)</td>
<td>Headache</td>
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<tr>
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<td>Blood bilirubin increased</td>
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<tr>
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<td>Constipation</td>
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<tr>
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<td>Micturition urgency</td>
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<td>3 mg/kg q2 weeks (CHO, n=3)</td>
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<td>Cough</td>
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<tr>
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<td>Fatigue</td>
<td></td>
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</tr>
<tr>
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<td>Vision blurred</td>
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<tr>
<td>10 mg/kg q2 weeks (CHO, n=3)</td>
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<tr>
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<td>Headache</td>
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<td>Pyrexia</td>
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<td>Bone pain</td>
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<tr>
<td>10 mg/kg q1 week (CHO, n=3)</td>
<td>Anemia</td>
<td></td>
<td></td>
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<td>2</td>
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<td>Dehydration</td>
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### 3.1.4.1.4. Phase 1 Efficacy

In the 105ST101 phase 1 first-in-human study, stable disease ≥ 2 months was observed in 22 of 45 patients (49%) and stable disease ≥ 4 months in 6 of 44 patients (14%). Decreases in CEA, PSA, or CA-125 were noted in 8 of 21 patients (38%) and a global decrease in key angiogenic biomarkers was observed with treatment. One patient with castrate-refractory prostate cancer remains on study after 3.75 years of treatment at a TRC105 dose of 0.01 mg/kg every 2 weeks. He had a complete PSA response, resolution of bone pain and bone scan normalization. One uterine carcinosarcoma patient remains on study at 17 months of treatment with a minor radiographic response. TRC105 treatment duration of the patient with uterine cancer has exceeded prior treatment duration with all prior therapies including a cisplatin-paclitaxel, anastrozole and ifosfamide.

### 3.1.5. Population to be Studied

The population will consist of histologically confirmed recurrent or progressive GBM (or any grade IV astrocytoma including gliosarcoma and small cell glioblastoma) whose disease progresses during antiangiogenic therapy.

### 3.1.6. Potential Risks and Benefits to Human Patients

#### 3.1.6.1. Potential Risks

**TRC105**

Gastrointestinal hemorrhage has occurred with TRC105 therapy. One patient on the 105ST101 phase 1 study with an undiagnosed gastric ulcer started TRC105 at 0.1 mg/kg every 2 weeks and experienced grade 4 hemorrhage from the ulcer requiring transfusion of two units of packed red blood cells. Following this event, the protocol was amended to exclude patients with risk factors for ulcer disease. Additional severe or life-threatening hemorrhage has not occurred. Other episodes of bleeding associated with TRC105 have been limited to grade 1 and grade 2 including superficial gingival bleeding, epistaxis, and intermittent postcoital vaginal bleeding in a patient with uterine cancer recurrent at the vaginal cuff.
Two patients on Study 105ST101 developed grade 1 cutaneous telangiectasias related to TRC105 early in the course of therapy including one at 10 mg/kg and one at 15 mg/kg weekly. Telangiectasias are also seen in patients with hereditary hemorrhagic telangiectasia (HHT), a disease of CD105 haplotype insufficiency. Patients with HHT are at risk of hemorrhage from abnormal blood vessels and this could be exacerbated by treatment with TRC105. Other contraindications to TRC105 therapy include a history of significant hemorrhage or tumors located in the central chest or another location where bleeding is associated with high morbidity. All patients treated with TRC105 should be monitored for signs of hemorrhage and the risks and benefits of drug treatment reevaluated in any patient with hemorrhage.

Infusion reactions are a known risk of therapeutic antibodies, and the risk may be highest for antibodies with an intravascular target. Infusion reactions occurred in nine patients on Study 105ST101 including six with grade 2 and three with grade 3 reactions. These events generally happened early in the course of therapy, usually with the first TRC105 dose. Two patients had a second infusion reaction after the first dose; both occurring when the infusion duration was reduced by half from the previous dose.

TRC105 infusion reactions observed in Study 105ST101 included hypertension, hypotension, dyspnea, bronchospasm, chills/rigors, chills, sweats, fever, nausea, tachycardia, bradycardia, EKG changes, flushing, urticaria, pruritus, and headache. Potential infusion reactions seen with other therapeutic antibodies include angioedema, asthenia, throat irritation, rhinitis, vomiting, joint pain, fatigue and neurologic disorders including inflammation of the spine and/or brain. Less common side effects are disease-related pain, dizziness, myalgia, peripheral edema, chest pain, and heart rhythm disturbance. The most severe reactions seen with other therapeutic antibodies, some of which were fatal, typically occurred within one to two hours of starting the first infusion.

After the second grade 3 infusion reaction on Study 105ST101, the protocol was amended to extend the duration of the initial infusion from one to four hours and require a dexamethasone-based premedication regimen prior to each dose. This amendment reduced the frequency and severity of infusion reactions and allowed dose escalation to continue. In the absence of infusion-related toxicity, subsequent infusions durations were allowed to be decreased by half down to a minimum duration of one hour. The premedication regimen was allowed to be tapered, but not concurrent with a decrease in infusion duration.

Hypersensitivity reactions with infusions are a potential risk for sensitized patients, and TRC105 should be used with caution in patients with known hypersensitivity to any component of the drug product. Host anti-TRC105 antibodies to the murine or human portions of NS0-produced TRC105 have been reported, but host antibodies to CHO-produced TRC105 have not occurred. In general, the risk of immunogenicity to therapeutic chimeric antibodies is small (<10%) and the clinical significance of immunogenicity is not well defined. The current trial will collect serial blood samples will be collected for human antichimeric antibody (HAMA) and human antichimeric antibody (HACA) concentrations to further characterize the immunogenicity of TRC105 and potential clinical implications.

Grade 3 and 4 anemia has occurred with TRC105 therapy at the higher doses, particularly with weekly dosing at 15 mg/kg, which is above the recommended phase 2 dose level and during which TRC105 concentrations gradually accumulated. One patient at 15 mg/kg weekly
developed grade 4 anemia in cycle 3, and the other two evaluable patients at this dose developed grade 3 hypoprotective anemia in cycle 2. In these patients, the reticulocyte count was relatively low for the degree of anemia, and studies performed to identify common causes of anemia were unrevealing. The most likely explanation for TRC105-associated anemia is antibody binding to proerythroblasts which are red blood cell precursors that are known to express CD105, the target of TRC105. All patients treated with TRC105 should be monitored closely for anemia and treated appropriately, including the possibility of TRC105 dose reductions. The anemia is treatable with erythropoietin or transfusion and reversible after dose-reduction (Section 7.7.1) or dose-interruption.

MRI Scans

There is a small risk for developing of Nephrogenic Systemic Sclerosis (NSS) in patients receiving gadolinium which is administered prior to the MRI. NSS generally occurs in patients with poor kidney function who will be ineligible for the study.

Venipuncture

Patients could also experience side effects from venipuncture for tests that will be done as part of this study including pain, tenderness or bruising at the site of collection, and rarely infection may occur at the spot where the needle is inserted.

Other Risks

This study treatment may involve risks to unborn children; therefore, patients should not become pregnant or father a baby while participating in this study. Patients should not nurse while on this study. Women of childbearing potential must have a negative pregnancy test before taking part in this study. Patients will be asked to practice an effective method of birth control during participation in this study and for three months after the last treatment.

Potential Benefits

TRC105 is an investigational product, and its efficacy has not been established. It is possible that the administration of TRC105 may result in clinical benefit (i.e., tumor response or prolonged stable disease).

3.1.7. Justification of the Dose, Schedule and Route of Administration of TRC105

The dose and schedule of TRC105 (10 mg/kg weekly) were selected based on safety, pharmacokinetics and early evidence of activity in the phase 1 study of TRC105 for patients with solid tumors (Study 105ST101). In phase 1, the maximum tolerated weekly dose was 10 mg/kg. Patients administered 15 mg/kg weekly experienced accumulation of TRC105 to very high levels and this was associated with grade 3 and 4 anemia. TRC105-associated anemia is believed to result from inhibition of CD105-positive red blood cell progenitors, also known as proerythroblasts. The anemia is treatable with erythropoietin or transfusion and reversible after dose-reduction (Section 7.7.1) or dose-interruption. This study will evaluate TRC105 pharmacokinetics and evaluate potential correlations with clinical outcome, including anemia.
3.1.8. Conduct

The clinical trial will be conducted in compliance with the protocol, and the applicable regulatory requirements.
4. **TRIAL OBJECTIVES AND PURPOSE**

4.1. **Primary objectives**

- Determine median time to progression in patients with recurrent or progressive GBM who have progressed on anti-angiogenic therapy (including anti-VEGF therapy).

4.2. **Secondary objectives**

- Assess safety and tolerability of TRC105 by CTCAE version 4.0.
- Determine objective response rate (ORR) by modified RANO criteria.
- Determine progression free survival at 6 months (PFS-6).
- Determine median overall survival (OS).
- Explore associations between clinical outcome and VEGF-A, VEGF-C, VEGF-D, PIGF, PDGF-AA, PDGF-BB, HGF, ANG-2, IGFBP-1, IGFBP-3, PEDF, sVEGF-R1, sVEGF-R2, sTie-2, MMP2, MMP9, TGF-β1, TGF-β2, osteopontin, TSP-1, TSP-2, TGF-β R3, tissue factor, PAI-1, CRP, d-dimer, von Willebrand factor, Gro-α, P-selectin, E-selectin, ICAM-1, VCAM-1, MCP-1, E-cadherin, sCD105, SDF-1α, IL-6, IL-8 and FGF at baseline, during treatment, and time of progression.
5. **INVESTIGATIONAL PLAN**

5.1. **Overall Study Design and Plan**

5.1.1. **Overview**

All patients must sign a consent form prior to undertaking any study-related procedures. Prospective patients will be screened to determine if they qualify for the study within 28 days of enrollment.

Patients who qualify will receive TRC105 i.v. over 1 to 4 hours on day 1, day 8, day 15 and day 22 of each 28-day cycle. Those who tolerate TRC105 without any infusion reactions may be eligible for reduced infusion durations and decreased premedication (see Section 7.7).

Toxicities will be graded according to the NCI CTCAE Version 4.0.

5.1.2. **Trial Procedures**

All on-study procedures are permitted within the time window indicated in the Schedule of Assessments (Table 5).

5.1.2.1. **Screening**

The following screening procedures must be performed within 28 days prior to the first day of study therapy. Qualifying hematology, serum chemistry, coagulation, and urinalysis collected within 7 days of cycle 1 day 1 do not need to be repeated. The following will be performed according to the Schedule of Assessments (Table 5).

- Patient signature on current Institutional Review Board (IRB) approved informed consent form. Prior to undergoing any study-specific procedure, patients must read and sign the current Institutional Review Board (IRB) approved informed consent form. Patients may sign consent prior to the 28 day screening period.
- Medical history, prior cancer therapy, prior cancer surgery, prior radiation therapy, drug allergies, disease present at screening, primary diagnosis and demographics.
- Physical examination including examination of all major body systems, performance status (KPS), and vital signs.
- Hematology, coagulation (PT or INR) and serum chemistry to be performed locally.
- Serum or urine pregnancy test for all females of childbearing potential to be performed locally.
- Urinalysis to be performed locally. Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated.
- MRI scans of Brain as clinically indicated or as per protocol.
- Single tracing 12-Lead ECG (QT, PR and QRS intervals and heart rate will be captured).
• Assessment of Baseline Emergent Adverse Events (serious and nonserious) from the date of informed consent.

• Assessment of concomitant medications from 28 days prior to the start of study treatment.

5.1.2.2. Trial Period
Qualifying hematology, blood chemistry, urinalysis, physical examination, and pregnancy test do not need to be repeated on cycle 1 day 1 if acceptable screening assessments are performed within 7 days prior to the start of study therapy. On days of dosing, all assessments should be performed prior to dosing with TRC105 unless otherwise indicated in the Schedule of Assessments. Patients will receive 2 cycles (approximately 8 weeks) of treatment. Patients who demonstrate a response of CR, PR or SD, will be eligible for additional treatment until progression. Each cycle is 4 weeks in duration. The following will be performed according to the Schedule of Assessments (Table 5).

• Physical examination including examination of all major body systems, performance status, weight and vital signs (heart rate, temperature, blood pressure, respiratory rate).
  
  o Assessment of vital signs during TRC105 infusion: Vital signs are to be assessed pre-infusion and every 30 minutes during the infusion. Vital signs should be monitored more frequently and/or beyond the completion of the infusion if medically indicated (e.g. if the patient experiences an infusion reaction that has not yet resolved).

• Hematology, coagulation (PT or INR) and serum chemistry to be performed locally.

• Urinalysis to be performed locally. Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated.

• Blood sampling for immunogenicity and PK to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).

• Blood sampling for protein biomarker analysis by a third party laboratory (see laboratory manual for specific instructions regarding collection processing, storage and shipment)

• MRI of the brain to be performed on-study as outlined in the assessment table. Assessments should be performed whenever disease progression is suspected. Allowable window for tumor imaging studies is +/- 7 days.

• Administration of TRC105. TRC105 diluted in normal saline will be administered as a 1 to 4 hour infusion on day 1, day 8, day 15 and day 22 of each 28 day cycle following premedication (see Section 7.7). TRC105 will be administered intravenously utilizing an infusion pump. TRC105 must be administered using a low protein binding, non-DEHP infusion set with a 0.2 micron downstream filter. Duration of infusion administration may be increased as medically necessary.

• Assessment of Adverse Events.

• Assessment of concomitant medications and concomitant treatments.
5.1.3. **End of Study Assessments**

Assessments other than TRC105 pharmacokinetics only need to be completed if they were not completed during the previous 2 weeks on study (during the last 8 weeks on study for radiologic tumor assessments). The following will be performed according to the Schedule of Assessments (Table 5).

- Physical examination including examination of all major body systems, performance status, and vital signs.
- Hematology, coagulation (PT or INR) and serum chemistry to be performed locally.
- Urinalysis to be performed locally. Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated.
- Blood sampling for immunogenicity and PK to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).
- Blood sampling for protein biomarker analysis by a third party laboratory (see laboratory manual for specific instructions regarding collection processing, storage and shipment).
- MRI of the brain.
- Assessment of Adverse Events.
- Assessment of concomitant medications and concomitant treatments.

5.1.4. **Post Treatment Follow-up**

The following will be performed according to the Schedule of Assessments (Table 5). Samples should be collected even if new anti-cancer therapy commences during the follow-up period.

- Assessment of Adverse Events. The Investigator should continue to report any related or possibly related adverse events that occur beyond the adverse event reporting period.
- Blood sampling for immunogenicity and PK to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).
- Assessment of concomitant medications and concomitant treatments.
### Table 5: Schedule of Assessments

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<th>Protocol Activities</th>
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<th>*Cycle 3+ [19]</th>
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<th>**Post Treatment Follow-up [20]</th>
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*Allowable window for each visit within the cycle is +/- 3 day unless otherwise stated.

**Allowable window for each visit within Post Treatment Follow-up is +/- 1 week.
Schedule of Assessments Footnotes

1. **Days of Treatment with TRC105**: All assessments should be performed prior to the TRC105 infusion unless otherwise indicated. Each cycle is 28 days in duration.
2. **Cycle 1 day 1**: Hematology, blood chemistry, urinalysis, physical examination, and pregnancy test not required if acceptable screening assessment is performed within 7 days prior to the start of treatment with TRC105 on cycle 1 day 1.
3. **End of Study**: Assessments do not need to be repeated if performed within the previous 2 weeks (previous 8 weeks for radiologic tumor assessments). Follow-up visits should occur following the completion of the End of Study Visit as outlined in the Schedule of Assessments.
4. **Informed Consent**: Must be obtained prior to undergoing any study specific procedure and may occur prior to the 28-day screening period.
5. **Medical/Oncologic History and Demographics**: To include information on prior anticancer therapy.
6. **Physical Examination**: Examination of major body systems and Karnofsky performance status.
7. **Vitals**: Heart rate, temperature, blood pressure, respiratory rate, weight. Assessment of Vital Signs during TRC105 Infusion: Vital signs are to be assessed pre-infusion and every 30 minutes during the infusion. Vital signs should be monitored more frequently and/or beyond the completion of the infusion if medically indicated (e.g. if the patient experiences an infusion reaction that has not yet resolved).
8. **Hematology, Chemistry & Coagulation**: Testing to be performed locally. Lab assessments may be performed within 3 days prior to TRC105 dosing. In addition to the assessments scheduled for the clinical trial, patients should undergo assessment as appropriate to ensure safe treatment. See Section 9.1.1.1 for specific panel collection requirements.
9. **Pregnancy Test**: Testing to be performed locally. All female patients of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to cycle 1 day 1 in order to be enrolled in the trial.
10. **Urinalysis**: To be performed locally via dipstick or urinalysis. Microscopic analysis and/or urine protein creatinine ratio or 24-hour urine protein collection should be performed as clinically indicated.
11. **TRC105 Administration**: Intravenous TRC105 diluted in normal saline will be administered every 7 days. See Section 7.7 for specific TRC105 administration guidelines.
12. **MRI Tumor Imaging**: MRI Images of the brain to be performed at screening, and on-study as outlined in the assessment table. Partial and complete responses must be confirmed by MRI at least 4 weeks after initial documentation.
13. **12-Lead ECG**: Single tracing 12-lead ECG will be performed at screening (pre-dose). If the patient develops an arrhythmia, the ECG should be repeated on day 1 of each subsequent cycle.
14. **Concomitant Medications and Treatments**: Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 28 days following the last dose of study treatment. Required TRC105 premedications should be recorded on the concomitant medications CRF.
15. **Baseline Emergent Adverse Events/Adverse Events**: Patients must be followed for safety from the day of informed consent until at least 28 days after the last dose of study treatment, or until all serious or TRC105 related toxicities have resolved or are determined to be “chronic” or “stable”, whichever is later. Adverse events occurring prior to the initiation of the study treatment will be considered “Baseline-Emergent Adverse Events” and will be recorded on corresponding case report forms. Events that occur from the time the patient has taken the first dose of TRC105 study drug through 28 days after the last dose of TRC105 study drug will be recorded on “Adverse Event” CRFs. Any serious AE that is possibly related to TRC105 occurring from the time of first dose or at any point after the reporting period must be promptly reported to TRACON.
16. **HAMA/HACA**: 5 mL blood samples will be collected to assess HAMA and HACA on cycle 1 day 1 pre-dose, and 28 days after the EOS visit. Sera will be separated and stored at approximately -70°C. Testing to be performed locally. Lab assessments may be performed within 3 days prior to TRC105 dosing. In addition to the assessments scheduled for the clinical trial, patients should undergo assessment as appropriate to ensure safe treatment. See Section 9.1.1.1 for specific panel collection requirements.
17. **Pharmacokinetics**: 5 mL blood samples will be collected at the time points indicated in the Schedule of Assessments. Pre-dose trough concentration samples will be collected immediately prior to starting the TRC105 infusion. Peak concentrations will be collected within 10 minutes of the completion of the TRC105 infusion. Additional samples may also be collected at the time of unexpected clinical events. Samples will be stored at approximately -70°C. Samples will be batch shipped to a 3rd party laboratory for analysis. See separate laboratory guide for further collection and shipment information.
18. **Protein Biomarkers**: 5 mL of plasma (K3EDTA) will be collected as indicated in the schedule of assessments and stored at approximately -70 degrees C to be analyzed by a central laboratory. See separate laboratory guide for further collection and shipment information. The window for sample collection is ±3 days.
19. **Cycle 3+ Treatment**: Patients who demonstrate a response of CR, PR or SD will be eligible for additional treatment until progression. See separate laboratory guide for further collection and shipment information.
20. **Follow-up**: The follow-up visit should occur 28 days following the completion of the End of Study Visit as outlined in the Schedule of Assessments.
6. **SELECTION AND WITHDRAWAL OF PATIENTS**

6.1. **Patient Inclusion Criteria**

1. Patients with histologically confirmed glioblastoma or other grade IV malignant glioma (i.e. gliosarcoma, small cell glioblastoma, etc.), recurrent after prior external-beam fractionated radiotherapy and temozolomide chemotherapy.

2. Patients who have received prior anti-angiogenic therapy for treatment of grade IV malignant glioma (e.g. bevacizumab, cediranib, and cilengitide, etc.)

3. Patients with any number of recurrences are allowed.

4. Karnofsky performance status ≥ 60%.

5. Age ≥ 18 years old.

6. Patients must have the following laboratory values:
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10⁹/L
   - Platelets ≥ 100 x 10⁹/L
   - Hemoglobin (Hgb) > 9 g/dL
   - Serum total bilirubin: ≤ 1.5 x ULN
   - ALT and AST ≤ 3.0 x ULN
   - Serum creatinine ≤ 1.5 x ULN
   - Blood coagulation parameters: INR ≤ 1.5

7. Minimum interval since completion of radiation treatment is 12 weeks

8. Minimum interval since last drug therapy:
   - 3 weeks since last non-cytotoxic therapy
   - 3 weeks must have elapsed since the completion of a non-nitrosourea containing chemotherapy regimen
   - 6 weeks since the completion of a nitrosourea containing chemotherapy regimen.

9. Patients must have signed an approved informed consent and authorization permitting release of personal health information.

10. Patients with the potential for pregnancy or impregnating their partner must agree to follow acceptable birth control methods to avoid conception. The anti-proliferative activity of this experimental drug may be harmful to the developing fetus or nursing infant. Female patients of child-bearing potential must have a negative pregnancy test.

11. Patients must have no concurrent malignancy except curatively treated basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix and breast, adequately treated
stage I or II cancer from which the patient is in complete remission. Patients with other prior malignancies must be disease-free for ≥ three years.

12. Patients must be maintained on a stable or decreasing corticosteroid regimen from the time of their baseline scan until the start of treatment and/or for at least 5 days before starting treatment.

13. Patients must have a Mini Mental State Exam score ≥ 15.

6.2. **Exclusion Criteria:**

1. Patients who have had previous treatment with TRC105.

2. Patients who have undergone major surgery (e.g. intra-thoracic, intra-abdominal or intra-pelvic), open biopsy or significant traumatic injury ≤ 4 weeks prior to starting study drug, or patients who have had minor procedures, percutaneous biopsies or placement of vascular access device ≤ 1 week prior to starting study drug, or who have not recovered from side effects of such procedure or injury.

3. Patients with impaired cardiac function or clinically significant cardiac diseases, including any of the following:
   - History or presence of serious uncontrolled ventricular arrhythmias
   - Clinically significant resting bradycardia
   - Any of the following within 6 months prior to starting study drug: myocardial infarction (MI), severe/unstable angina, Coronary Artery Bypass Graft (CABG), Congestive Heart Failure (CHF), Cerebrovascular Accident (CVA), Transient Ischemic Attack (TIA), Pulmonary Embolism (PE)
   - Uncontrolled hypertension (defined by a SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg with anti-hypertensive medications)

4. Patients with cirrhosis, or active viral or nonviral hepatitis.

5. Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory)

6. Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. active or uncontrolled infection, uncontrolled diabetes) that could cause unacceptable safety risks or compromise compliance with the protocol.

7. Pregnant or breast-feeding women.

8. Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human, chimeric, or humanized antibodies.

9. Patients with active bleeding or pathologic conditions that carry a high risk of bleeding, (i.e. hereditary hemorrhagic telangiectasia).


11. Patients unwilling or unable to comply with the protocol.
6.3. **Patient Withdrawal Criteria**

A patient should be withdrawn from study treatment if, in the opinion of the Investigator, it is medically necessary, or if it is the wish of the patient. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome. Data to be collected at the end of study visit are described in the Schedule of Assessments (Table 5). Patients will be followed for at least 28 days after the last dose of TRC105 study drug for adverse events. If the patient withdraws consent, no further evaluations should be performed, and no attempts should be made to collect additional data. In addition, patients will be withdrawn from treatment in the case of:

1. Modified RANO criteria defined disease progression. In cases where RANO cannot be applied, progression should be based on unequivocal evidence of progressive disease sufficient to require a change in therapy.

2. A need for surgery, radiation, or for other anticancer therapy not specified in the protocol.

3. Lost to follow-up or noncompliant.

4. Any TRC105 dose delay > 6 weeks.

5. Pregnancy. Pregnant patients should be followed for the duration of the pregnancy and the outcome of the pregnancy should be documented.

6. Arterial thrombosis of any grade (including cerebrovascular ischemia, cardiac ischemia/infarction, or peripheral or visceral arterial ischemia) or arterial or venous thrombosis of any grade requiring anticoagulation (including pulmonary embolism).
7. TREATMENT OF PATIENTS

7.1. Description of TRC105 Study Drug
TRC105 is a genetically engineered human/murine chimeric monoclonal antibody directed against human CD105 found on the surface of proliferating endothelial cells.

7.2. Composition of TRC105
TRC105 is an IgG1, kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. TRC105 has an approximate molecular weight of 148 kDa.

7.3. TRC105 Dose Level
Each patient will be dosed with 10 mg/kg up to a maximum dose of 850 mg for women and 1,000 mg for men of TRC105 on days 1, 8, 15 and 22 of each 28 day cycle (i.e.: 85 kg for women and 100 kg for men is the maximum weight that should be used for purposes of dose calculation on this study).

7.4. TRC105 Packaging and Labeling
TRC105 will be supplied at 5 mg/mL in phosphate-buffered saline (PBS) in sealed 15 mL glass vials containing 15 mL of TRC105. Vials of TRC105 are labeled with the following:

TRC105
NSC# 754227
75 mg per vial (5 mg/mL, 15 mL vial)
Store refrigerated at 2-8°C.
For Intravenous Use Only. Single-use vial.
Lot: XXXXXXX Mfg Date: XX/XX/XXXX
Caution: New Drug Limited by
Federal (or United States) law to investigational use.
TRACON Pharmaceuticals Inc., San Diego, CA 92122 USA

7.5. TRC105 Storage and Shipping
TRC105 must be stored upright between 2 °C and 8 °C (36 °F to 46 °F).

7.6. TRC105 Preparation
TRC105 will be prepared in the pharmacy and diluted into normal saline in a DEHP-free and PVC-free polyolefin bag; one 500 mL bag should be used for this purpose. TRC105 will be administered using an in-line 0.2 micron low protein binding filter. Compatibility studies support the use of tubing that is polyethylene lined and non-DEHP. Following dilution in normal saline, TRC105 will be administered at room temperature within 24 hours of reconstitution. Multiple vials will be required for a single dose. The following formulae should be used to calculate the volume of TRC105 to be added to normal saline:
• Patient weight (kg) \times \text{dose level (mg/kg)} \div \text{TRC105 concentration (mg/mL)} = \text{volume of TRC105 (mL) to be administered.}

The volume of TRC105 that is to be administered can be rounded up or down to the nearest 0.1 mL; in the case of an increment of 0.05 mL the volume should be rounded up. The maximum weight that should be used for dose calculation in this study is 85 kg for women and 100 kg for men (note: there is not a weight restriction for enrollment purposes). If the patient’s weight changes by > 10% during the study, the dose of TRC105 will be recalculated. At that time a new baseline weight will be established such that subsequent weight changes by >10% from the new baseline weight would require further recalculation of the TRC105 dose. The calculated volume of TRC105 will be diluted with normal saline. Appropriate judgment should be exercised in withdrawing an adequate amount of saline necessary to permit injection of the appropriate volume of antibody into a normal saline bag in accordance with the dose needed. The final TRC105 concentration must be between 0.03 mg/mL and 5 mg/mL (undiluted). The prepared TRC105 must be gently inverted several times in order to ensure a homogeneous solution.

7.7. TRC105 Administration

Patients should be encouraged to drink abundant fluid prior to the first treatment. IV hydration prior to and during therapy is left to the discretion of the Investigator, but should be considered for patients that may be volume depleted.

The following TRC105 premedications should be administered 2 hours to 30 minutes prior to the start of each infusion:

- Acetaminophen 650 mg p.o. x 1
- Dexamethasone 20 mg i.v. x 1
- Famotidine 20 mg i.v. (or similar H2 blocker) x 1
- Cetirizine 10 mg i.v. or p.o. x 1 (or similar oral or intravenous antihistamine)

TRC105 will be administered intravenously utilizing an infusion pump. TRC105 must be administered using a low protein binding, non-DEHP infusion set with a 0.2 micron downstream filter. The attachment of the infusion pump administration set to the i.v. bag and transport of the TRC105 study drug to the patient will be performed as per standard study site procedures.

The day 1 TRC105 infusion will begin 2 hours to 30 minutes following the completion of the day 1 TRC105 premedications.

On cycle 1 day 1, TRC105 will be infused over a period of 4 hours. For patients who complete at least one 4 hour infusion without the development of any infusion reactions, the subsequent TRC105 infusion may be reduced to 2 hours. For patients who complete a 2 hour infusion without the development of any infusion reactions, subsequent TRC105 infusions may be reduced to 1 hour. Patients with infusion reactions of any kind should be managed appropriately (see Section 7.7.2) and are not permitted to reduce the duration of the next planned infusion.

After the minimum TRC105 infusion duration of 1 hour has been safely administered, at the discretion of the PI the dexamethasone should be gradually tapered as tolerated with each subsequent infusion and eventually discontinued if possible at a minimum as outlined in Table 6.
The dexamethasone dose should only be reduced if the prior infusion was well-tolerated (no infusion reaction of any grade).

### Table 6: Recommended Dexamethasone Taper Schedule

<table>
<thead>
<tr>
<th>Infusion</th>
<th>Dexamethasone Dose and Schedulea</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 1 hr infusion</td>
<td>20 mg i.v. 30 minutes to 2 hours prior to each infusion</td>
</tr>
<tr>
<td>Second 1 hr infusion</td>
<td>10 mg i.v. 30 minutes to 2 hours prior to each infusion</td>
</tr>
<tr>
<td>Third 1 hr infusion</td>
<td>5 mg i.v. 30 minutes to 2 hours prior to each infusion</td>
</tr>
<tr>
<td>Subsequent infusions</td>
<td>No dexamethasone</td>
</tr>
</tbody>
</table>

*The dexamethasone dose should only be reduced if the prior infusion was well-tolerated (i.e. no infusion reaction of any grade). If an infusion reaction occurs following dexamethasone dose reduction, the dexamethasone dose can be increased at the discretion of the investigator.*

The rate of TRC105 infusion must not exceed 25 mg/min. The infusion must be completed within 24 hours of preparation of the i.v. bag; the expiration time should be labeled on the bag. When the i.v. bag containing TRC105 is empty, flush the i.v. line with a 20 mL normal saline at the same rate of infusion. The dose level, time of transfer to i.v. bag, and the infusion start and stop times must be recorded in the source documents.

If a patient misses a weekly dose, the dexamethasone dose should be reinstituted as per the initial infusion. The dexamethasone dose may be gradually reduced again as previously described.

#### 7.7.1. TRC105 Dose Reduction

TRC105 dose reductions are recommended for grade 3 or 4 toxicity, including anemia. TRC105 dose delays cannot exceed 6 weeks per Section 6.3 of the protocol.

### Table 7: Allowable TRC105 Dose Modifications

<table>
<thead>
<tr>
<th>Toxicity Attributed to TRC105</th>
<th>Dose Adjustment for Next Dose of TRC105 (% of Starting Dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 or 2</td>
<td>Maintain Dose Level</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td></td>
</tr>
<tr>
<td>• 1st appearance</td>
<td>75%</td>
</tr>
<tr>
<td>• 2nd appearance</td>
<td>50%</td>
</tr>
<tr>
<td>• 3rd appearance</td>
<td>Discontinue treatment permanently</td>
</tr>
</tbody>
</table>

#### 7.7.2. Management of TRC105 Infusion Reactions

If a patient experiences a grade 2 or higher adverse reaction during infusion, the infusion should be interrupted and the patient treated accordingly. Antipyretic, antihistamine, antiemetic, anti-inflammatory, or other symptomatic medications including epinephrine may be administered as indicated. For grade 2 and certain grade 3 infusion reactions, the infusion may be restarted at half of the previous rate if and when the infusion reaction has resolved. For grade 4 infusion reactions, the infusion should not be restarted and the patient should be discontinued from study.
treatment. Infusion reactions will be recorded as AEs in the case report form. Interventions should be documented as concomitant medications or concomitant treatments as appropriate.

### Table 8: Management of TRC105 Infusion Reactions

<table>
<thead>
<tr>
<th>Infusion Reaction Severity</th>
<th>Recommended Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (mild)</td>
<td>1. No intervention&lt;br&gt;2. Continue infusion unless symptoms worsen</td>
</tr>
<tr>
<td>Grade 2 (moderate)</td>
<td>1. Interrupt infusion&lt;br&gt;2. Treat with symptomatic medications&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt;3. Resume infusion at half the previous rate when infusion-related symptoms improve to baseline</td>
</tr>
<tr>
<td>Grade 3 (severe)</td>
<td>1. Interrupt infusion&lt;br&gt;2. Treat with symptomatic medications&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt;3. Monitor patient until infusion-related symptoms resolve, including hospitalization if necessary&lt;br&gt;4. Withdraw patient from study unless other factors that contributed to the infusion reaction are identified and corrected</td>
</tr>
<tr>
<td>Grade 4 (life-threatening)</td>
<td>1. Discontinue infusion&lt;br&gt;2. Treat with symptomatic medications&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt;3. Hospitalize patient&lt;br&gt;4. Withdraw from study</td>
</tr>
</tbody>
</table>

<sup>a</sup>Symptomatic medications may include, but are not limited to, diphenhydramine 50 mg i.v. and/or hydrocortisone 100 mg i.v. (for fever, rash, hypoxia, or other hypersensitivity reactions), meperidine 50-100 mg i.v. (for shaking chills/rigors), oxygen by mask or nasal cannula (for hypoxia), epinephrine 0.5 mg i.m. (for hypotension or bronchospasm), albuterol inhaler or nebulizer (for bronchospasm), i.v. fluids (for hypotension), and ondansetron 0.15 mg/kg i.v. (for nausea).

### 7.8. TRC105 Study Drug Accountability

The Investigator must maintain an accurate accounting of TRC105 supplied by TRACON. During the study, the following information must be recorded:

- Date of receipt, quantity and lot number of the TRC105 study drug received from TRACON
- ID number of the patient to whom the product is dispensed
- The date(s) and quantity of the product dispensed
- Dates and quantity of product returned, lost or accidentally or deliberately destroyed

Investigational Drug Accountability Logs should be maintained by the site and must be readily available for inspection.
7.9. TRC105 Study Drug Handling and Disposal

TRC105 must be stored upright between 2 °C and 8 °C (36 °F to 46 °F). The Investigator should not return clinical study materials to TRACON unless specifically instructed to do so by TRACON. Used vials do not need to be maintained. All expired vials of TRC105 should be retained until destruction is authorized by a TRACON representative. The Site Pharmacist will be responsible for documenting the destruction (according to institutional requirements) of used or expired vials.

7.10. Concomitant Medications

No other approved or investigational anticancer treatment will be permitted during the study period. No other investigational drug may be used during treatment on this protocol, and concurrent participation in another clinical trial is not allowed.

Patients who receive NSAIDs on study should also receive peptic ulcer disease prophylaxis with an H2 or proton pump blocker.

Narcotic analgesics, nonsteroidal anti-inflammatory drugs, and triptans (e.g. sumatriptan) may be offered as needed for relief of pain or headaches. Antihistamines and decongestants may be offered for the treatment of sinus congestion.

Packed red blood cell, colony stimulating factors, and platelet transfusions should be administered as clinically indicated.

7.11. TRC105 Study Drug Treatment Compliance

All TRC105 infusions will occur at the trial site under the direct supervision of the treating physician or his or her designee.

7.12. Patient Enrollment

Patients will be manually enrolled by TRACON Pharmaceuticals and assigned an eight digit patient number. This eight digit number will be used to identify patients throughout their participation in the trial. A regulatory binder will be provided and will include detailed instructions for the manual enrollment process.
8. ASSESSMENT OF EFFICACY

8.1. Response Assessment

Optimal guidelines for determining GBM response to therapy are not yet well established. The most accepted are the Macdonald criteria [60]. However, increasingly specific criteria are being developed by the Response Assessment in Neuro-Oncology (RANO) Group through the American Society of Clinical Oncology. Using these developing guidelines, we have designed response criteria detailed in Table 9. These are largely based on standardized response criteria using bi-dimensional measurements of the largest contrast-enhancing area [61]. However, it has been demonstrated that contrast-enhanced images can be altered by agents inhibiting angiogenesis with occasional progression of T2-weighted or FLAIR abnormality as well as clinical decline despite improvement in the contrast-enhancing signal [62, 63]. In light of this, FLAIR imaging and clinical status will be part of the response criteria in addition to the widely used Macdonald criteria. Hence, the largest cross-sectional area on the T1-weighted contrast-enhanced images will be selected and measured in 2 dimensions with linear measures on the baseline MRI axial sequence. In addition, the largest cross-sectional area of a contiguous hyperintense lesion on FLAIR sequences will be measured on the baseline MRI axial sequence. All subsequent scans will be compared against these baseline measures (for both CE and FLAIR). New foci of FLAIR signal abnormality will be recorded on each subsequent evaluation. Response will be scored based on a combination of imaging and clinical features as defined by the modified RANO criteria (Table 9).

Table 9: Modified RANO Response Criteria

<table>
<thead>
<tr>
<th>Response</th>
<th>T1 Contrast Enhancement (CE)</th>
<th>FLAIR Images</th>
<th>Steroids</th>
<th>Neurologic Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>No residual CE (complete disappearance of all enhancing measurable disease for at least 4 weeks; confirmatory MRI at 4 weeks is required to score as CR) and no new lesions.</td>
<td>Stable or reduced area of FLAIR signal abnormality</td>
<td>No steroids</td>
<td>Stable or improved from prior evaluation</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>&gt;50% reduction in sum of products of the perpendicular diameters of all measureable enhancing lesions sustained for at least 4 weeks and no new lesions or progression of non-measurable lesions</td>
<td>Stable or reduced area of FLAIR signal abnormality</td>
<td>Stable or reduced glucocorticoids from baseline MRI</td>
<td>Stable or improved from prior evaluation</td>
</tr>
<tr>
<td>Minor response (MR)</td>
<td>&gt;25% reduction in sum of products of the perpendicular diameters of all measureable enhancing lesions and no new lesions (confirmatory MRI at 4 weeks is required to score as PR)</td>
<td>Stable or reduced area of FLAIR signal abnormality</td>
<td>Stable or reduced glucocorticoids from baseline MRI</td>
<td>Stable or improved from prior evaluation</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>&lt;25% reduction in area of CE maintained for at least 4 weeks duration. Does not qualify for CR, PR or progression</td>
<td>Stable or reduced area of FLAIR signal abnormality</td>
<td>Stable or reduced glucocorticoids from baseline MRI</td>
<td>Stable or improved from prior evaluation</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>&gt;25% in the sum of products of the perpendicular diameters of CE lesions; evidence of new lesion(s).</td>
<td>Measurable increase in the sum of products of the perpendicular diameters of FLAIR signal abnormality from the baseline scan or the scan representing the best response (if there was a response) following therapy and not attributable to other co-morbid events (seizure, radiation, injury, infection, ischemia, etc.) OR presence of a new focus of FLAIR signal abnormality that cannot be explained by any other pathologic process.</td>
<td>Stable or increased dose of glucocorticoids</td>
<td>Stable or worsening neurologic symptoms</td>
</tr>
</tbody>
</table>

Radiological tumor assessments will be performed at screening, as outlined in the Schedule of Assessments (Table 5), and whenever disease progression is suspected. Another tumor assessment will be performed at the End of Study Visit if an assessment has not been performed within the prior 8 weeks. All patient files and radiological images must be available for CRF source verification.
9. ASSESSMENT OF SAFETY

9.1. Safety Parameters

Safety will be characterized in terms of the incidence, timing, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.0), seriousness, and relatedness of adverse events and laboratory abnormalities. In addition, physical examination, vital signs, and Karnofsky performance status will be serially monitored. Laboratory safety analyses will be based on the local laboratory data, and will include hematology, serum chemistry (including liver and kidney function), urinalysis, serum or urine pregnancy testing, and coagulation profile. Serum will also be assessed for immunogenicity to TRC105 (including HACA and HAMA titers). In addition, an ECG will be recorded at baseline and as clinically indicated throughout the study.

9.1.1. Laboratory Safety Assessments

Abnormal and clinically significant laboratory tests should be recorded as adverse events. To meet the definition of clinically significant, the test result generally requires a change in medical management (e.g. new medication, unplanned treatment, additional tests, etc.).

9.1.1.1. Hematology, Serum Chemistry, Coagulation, Pregnancy Test

Assessments will be performed at the time points indicated in the Schedule of Assessments (Table 5) and analyzed at local laboratories. Investigators may have additional blood tests performed for the purpose of planning treatment administration, or for following adverse events as clinically indicated.

- Hematology: CBC with differential and platelet count
- Coagulation: Prothrombin Time (PT) or Internalized Normalized Ration (INR) will be assessed
- Serum Chemistry: Total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, total protein, albumin, sodium, potassium, bicarbonate, chloride, calcium, phosphorus, blood urea nitrogen, creatinine, and glucose
- Pregnancy Test: Serum or urine pregnancy tests will be performed locally on all female patients of childbearing potential. Patients must be surgically sterile (i.e.: hysterectomy) or be postmenopausal, or must agree to use effective contraception during the study and for 3 months following last dose of TRC105. The definition of effective contraception will be based on the judgment of the Principal Investigator or a designated associate.

9.1.1.2. Urinalysis

Urinalysis will be performed at time points indicated in the Schedule of Assessments (Table 5) and analyzed by local laboratories. Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated.
9.1.1.3. Physical Examination

A physical examination including, but not limited to, general appearance, head, eyes, ears, nose, throat, neck, heart, chest, abdomen, musculoskeletal, extremities, skin, lymph nodes, neurological genitourinary (as appropriate), and rectal (as appropriate) will be assessed at time points indicated within the Schedule of Assessments (Table 5). The physical examination will include examination of known and suspected sites of disease.

9.1.1.4. Vital Signs

Heart rate, temperature, blood pressure, respiratory rate and weight will be assessed at time points indicated within the Schedule of Assessments (Table 5). Heart rate, temperature, blood pressure, and respiratory rate will also be assessed during TRC105 infusions as described in Section 5.1.2.2 and the footnotes of the Table 5 Schedule of Assessments.

9.1.1.5. Performance Status

The Karnofsky scale will be used to assess performance status at Screening.

9.1.1.6. ECG

A single 12-lead (with a 10–second rhythm strip) tracing will be used for all ECGs. It is preferable that the machine used has a capacity to calculate standard intervals automatically. ECG will be performed according to the Schedule of Assessments (Table 5) and as clinically indicated throughout the study.

9.2. Adverse Events

All observed or volunteered adverse events regardless of suspected causal relationship to TRC105 study drug will be reported as described below.

9.2.1. Definition of Adverse Event

An adverse event is any untoward medical occurrence in a trial patient who is administered a drug or biologic (medicinal product); the event may or may not have a causal relationship with the medicinal product. Examples of adverse events include, but are not limited to the following:

- Clinically significant symptoms and signs including:
  - Worsening of signs and symptoms of the malignancy under trial (disease progression without worsening of signs and symptoms assessed by measurement of malignant lesions on radiographs or other methods should not be reported as adverse events).
  - Signs and symptoms resulting from drug overdose, abuse, misuse, withdrawal, sensitivity, dependency, interaction or toxicity.
  - All possibly related and unrelated illnesses, including the worsening of a preexisting illness.
  - Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (hip fracture from a fall secondary to dizziness), the medical
condition (dizziness) and the outcome of the accident (hip fracture from a fall) should be reported as 2 separate adverse events.

- Symptoms or signs resulting from exposure \textit{in utero}.

- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat confirmatory test).

- Laboratory abnormalities that meet any of the following (Note: merely repeating an abnormal test, in the absence of any of the below conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.):
  - Test result that is associated with accompanying symptoms
  - Test result that requires additional diagnostic testing or medical/surgical intervention
  - Test result that leads to a change in TRC105 study drug dosing outside of protocol-stipulated dose adjustments or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy
  - Test result that is considered to be an adverse event by the Investigator or TRACON

9.2.2. **Serious Adverse Events**

An adverse event that meets one or more of the following criteria/outcomes is classified as serious:

- Results in death
- Is life-threatening (at immediate risk of death)
- Requires in patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect
- Other important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependence or drug abuse.

Serious also includes any other event that the Investigator or sponsor judges to be serious, or which is defined as serious by the HRA in the country in which the event occurred.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as SAEs unless the outcome is fatal during the trial or within the safety reporting period. Hospitalizations due to signs and symptoms of disease progression should not
be reported as SAEs. If the malignancy has a fatal outcome during the trial or within the safety reporting period, then the event leading to death must be recorded as an adverse event and as an SAE with CTC grade 5.

The onset date of an SAE is defined as the date on which the event initially met serious criteria (e.g., the date of admission to a hospital). The end date is the date on which the event no longer met serious criteria (e.g., the date the patient was discharged from a hospital).

### 9.2.2.1. Hospitalization

Adverse events associated with in-patient hospitalization, or prolongation of an existing hospitalization, are considered serious. Any initial admission, even if the duration is less than 24 hours is considered serious. In addition, any transfer within the hospital to an acute/intensive care unit is considered serious (e.g., transfer from the psychiatric wing to a medical floor or transfer from a medical floor to a coronary care unit). However, the following hospitalizations **should not** be considered serious:

- Rehabilitation facility admission
- Hospice facility admission
- Respite care
- Skilled nursing facility admission
- Nursing home admission
- Emergency room visit
- Same day surgery
- Hospitalization or prolongation of hospitalization in the absence of precipitating clinical adverse events as follows:
  - Admission for treatment of preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition
  - Social admission
  - Administrative admission (e.g. for yearly physical exam)
  - Protocol-specified admission during a clinical trial
  - Optional admission not associated with a precipitating clinical adverse event (e.g. for elective cosmetic surgery)
  - Preplanned treatments or surgical procedures
  - Admission exclusively for the administration of blood products

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as adverse events. The medical condition for which the procedure was performed **should** be reported if it meets the definition of an adverse event (e.g. acute...
appendicitis that begins during the adverse event reporting period should be reported as an adverse event and the appendectomy should be recorded as a concomitant treatment).

9.3. Reporting Adverse Events

9.3.1. Eliciting Adverse Event Information

The Investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the trial patient using concise medical terminology. In addition, each trial patient will be questioned about adverse events at each clinic visit following initiation of treatment. The question asked will be, “Since your last clinic visit have you had any health problems?”

9.3.2. Adverse Event Reporting Period

Safety information for each patient will be collected from the date of informed consent. Adverse events occurring prior to the initiation of the study treatment will be considered "baseline-emergent adverse events” and will be recorded on corresponding case report forms. The adverse event reporting period for this trial begins when the patient has taken the first dose of TRC105 study drug and ends 28 days after the last dose of TRC105 study drug is administered.

All adverse events that occur in trial patients during the adverse event reporting period specified in the protocol must be reported to TRACON, whether or not the event is considered study treatment-related. In addition, any known untoward event that occurs beyond the adverse event reporting period that the Investigator assesses as possibly related to the investigational medication/product should also be reported as an adverse event.

9.3.3. Reporting Requirements

Each adverse event is to be classified by the Investigator as SERIOUS or NONSERIOUS. This classification of the gravity of the event determines the reporting procedures to be followed. If an SAE occurs, reporting will follow local and international regulations, as appropriate.

The Investigator must notify the Sponsor of any event that meets one of the criteria for an SAE immediately upon learning of the event. This notification should be made to:

ChalresTheuer, MD PhD
TRACON Pharmaceuticals Inc.
8910 University Center Lane, Suite 700
San Diego, California 92122
Email: ctheuer@traconpharma.com
Cell Phone: 858.344.9400
Office Phone: 858.550.0780 x233

Following notification, the Investigator will report the SAE via the AE CRF via the data management system. The initial AE CRF is to be updated with followed more detailed adverse event information within 5 calendar days of the event.
In the rare event that the Investigator is not immediately aware of an SAE (for example, if the study subject seeks urgent medical attention elsewhere), the Investigator is to notify the Sponsor immediately upon learning about the event and document his/her first awareness.

Each SAE should be followed until resolution, or until such time as the Investigator determines its cause or determines that it has become stable. Information pertaining to follow-up of SAEs should also be sent to the TRACON Pharmaceuticals Inc.

Serious adverse events that are unexpected and associated with use of the study medication will be reported to the US Food and Drug Administration (FDA) and all participating clinical sites by TRACON via MedWatch forms. For events which are fatal or life-threatening, unexpected, and associated with use of the investigational product, a 7-Day Alert Report will be submitted to the FDA within 7 calendar days of receipt of the SAE information. For all other events that are serious, unexpected, and associated with use of the investigational product, a written report will be made no more than 15 calendar days from the date TRACON learns of the event. Participating clinical sites will be notified of these events in parallel.

All adverse events, including SAEs, are to be reported on the adverse event CRFs.

9.3.4. **Recording Adverse Events in the Case Report Forms**

The Investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the trial patient. In addition, each trial patient will be questioned about adverse events. All adverse events that meet the criteria specified in Section 9.2.1 are to be recorded on patient source documents and on the CRFs. Adverse events should be reported using concise medical terminology on the CRFs.

9.3.5. **Grading of Adverse Event Severity**

To report adverse events on the CRFs, the Investigator will use the severity grading as described in NCI CTCAE (Version 4.0).

Every effort should be made by the Investigator to assess the adverse event according to CTCAE criteria. If the Investigator is unable to assess severity because the term is not described in NCI (Version 4.0), severity of MILD, MODERATE, SEVERE, LIFE-THREATENING, or FATAL may be used to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Non-CTCAE Severity</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild</td>
<td>Does not interfere with patient’s usual function</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>Interferes to some extent with patient’s usual function</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>Interferes significantly with patient’s usual function</td>
</tr>
<tr>
<td>4</td>
<td>Life-Threatening</td>
<td>Results in immediate risk of patient’s death</td>
</tr>
<tr>
<td>5</td>
<td>Fatal</td>
<td>Results in patient’s death</td>
</tr>
</tbody>
</table>
Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with patient’s usual function) but would not be classified as serious unless it met one of the criteria for serious events.

9.3.6. Relationship to TRC105 Study Drug

In this study, TRC105 study drug is given as monotherapy. The relationship of an adverse event to TRC105 study drug should be classified by the Investigator using the following guidelines:

- Suspected Adverse Reaction: There is a reasonable possibility that TRC105 caused the adverse event (i.e.: there is evidence to suggest a causal relationship between TRC105 and adverse event).
- Not Related: There is no reasonable possibility that the adverse event is associated with TRC105 study drug.

AE’s related to TRC105 study drug are considered Adverse Drug Reactions (ADR).

9.3.7. Expectedness

All adverse events and adverse drug reactions are reaction considered “unexpected” if it not listed in the investigator brochure or not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, 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.

9.3.8. Exposure in Utero

An exposure in utero (EIU) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (e.g., environmental exposure) the investigational product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational product (maternal exposure)
- A male has been exposed, either due to treatment or environmental, to the investigational product prior to or around the time of conception and/or is exposed during the partner’s pregnancy (paternal exposure)

If any trial patient becomes or is found to be pregnant during the study or within 28 days of discontinuing the investigational medication/product, the Investigator must report the information to TRACON, or designee via the Pregnancy Notification Report Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery.
The Investigator will follow the patient until completion of the pregnancy or until pregnancy termination (i.e., induced abortion) and then notify TRACON, or its designee, of the outcome within 5 days or as specified below. The Investigator will provide this information as a follow-up to the initial report. The reason(s) for an induced abortion must be specified.

The Investigator should follow procedures for reporting an SAE if pregnancy outcome meets criteria for an SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]).

In the case of a live birth, the “normality” of the newborn can be assessed at the time of birth and the Pregnancy Outcome Report Form should be completed (i.e., no minimum follow-up period of a presumably normal infant must pass before a Pregnancy Outcome Report Form can be completed). The “normality” of an aborted fetus can be assessed by gross visual inspection unless pre-abortion laboratory findings are suggestive of a congenital anomaly.

Additional information about pregnancy outcomes that are classified as SAEs follows:

- “Spontaneous abortion” includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 1 month that the Investigator assesses as possibly related to the in utero exposure to the investigational medication should also be reported.

### 9.3.9. Follow-up of Unresolved Adverse Events

All adverse events should be followed until they are resolved or the Investigator assesses them as chronic or stable. Any increase or decrease in adverse event grade should be recorded as a new adverse event.

All serious and those non-serious events assessed by the Investigator as possibly related to the investigational medication/product should continue to be followed even after the patient’s participation in the trial is over. Such events should be followed until they resolve or until the Investigator assesses them as “chronic” or “stable.” The event should also be documented on the adverse event CRF.

### 9.4. Safety Monitoring

The TRACON Clinical Team will monitor safety throughout the study via the following activities:

- Surveillance for SAEs according to regulatory guidelines
- Routine monitoring of non-serious adverse experiences as they are recorded in the case report forms and the source documents at study sites
- A formally chartered TRACON in-house Safety Review Team that includes, among other staff, two physicians
- Periodic teleconferences with the Principal Investigators to share experiences and ensure communication
Toxicity information that may affect the treatment of patients on this study will be promptly communicated in writing to all participating clinical sites and institutions participating in this clinical trial.
10. OTHER ASSESSMENTS

10.1. Laboratory Assessments

10.1.1. TRC105 Immunogenicity

HAMA and HACA concentrations will be measured using validated ELISA methods at the time points specified in the Schedule of Assessments (Table 5) in all patients. HAMA and HACA concentrations will be evaluated in the context of pharmacokinetic parameters and AE profiles. Samples will be separated and stored at approximately -70 °C for shipment every 6 months. See separate laboratory guide for further collection and shipment information.

10.1.2. Protein Biomarkers

Blood biomarkers offer a minimally invasive means to repeatedly probe the effects of TRC105 on tumor biology during treatment. The discovery of mechanism-based biomarkers may lead to more efficient development of new cancer therapeutics and optimization of TRC105.

Plasma will be collected at the time points listed in the Schedule of Assessments (Table 5).

Plasma will be analyzed for potential biomarkers using multiplexed ELISA kits (96-well plates, 4-10 analytes) or single cytokine ELISA (for analytes unavailable in multiplex, e.g. collagen IV, SDF-1α). Using this technology, we will be able to assess VEGF-A, VEGF-C, VEGF-D, PlGF, PDGF-AA, PDGF-BB, HGF, ANG-2, IGFBP-1, IGFBP-3, PEDF, sVEGF-R1, sVEGF-R2, sTie-2, MMP2, MMP9, TGF-β1, TGF-β2, osteopontin, TSP-1, TSP-2, TGF-β R3, tissue factor, PAI-1, CRP, d-dimer, von Willebrand factor, Gro-α, P-selectin, E-selectin, ICAM-1, VCAM-1, MCP-1, E-cadherin, sCD105, SDF-1α, Il-6, IL-8 and FGF at baseline, during treatment, and time of progression. This broad array of proteins to be tested will permit complete evaluation of the most promising known angiogenic markers.

Samples will be separated and stored at approximately -70 °C for shipment every 6 months. See separate laboratory guide for further collection and shipment information.
11. **STATISTICS**

A one stage accrual design with an accrual goal of 14 evaluable patients will be employed in order to test the hypothesis that TRC105 can double the historical median time to progression in this population (i.e. 1.5 months to 3.0 months). Assuming an approximately 10% exclusion rate an additional 3 patients may be entered to replace ineligible patients or patients who withdraw consent prior to receiving study treatment. Assuming time to progression follows an exponential distribution, accrual takes approximately 6 months, and that there is ≥6 months of additional follow-up once accrual has been completed, there will be 80% power to detect the specified difference using a two-sided test with 10% type I error.

A number of potential biomarkers are being assessed, and therefore to simplify the sample size discussion calculations are expressed in terms of standard deviations of the biomarker under study. Assuming 12-14 patients have correlative data there will be statistical power >80% to detect moderate to large treatment effects on the biomarkers and differences in them between specified patient groups (e.g. responders versus non-responders). That is, with 12-14 patients there will be ≥85% power to detect changes in a biomarker following treatment ≥1.0 standard deviation, and ≥84% power to detect differences ≥2.5 standard deviations between any two groups of patients even if only 1/3 of patients are in one of the groups. As an example, if the variability of the relative change in biomarker following treatment is as much as 50% there will be >85% power to detect a mean decrease >50%. Calculations are based on 2-sided Wilcoxon signed rank and rank sum tests with 5% Type I errors, respectively. The data will be analyzed primarily using non-parametric methods such as the Wilcoxon signed-rank test (for paired data such as pre- versus post-treatment changes) and rank sum test (to assess differences between groups of patients). Multivariable models such as linear and logistic regression will be used to assess multiple factors. All tests of statistical significance will be two-sided and no adjustment will be made for multiple comparisons.

11.1. **Definition of Analyzed Study Populations**

Only those patients who are deemed "ineligible" or who receive no therapy will be eliminated from the analysis. All patients who receive any therapy will be evaluated for both treatment efficacy and toxicity.

11.2. **Data Analysis**

Descriptive statistics (such as means, medians, standard deviations and ranges for continuous data and percentages for categorical data) will be used to summarize patient characteristics, treatment administration/compliance, immunogenicity (HAMA and HACA), efficacy, pharmacokinetic parameters and protein biomarkers. Data will also be displayed graphically, where appropriate.

11.2.1. **Analysis of Efficacy and Safety**

The primary efficacy analysis will calculate the proportion of patients who are progression free at 6 months and the proportion of patients who have objective tumor response (complete or partial) by modified RANO criteria. Overall survival and progression-free survival will be
presented as Kaplan-Meier plots and estimates of the median time until death or the earlier of documented progression or death.

For a given event, the number and proportion of patients reporting it will be tabulated according to the worst severity experienced. Severity will be graded per NCI (Version 4.0). Individual tables will be constructed for (a) all reported adverse events, (b) adverse events reported as treatment related, and (c) serious adverse events.

11.2.2. Analysis of Protein Biomarkers

Angiogenic protein biomarker data for each patient who received at least one dose of study drug will be listed tumor type.

11.2.3. Analysis of Immunogenicity

HAMA and HACA concentrations will be measured using validated ELISA methods at the time points specified in the Schedule of Assessments (Table 5). HAMA and HACA concentrations will be evaluated in the context of pharmacokinetic parameters and AE profiles.
12. QUALITY CONTROL AND QUALITY ASSURANCE

Monitoring visits to trial sites will be made periodically during the trial to ensure that GCPs and all aspects of the protocol are followed. All data entered on CRFs must be verifiable within the patients’ source documents (written or electronic record). The Investigator/institution guarantees direct access to source documents by TRACON and appropriate regulatory authorities.

The trial site may also be subject to inspection by the institutional review board (IRB) or independent ethics committee (IEC) or other appropriate regulatory authority or to quality assurance audits performed by TRACON.

It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits and audits or inspections and that sufficient time is devoted to the process.

Protected health information will be securely stored with limited access by the participating institutions. TRACON (or designee) will review data on site and will not remove any protected health information.
13. **ETHICS**

13.1. **Institutional Review Board (IRB)/Independent Ethics Committee (IEC)**

It is the responsibility of the Investigator to have approval of the trial protocol, protocol amendments, informed consent forms, and advertisements from the IRB/IEC before potential patients are consented for participation on the trial. All correspondence with the IRB/IEC should be retained in the Investigator/site files. Copies of all IRB/IEC approvals should also be forwarded to TRACON.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the Investigator must notify the IRB/IEC and TRACON in writing within 5 business days after the implementation.

13.2. **Ethical Conduct of the Study**

The trial will be performed in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki (1996 Version), and applicable local regulatory requirements and laws.

13.3. **Written Informed Consent**

The informed consent form language must be agreed upon by TRACON and the IRB/IEC and must be in compliance with ICH GCP, local regulatory requirements, and legal requirements. The informed consent information must not be changed without prior approval by TRACON and the IRB/IEC. The informed consent form used in this trial, and any changes made during the course of the trial, must be approved by both the IRB/IEC and TRACON, or designee, before use.

It is the responsibility of the Investigator to give each patient full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. This information must be provided to the patient prior to undertaking any trial-related procedure. Patients must be informed about their right to withdraw from the trial at any time. Furthermore, it is the responsibility of the Investigator to obtain signed informed consent from all patients, and a signature from the persons conducting the informed consent discussion, prior to undertaking any trial-related procedure. Consent by a legally authorized representative is not permitted. The Investigator will retain the original of each patient’s signed consent form in the Investigator/site files.

13.4. **Patient Compensation**

Patients will not be compensated for participation in this trial; this will be outlined in the patient informed consent form.
14. DATA HANDLING AND RECORDKEEPING

14.1. Inspection of Records

CRF’s are required and should be completed for each patient who receives treatment with TRC105. Screen failure CRF’s will not be collected unless the patient experiences an SAE prior to receiving his/her first dose of TRC105, in which case demography and AE CRF’s should be completed. The completed original CRFs are the sole property of TRACON and should not be made available in any form to third parties without written permission from TRACON (except for authorized representatives of the HRA and in accordance with HIPAA regulations).

It is the Investigator’s responsibility to ensure completion and to review and approve all CRFs. CRFs must be signed by the Investigator. These signatures serve to attest that the information contained on the case report forms is true. At all times, the Investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs. All CRF data must be verifiable in the patient’s source documentation by TRACON. TRACON will review CRF data as compared to available source in an attempt to identify missing and spurious data and notify the investigator of findings so that proper corrections can be made.

TRACON (or its designee) will perform all data management functions associated with the study. Data will be captured electronically. Computer edit checks will be used to ensure that the data are logical and consistent.

14.2. Retention of Records

To allow for appropriate evaluations and/or audits by regulatory authorities or TRACON, the Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, source documents, and detailed records of treatment disposition. The Investigator should retain these records according to local regulations or as specified in the Clinical Trial Agreement, whichever is longer.

If the Investigator relocates, retires, or for any reason withdraws from the study, then TRACON should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to TRACON. The Investigator must obtain TRACON’s written permission before disposing of any records.
15. DEFINITION OF END OF TRIAL

Premature termination of this trial may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of TRACON. In addition, TRACON retains the right to discontinue development of TRC105 at any time.

TRACON reserves the right to discontinue the trial prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons. If a trial is prematurely terminated or discontinued, TRACON will promptly notify the Investigator. After notification, the Investigator must contact all participating patients within a 28 day time period. As directed by TRACON, all trial materials must be collected and all CRF data must be completed to the greatest extent possible.
16. PUBLICATION OF TRIAL RESULTS

Publication of trial results is discussed in the Clinical Trial Agreement.
17. FINANCING AND INSURANCE

Financing and Insurance are discussed in the Clinical Trial Agreement.
18. INVESTIGATOR PROTOCOL AGREEMENT: 105GM201

I understand that all information concerning this study supplied to me by TRACON Pharmaceuticals, Inc. is confidential information. I have read this protocol and agree to conduct the study according to Good Clinical Practice Guidelines and in accordance with the Clinical Trial Agreement.

I understand that this protocol and all amendments must be submitted to the appropriate IRB/IEC.

Investigator Name (PLEASE PRINT): ______________________________________________

Signature: ___________________________________________ Date: _______________

Please sign and return this agreement to:

TRACON Pharmaceuticals, Inc.
Attn: Clinical Operations
8910 University Center Lane, Suite 700
San Diego, CA 92122

Please keep a copy for your records.
19. REFERENCES


20. APPENDICES


The NCI CTCAE (Version 4.0) should be used to assess Adverse Events and may be reviewed on-line at the following NCI website:

20.2. Appendix 2: Karnofsky performance scale

<table>
<thead>
<tr>
<th>Status</th>
<th>Karnofsky</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, no complaints</td>
<td>100</td>
</tr>
<tr>
<td>Able to carry on normal activities. Minor signs or symptoms of disease</td>
<td>90</td>
</tr>
<tr>
<td>Normal activity with effort</td>
<td>80</td>
</tr>
<tr>
<td>Care for self. Unable to carry on normal activity or to do active work</td>
<td>70</td>
</tr>
<tr>
<td>Requires occasional assistance, but able to care for most of his needs</td>
<td>60</td>
</tr>
<tr>
<td>Requires considerable assistance and frequent medical care</td>
<td>50</td>
</tr>
<tr>
<td>Disabled. Requires special care and assistance</td>
<td>40</td>
</tr>
<tr>
<td>Severly disabled. Hospitalization indicated though death nonimminent</td>
<td>30</td>
</tr>
<tr>
<td>Very sick. Hospitalization necessary. Active supportive treatment necessary</td>
<td>20</td>
</tr>
<tr>
<td>Moribund</td>
<td>10</td>
</tr>
<tr>
<td>Dead</td>
<td>0</td>
</tr>
</tbody>
</table>
20.3. **Appendix 3: New York Heart Association Functional Capacity Classification**

**Class I.** Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.

**Class II.** Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.

**Class III.** Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.

**Class IV.** Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.