CLINICAL PROTOCOL	
Title:	A SINGLE PATIENT PROTOCOL OF TRC105 COMBINED WITH STANDARD-DOSE BEVACIZUMAB FOR A PATIENT WITH METASTATIC AND REFRACTORY CHORIOCARCINOMA
Protocol Number:	105CC201
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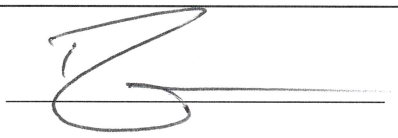
Signature & Date:	Signed:  Dated: 17DEC2015
Version Date:	Original Protocol: January 7th, 2015 Amendment #1: February 3rd, 2015 Amendment #2: April 6th, 2015 Amendment #3: December 17th, 2015

Statement of Confidentiality:

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

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1. SYNOPSIS

Name of Sponsor/Company: TRACON Pharmaceuticals, Inc.	
Name of Investigational Product: TRC105	
Name of Active Ingredient: TRC105	
Title of Study: **A SINGLE PATIENT PROTOCOL OF TRC105 COMBINED WITH STANDARD-DOSE BEVACIZUMAB FOR A SINGLE PATIENT WITH METASTATIC AND REFRACTORY CHORIOCARCINOMA**	
Study center(s): This study will be performed at one US center in one patient.	
Investigators: Neil Horowitz, MD	
Studied period (years): Estimated date patient enrolled: January 2015	**Phase of development:** 2
Rationale: Bevacizumab is a monoclonal antibody to vascular endothelial growth factor (VEGF) that inhibits angiogenesis and extends survival in patients with a wide variety of solid tumor types. TRC105, a monoclonal antibody to endoglin, an angiogenic target highly expressed on the tumor vessels and the tumor cells in choriocarcinoma. TRC105 has been well tolerated when dosed with bevacizumab in more than 50 patients with advanced cancer. Together, these antibodies may be efficacious in metastatic and refractory choriocarcinoma, a tumor type that is highly vascular and expresses endoglin.	
Objectives Primary: • To determine PFS and ORR of one patient with metastatic and refractory choriocarcinoma by RECIST 1.1 including measurement of serum β- hCG Secondary: • To determine the frequency and severity of adverse events as assessed by NCI CTCAE (Version 4.0) • To explore the effects of TRC105 and bevacizumab on circulating angiogenic protein biomarkers	
Methodology: This is a single patient study of TRC105 in combination with standard dose bevacizumab in a patient with metastatic and refractory choriocarcinoma for whom curative therapy is unavailable. TRC105 will be administered weekly in combination with bevacizumab. The patient will receive bevacizumab on days 1 and 15 of each 28 day cycle and will receive TRC105 on days 8, 11, 15 and 22 of cycle 1 and on days 1, 8, 15 and 22 of subsequent cycles. The first weekly dose of TRC105 will be split with 3 mg/kg administered on cycle 1 day 8 and 7 mg/kg administered on cycle 1 day 11, and then the full dose of 10 mg/kg given on cycle 1 day 15 and weekly thereafter.	
Number of patients (planned): One patient	

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

1. Willingness and ability to consent for self to participate in study
2. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures
3. Measurable disease by RECIST 1.1 and elevated serum β-hCG
4. Histologically proven choriocarcinoma that has progressed despite all described lines of chemotherapy for this condition

Exclusion Criteria:

1. Prior treatment with TRC105
2. Serious dose-limiting toxicity related to prior bevacizumab
3. Current treatment on another therapeutic clinical trial
4. Uncontrolled chronic hypertension defined as systolic > 140 or diastolic > 90 despite optimal therapy (initiation or adjustment of BP medication prior to study entry is allowed provided that the average of 3 BP readings at a visit prior to enrollment is < 140/90 mm Hg)
5. Symptomatic pericardial or pleural effusions
6. Uncontrolled peritoneal effusions requiring paracentesis more frequently than every 2 weeks
7. Active bleeding or pathologic condition that carries a high risk of bleeding (i.e. hereditary hemorrhagic telangiectasia)
8. Thrombolytic or anticoagulant use (except to maintain i.v. catheters) within 10 days prior to first day of study therapy
9. Cardiac dysrhythmias of NCI CTCAE grade ≥ 2 within the last 28 days
10. Known active viral or nonviral hepatitis
11. Open wounds or unhealed fractures within 28 days of starting study treatment
12. History of peptic ulcer disease or erosive gastritis within the past 6 months, unless treated for the condition and complete resolution has been documented by esophagogastroduodenoscopy (EGD) within 28 days of starting study treatment
13. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness
14. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for this study

Investigational product dose and mode of administration:

Following the appropriate premedication regiment, TRC105 is to be administered intravenously over 1 to 4 hours (+/- 15 minutes) on days 8, 11, 15, and 22 of cycle 1 and on days 1, 8, 15 and 22 of all subsequent cycles. There is a +/- 15 minute window for all infusions.

Duration of treatment:

The patient may continue on treatment until disease progression, unacceptable toxicity or withdrawal of consent, or other reasons.

The 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, the patient will be withdrawn from treatment in the case of:

1. Disease Progression. Progressive Disease as defined in RECIST 1.1 or rise in serum β- hCG on 2 consecutive cycles. Disease progression may also 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 ≥ 8 weeks OR discontinuation of study therapy for > 6 months following CR.
5. Arterial thrombosis of any grade (including cerebrovascular ischemia, cardiac ischemia/infarction, or peripheral or visceral arterial ischemia) or grade 4 thromboembolism. For grade 3 venous thromboembolism hold bevacizumab treatment. IF the planned duration of full dose anticoagulation is < 2 weeks, bevacizumab should be held until the full dose anticoagulation period is over. If the planned duration of full dose anticoagulation is > 2 weeks, bevacizumab may be resumed during full dose anticoagulation IF all the following criteria are met. 1. Subject does not have a pathologic condition that carries high risk of bleeding (i.e. tumor involving major vessels). 2. Subject has not had any hemorrhagic events on study. 3. The subject has a stable dose of heparin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab. 4. If thromboembolism worsens/recurs upon resumption of bevacizumab, despite anticoagulation, bevacizumab should be discontinued.

Reference therapy, dosage and mode of administration:

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab will be administered intravenously at a dose of 10 mg/kg on day 1 and 15 of each 28-day cycle prior to TRC105 (except on cycle 1 day 1 when TRC105 is not to be administered). The initial bevacizumab dose should be delivered over 90 minutes. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. Following bevacizumab, the line should be flushed with normal saline before TRC105 administration 30 minutes later.

Criteria for evaluation: Safety: A formally chartered in-house TRACON Safety Review Team will review safety data. Safety assessments include adverse events (AEs), physical exams, performance status, laboratory results (complete blood counts and serum chemistry) and 12-lead ECG's (if the patient develops an arrhythmia). Efficacy: Preliminary evidence of antitumor activity will be assessed by RECIST 1.1 and regression in β-hCG tumor marker.
Statistical methods: No statistical analyses are planned.

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Table 2: Abbreviations and Specialist Terms

Abbreviation or specialist term	Explanation
ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
AE	Adverse Event
AFP	Alpha Fetoprotein
AIDS	Acquired Immunodeficiency Syndrome
ALKs	Activin receptor-Like Kinases
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AUClast	Time of Last Measurable Concentration of Area Under the Curve
BALB/c mice	Mouse Strain
BUN	Blood Urea Nitrogen
β-hCG	Beta human chorionic gonadotropin
CA-125	Cancer Antigen-125
CABG	Coronary Artery Bypass Graft
CBC	Complete Blood Count
CEA	Carcinoembryonic Antigen
CHOP	Cyclophosphamide Hydroxydaunomycin Oncovin® Prednisone
CL	Clearance
C_{max}	Maximum Serum Concentration
CPA	Cyclophosphamide
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CTC	Common Terminology Criteria
dL	Deciliter
DLT	Dose Limiting Toxicity
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECM	Extracellular Matrix
EGFR	Epidermal Growth Factor Receptor
ELISA	Enzyme-Linked ImmunoSorbent Assay
EOS	End of Study
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practice
GTD	Gestational Trophoblastic Disease
GTN	Gestational Trophoblastic Neoplasia
HACA	Human Anti-Chimeric Antibodies
HAMA	Human Anti-Murine Antibodies
Her-2	Human epidermal growth factor receptor 2
HHT-1	Hereditary Hemorrhagic Telangiectasia Type 1
HIF-1-α	Hypoxia-Inducible Factor-1-α

HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HRA	Health Regulatory Authority
HUVECs	Human Umbilical Vein Endothelial Cells
ICH	International Conference on Harmonization
ID	Identification
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International Normalized Ratio
IP	Intraperitoneal
IRB	Institutional Review Board
i.v.	Intravenous
K_d	Avidity Binding Constant
kg	Kilogram
L	Liter
LDH	Lactate Dehydrogenase
LOQ	Limit of Quantification
µL	Microliter
Mg	Milligram
mL	Milliliter
MACA	Monkey Anti-Chimeric Antibody
MAMA	Monkey Anti-Murine Antibody
MI	Myocardial Infarction
mm	Millimeter
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCIC	National Cancer Institute of Canada
ng	Nanogram
NHP	Nonhuman Primate
NOAEL	No Adverse Effect Level
PBS	Phosphate-Buffered Saline
PD	Progressive Disease
PDGF	Platelet Derived Growth Factor
PlGF	Placental Growth Factor
pM	Picomolar
PR	Partial Response
PSA	Prostate Specific Antigen
PT	Prothrombin Time
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTT	Partial Thromboplastin Time
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
sCD105	Soluble CD105/endoglin
SCID	Severe Combined Immunodeficient
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase

SGPT	Serum Glutamic Pyruvic Transaminase
SN6j	Murine parent antibody of TRC105
sVEGFR2	Soluble VEGF Receptor 2
TGF-β	Transforming Growth Factor
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
US	United States of America
VEGF	Vascular Endothelial Growth Factor

2. INTRODUCTION

2.1. Background

2.1.1. Angiogenesis and Cancer

Angiogenesis is required for the survival and growth of solid cancers [1, 2]. It is generally accepted that solid cancers have two phases, an avascular phase and a vascular phase [2]. 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 that are 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 [3, 4]. Bevacizumab is also indicated for renal cell cancer, breast cancer and malignant glioma [5-7] with published evidence of clinical benefit in other solid tumor types. 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].

2.1.2. CD105 and Angiogenesis

CD105 (endoglin) is a homodimeric cell membrane glycoprotein that was initially identified as a human leukemia-associated antigen [12] and later also found on endothelial cells [13, 14]. The expression pattern of CD105 is relatively restricted and CD105 is mainly expressed on immature B-lineage/myeloid leukemia cells and endothelial cells [12, 13]. CD105 is a TGF-β coreceptor that is essential for angiogenesis [15, 16]. CD105 is strongly expressed on the proliferating vascular endothelium of solid tumors [14, 17]. All of these properties make CD105 a good target for the antiangiogenic therapy of cancer [18]. Vascular targeted therapy may be more effective for destroying large established tumors than conventional antiangiogenic therapy such as anti-VEGF therapy [19]. In animal models, CD105 targeted therapy has demonstrated both vascular

targeting effects and antiangiogenic effects by inducing regression of established tumors as well as by preventing new tumor formation and inhibiting expansion of existing tumors [14, 20-23]. Therefore, CD105 offers a novel alternative target relative to the VEGF inhibitors currently available for antiangiogenesis therapy. 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) [24, 25]. CD105 has also been show to protect hypoxic cells from apoptosis [26].

CD105 acts to modulate signaling of multiple kinase receptor complexes of the TGF-β superfamily, including TGF-β receptors, activin receptor-like kinases (ALKs) and activin receptors [27]. In the absence of CD105, activation of TGF-β receptors results in phosphorylation of SMAD proteins that inhibit endothelial cell growth. However, activation of CD105 by TGF-β modulates SMAD protein phosphorylation. The end result is release of the growth inhibitory effects of TGF-β receptor activation on endothelial. Not surprisingly, prevention of CD105 activation by anti-CD105 antibody acts synergistically with TGF-β to inhibit endothelial cell growth [28].

The expression of CD105 by endothelial cells is essential for the development of new vasculature. 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 [16].

CD105 is critical for normal human blood vessel development [29]. 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 [30]. 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 [31].

CD105 is highly expressed on the proliferating endothelial cells of tumor vessels including lung, breast, colorectal, gastric, liver, endometrial, renal cell, head and neck, and ovarian cancers. In adults, CD105 expression can be measured on activated monocytes and endothelial cells, and expression levels on endothelial cells exceed those on activated monocytes by approximately 10-fold [32, 33].

Importantly, CD105 expression is increased following inhibition of the VEGF pathway. CD105 expression increased more than two-fold in human pancreatic cancers grown in mice treated with an antibody that binds VEGF [34]. 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 [35].

CD105 expression is a prognostic factor in solid tumor patients. Higher numbers of tumor vessels expressing CD105 have been correlated with poor prognosis in clinical studies of breast cancer [36, 37], lung cancer [38], prostate cancer [39, 40], colorectal cancer [41, 42], gastric cancer [43], endometrial cancer [44], astrocytic brain tumors [45], hepatocellular carcinoma [46], ovarian cancer [47, 48], esophageal adenocarcinoma [49], and head and neck cancer [50, 51].

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 4-fold higher than the mean value in 40 healthy subjects without cancer [41]. In the study, a positive correlation was observed between CD105 concentration and stage of disease. For example, patients with advanced cancer had higher plasma CD105 levels than those with early-stage disease (r=0.20, p=0.0470). 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 [52]. 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 [37]. These sCD105 concentrations are relatively low compared to TRC105 concentrations > 100,000 ng/mL that were safely achieved in cancer patients treated with TRC105 monotherapy on Study 105ST101.

CD105 is expressed directly on certain cancers in addition to its expression on the tumor vessels. Choriocarcinoma is a vascular cancer that arises form trophoblast tissue that densely expresses CD105. CD105 has been shown to induce trophoblastic outgrowth and migration. Hence, patients with choriocarcinoma are viewed as excellent candidates for treatment with angiogenesis inhibitors, especially a therapy that directly targets CD105 expressed on choriocarcinoma.

2.2. TRC105 Background

TRC105 is a genetically engineered human/murine chimeric monoclonal antibody directed against human CD105 [53], a growth proliferation receptor found on the surface of normal and proliferating endothelial cells.

The antibody is an IgG1 kappa immunoglobulin containing murine variable region sequences and human constant region sequences [53]. 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 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 and to inhibit the growth of tumor xenografts [21]. Reactivity with tumor tissues is restricted to the tumor endothelium, as CD105 is not generally expressed on epithelial tumor cells [21]. TRC105 induces ADCC on proliferating HUVECs at low conentrations and induces apoptosis and growth inhibition at higher concentrations.

In trophoblastic cell line TRC105 was shown to directly inhibit growth in a dose dependent and methotrexate independent manner.

2.2.1. Studies with TRC105

Several studies with TRC105 are underway or have been completed. An open-label, phase 1, multicenter study of TRC105 (Study 105ST101) enrolled fifty patients, who were treated until disease progression with TRC105 at 0.01-15 mg/kg/q2wk or 10-15 mg/kg/wk. Studies of TRC105 in prostate, bladder, and ovarian cancer and a phase 1b study of TRC105 in

combination with bevacizumab have also been completed. Ongoing studies include a phase 1b study of TRC105 in combination with capecitabine in breast cancer, a phase 1b study of TRC105 in combination with sorafenib in liver cancer, a phase 1b study of TRC105 in combination with axitinib in renal cell carcinoma, and phase 2 studies of TRC105 monotherapy in liver cancer and in combination with bevacizumab in glioblastoma multiforme (2 studies) and renal cell carcinoma.

2.2.1.1. 105ST101 Phase 1 Monotherapy

2.2.1.1.1. 105ST101 Phase 1 Monotherapy 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.

2.2.1.1.2. 105ST101 Phase 1 Monotherapy Immunogenicity

In Study 105ST101, serum samples for evaluation of TRC105 immunogenicity, including HAMA and HACA, were collected pre-dose 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.

2.2.1.1.3. 105ST101 Phase 1 Monotherapy 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. Dose escalation proceeded stepwise until the top dose was reached. The maximum tolerated dose was exceeded at 15 mg/kg weekly and the recommended phase 2 dose of TRC105 was therefore determined to be 10 mg/kg weekly. Three of 4 patients at 15 mg/kg weekly developed grade 3 hypoproliferative anemia (without leucopenia or thrombocytopenia) in cycle 2, and one of the three progressed to grade 4 in cycle 3. Anemia was associated with accumulation of TRC105 and characterized by a low reticulocyte production index. Additional laboratory and clinical evaluations excluded common causes of anemia including blood loss, hemolysis, plasma volume expansion, inadequate erythropoietin, iron deficiency, and vitamin B-12 or folate deficiency. The anemia is believed to result from TRC105-mediated suppression of proerythroblasts, the only cells in the bone marrow known to express substantial levels of CD105 [55]. Anemia was reversible and manageable with dose reduction and standard supportive measures including erythropoietin and blood transfusion.

Infusion reactions, anemia, fatigue, epistaxis and headache were the most frequently observed adverse events considered related to TRC105. The majority of treatment-related adverse events were grade 1 or 2.

Infusion reactions, among the most common adverse events, were usually with the initial TRC105 dose and included one or more of the following signs or symptoms: rigors, bronchospasm, urticaria, hypertension, hypotension, tachycardia or bradycardia. Infusion reactions were initially reported at 1 mg/kg every 2 weeks for patients receiving TRC105 produced in NS0 cells without premedication. TRC105 produced in CHO cells was known to more potently engage ADCC *in vitro* than TRC105 produced in NS0 cells. Because of this, the initial dose level for patients receiving CHO-produced TRC105 was de-escalated to 0.3 mg/kg. Despite dose de-escalation, the first two patients at 0.3 mg/kg treated with CHO-produced TRC105 experienced grade 2 and grade 3 infusion reactions with the first dose in the absence of premedication. The protocol was therefore amended to require a glucocorticoids -based premedication regimen and extend the initial infusion duration from 1 to 4 hours.

The amendment mandating premedication and extended initial infusion duration successfully reduced the frequency and severity of infusion reactions and allowed dose escalation to continue. One additional patient who received CHO-produced TRC105 at 1 mg/kg developed a grade 3 infusion reaction with the third dose given over 2 hours. This patient had experienced a grade 2 infusion reaction when the dose was administered over 4 hours. In all three patients with grade 3 infusion reactions, TRC105 was not detectable in serum at the time of dosing, which allowed *de novo* binding of TRC105 to CD105 expressing endothelium within the vasculature. Grade 3 infusion reactions were not observed in patients dosed at 10 or 15 mg/kg who maintained TRC105 serum levels known to saturate CD105 binding sites for the full dosing interval. At dose levels where continuous TRC105 serum levels were achieved, glucocorticoids were safely discontinued and the infusion duration reduced to 1 hour.

Three patients developed grade 1 cutaneous telangiectasia on the trunk early in the course of therapy, all at dose levels of 10 or 15 mg/kg weekly that resulted in continuous serum levels of TRC105 known to saturate CD105 sites on human endothelium. Grade 1 or 2 hemorrhage was reported, including intermittent postcoital vaginal bleeding (that also occurred prior to TRC105 treatment), epistaxis, and superficial gingival bleeding.

Grade 1 or 2 headaches were observed, mainly in patients treated at doses of TRC105 above 3 mg/kg. Headaches began the day following infusion and were generally manageable with acetaminophen. However, grade 2 headache in one patient at 15 mg/kg weekly prompted discontinuation prior to completion of the dose-limiting toxicity evaluation period. Fatigue was one of the more common adverse events attributable to TRC105 and was more prevalent at doses above 3 mg/kg.

One patient developed dose-limiting toxicity of grade 4 hemorrhage presenting as melena from a gastric ulcer within 5 days of the initial TRC105 infusion at 0.1 mg/kg. He discontinued TRC105 treatment, was transfused 2 units of packed red blood cells and the bleeding resolved with nonsurgical management by the time of upper endoscopy. Serious bleeding was not observed following protocol amendment to exclude patients with a history of peptic ulcer disease (unless healing was documented) and patients on ulcerogenic medications including non-steroidal anti-inflammatory drugs.

Classic toxicities associated with VEGF inhibition, including hypertension, proteinuria and thrombosis were not prominent. One patient with recurrent anal cancer treated at 0.1 mg/kg developed proteinuria considered possibly related to TRC105, but proteinuria was also noted prior to TRC105 dosing. Transient hypertension (156/112) without QT changes occurred in a single patient one day following infusion of 15 mg/kg, and was controlled by a single dose of oral antihypertensive medication. There were no arterial or venous thromboembolic events, nor gastrointestinal or other perforations in these patients.

2.2.1.1.4. 105ST101 Phase 1 Monotherapy Efficacy

In study 105ST101 stable disease ≥ 2 months was observed in 21 of 45 patients (47%) and stable disease ≥ 4 months in 6 of 44 patients (14%). Decreases in CEA, PSA, or CA-125 were noted in 7 of 21 patients (33%) and a global decrease in key angiogenic biomarkers was observed with treatment. One patient with castrate-refractory prostate cancer remains on TRC105 treatment after 6 years at a TRC105 dose of 0.01 mg/kg every 2 weeks. He has an ongoing complete PSA response, with resolution of bone pain and bone scan normalization. One patient with metastatic carcinosarcoma, manifested decreased tumor burden on computerized tomographic scanning and maintained stable disease for 20 months on therapy. The latter is especially notable when one considers that this patient had received three prior treatments -- carboplatin + paclitaxel for 4 months, anastrozole for 8 months, and ifosfamide for 2 months -- and had manifested tumor progression on each. In effect, TRC105 provided the most favorable clinical outcome and did so as a fourth-line therapy.

2.2.1.2. Phase 1b 105ST102 Study with Bevacizumab

2.2.1.2.1. 105ST102 Summary of Safety

Administration of TRC105 at a dose of 3 mg/kg weekly in combination with bevacizumab was well tolerated by three patients without the development of dose limiting toxicity (DLT) and dose escalation occurred per the protocol to cohort 2 (6 mg/kg TR105 weekly). However, the concurrent administration of 6 mg/kg TRC105 and bevacizumab on day 1 resulted in the development of moderate or severe headaches (including two grade 3 headaches) in four of five treated patients. The 6 mg/kg dose of TRC105 was tolerated when the initial TRC105 dose was delayed one week following bevacizumab dosing at 10 mg/kg every two weeks. Tolerability was further improved when the initial dose of TRC105 was given over two days during the first week of TRC105 dosing, and dose escalation proceeded to the recommended phase 2 dose of 10 mg/kg TRC105 weekly. At the recommended phase 2 dose of both drugs (10 mg/kg), TRC105 serum concentration were present above target concentration continuously and immunogenicity was rarely observed.

A total of 38 patients were dosed on study across six cohorts and four dose levels. Other than headaches that were mitigated by adjusting the dosing schedule of TRC105, the combination of TRC105 and bevacizumab was well tolerated. Two patients experienced grade 3 serious adverse suspected events as described below. Most adverse events were graded as 1 or 2 and Grade 4 and 5 suspected adverse events were not observed. Grade 3 suspected adverse reactions included anemia (the dose limiting toxicity of TRC105 established as a single agent; 9 patients), headache (4 patients; three of which occurred prior to adjusting the schedule of TRC105), fatigue (2 patients), brain abscess (1 patient), infusion reaction (in a patient dosed at 6 mg/kg), and

decreased appetite (1 patient). Headache was the most common suspected adverse event and occurred in 31 patients (86.1%); three patients (7.9%) experienced migraine headaches (two of grade 1 and one of grade 2 severity). Headaches were treated with triptans and NSAIDs.

Two patients experienced serious adverse suspected events as described below. One of the grade 3 headaches (in a patient dosed at 8 mg/kg without splitting the initial TRC105 dose over two days) resulted in hospitalization and patient discontinuation. One patient dosed at 10 mg/kg of TRC105 experienced a serious suspected event of grade 3 brain abscess. Serious adverse events, considered unrelated to TRC105 treatment, included: grade 3 pneumonia and subsequent grade 4 MRSA sepsis that was complicated by a non Q-wave myocardial infarction during a period of hemodynamic instability while hospitalized; grade 3 ileus at the time of symptomatic disease progression; grade 5 disease progression; grade 3 left foot cellulitis; grade 3 recurrent pneumothorax; grade 3 small bowel obstruction; grade 4 urosepsis.

At least one sign of the triad of epistaxis, gingival bleeding and telangiectasia, reflecting vascular ectasia characteristic of the Osler-Weber-Rendu syndrome of endoglin haplotype insufficiency (i.e., an autosomal dominant genetic disorder of heterozygous endoglin expression) was observed frequently. One of these signs or symptoms (of grade 1 or 2 severity) was noted in one of three patients treated at 3 mg/kg, four of eight patients treated at 6 mg/kg, four of eight patients treated at 8 mg/kg and in all nineteen patients treated at 10 mg/kg of TRC105, generally within the first month of dosing. These signs and symptoms are an expected pharmacologic effects of TRC105 binding to the endoglin receptor (i.e., they are characteristic of the Rendu-Osler-Weber syndrome, that is caused by endoglin haploinsufficiency), and were also observed routinely within the first month of dosing of 10 mg/kg weekly in the single agent TRC105 dose escalation study.

Infusion reactions were, as expected, more notable at lower doses, and were rare at the MTD of TRC105 of 10 mg/kg, when TRC105 serum concentrations were maintained continuously. Two of nineteen patients (10%) dosed with 10 mg/kg of TRC105 each experienced a single infusion reaction of grade 2 severity, both with the initial dose of TRC105, that required a brief interruption of the infusion prior to completion of the scheduled dose.

Clinically significant anemia was not reported in patients dosed with 3 mg/kg or 6 mg/kg of TRC105, was reported in three of seven patients (43%; all grade 3) dosed with 8 mg/kg of TRC105, and was observed in nine of 19 (47%; three of grade 2 and six of grade 3 severity) of patients dosed with 10 mg/kg of TRC105. Anemia prompted transfusion of packed red blood cells in 10 patients and growth factors were used in five patients.

Other, less frequent, suspected adverse reactions included hypothyroidism, periorbital edema (which was generally noted prior to splitting the initial dose of TRC105), gingival pain, nausea, oral pain, vomiting, edema, decreased appetite, dyspnea, nasal congestion, rash and flushing.

Other adverse events characteristic of each individual drug were not increased in frequency or severity when the two drugs were administered together. Of note, the concurrent administration of bevacizumab and TRC105 did not potentiate the known toxicities of bevacizumab of hypertension, hemorrhage (including tumor-associated hemorrhage, and pulmonary hemorrhage or hemoptysis), or proteinuria. Reversible posterior leukoencephalopathy syndrome (RPLS), congestive heart failure, fistulae, gastrointestinal perforation impaired wound healing, and arterial thromboembolic events, were not observed.

Notably, hypertension and proteinuria, known adverse events of bevacizumab, were rarely observed when bevacizumab was given with TRC105. Mild and transient clinically significant hypertension or blood pressure increases were observed in five patients (13%; grade 3 in one case (prior to dosing with study drugs) and grade 2 in four cases) and mild transient proteinuria was observed in two patients (5%; both grade 2).

2.2.1.2.2. 105ST102 Summary of Efficacy

The combination of TRC105 and bevacizumab was active in patients with advanced refractory cancer who had progressed on prior bevacizumab or other VEGF inhibitor treatment. Thirty-three patients had measurable disease (31 patients) or evaluable disease (2 patients) at baseline and received at least one follow up scan and were evaluable for the primary efficacy outcome of ORR by RECIST 1.1. Eighteen patients with measureable disease (58%) had a best response of stable disease or partial response. Two patients (6%), both of whom had been treated with bevacizumab and chemotherapy prior to study entry and were then treated at the top dose level of TRC105 and bevacizumab, had RECIST 1.1- defined partial responses, including one patient with colorectal cancer remained on treatment for more than 28 months. A total of 14 patients (45%) had decreases in overall tumor burden, of whom 10 received prior VEGF inhibitor treatment (usually bevacizumab with chemotherapy). Notably, the duration of treatment with TRC105 and bevacizumab of six patients (20% of those with measureable disease) exceeded the duration of treatment of the most recent treatment regimen containing a VEGF inhibitor (i.e., VEGFR TKI or bevacizumab), received prior to study entry. These six patients had decreases in tumor burden and several were responders by Choi criteria or RECIST. Time to progression ranged from 0 to 861 days. Reductions in tumor markers ranging from 5% to 85% were observed in 15 of 28 (54%) patients with relevant tumor markers. Three patients demonstrated clinical benefit throughout the study (patient 10038102 at cycle 12 day 22, patient 10018106 at cycle 7 day 22 and patient 10028101 at cycle 17 day 1); two of them continue to receive treatment under a continuation protocol (105CON101).

2.2.1.2.3. Background on Choriocarcinoma

Gestational trophoblastic disease (GTD) is the term used to describe a group of rare diseases that originate in the placenta and have the potential to locally invade the uterus and metastasize. The pathogenesis of GTD is unique because the maternal tumor arises from gestational rather than maternal tissue. The major histologic entities for this disease include complete molar pregnancy, partial molar pregnancy, invasive mole, and choriocarcinoma. Molar pregnancies although benign are considered to be premalignant because they have the capability of developing into a malignancy. The term gestational trophoblastic neoplasia (GTN) is used when molar and non-molar pregnancies become malignant, and comprise the morphologic entities of invasive mole and choriocarcinoma. Choriocarcinoma consists of invasive, highly vascular and anaplastic trophoblastic tissue made up of cytotrophoblasts and syncytiotrophoblasts without villi. Choriocarcinoma metastasizes hematogenously and can follow any type of pregnancy, but most commonly develops after complete hydatidiform mole. The most common metastatic site is the lungs which are involved in over 80 percent of patients with metastases. Staging for GTN is based on a number of unique criteria that differs from the usual staging procedures and prognosis is dependent upon factors that are not reflected in the anatomic extent of disease such as age,

type of antecedent pregnancy, interval between the antecedent pregnancy and the persistent disease and serum β-hCG level. These risk factors are used to establish a WHO Risk score.

Almost all trophoblastic malignancies develop from the cyto-and syncytial cells of the villous trophoblast and produce abundant amounts of β-hCG, the measurement of which serves as a reliable tumor marker for diagnosis, monitoring treatment response and follow-up to detect recurrence. Currently, with sensitive quantitative assays for β-hCG and highly effective chemotherapy, most women with GTN can be cured and their reproductive function preserved providing they are managed according to well-established guidelines.

GTN is uniquely sensitive to chemotherapy which is the major treatment modality. Selection of an appropriate regimen should take into account the FIGO Stage and WHO Prognostic Score as defined above. Despite the success of chemotherapy, other modalities such as surgery and radiation therapy should also be utilized where indicated, particularly in the patients with high-risk scores. Most patients with low risk disease are cured with single agent chemotherapy with the most active agents being methotrexate and actinomycin D. For those that present with high risk disease or have relapse/resistance to monotherapy, multiagent chemotherapy regimens are used. These regimens include EMA-CO, EMA-EP, TE-TP and are often able to produce cure for these women. Rarely, if standard chemotherapy options have been ineffective there are reports of salvage with use of 5-FU or stem cell transplant.

2.2.2. Description of Bevacizumab

Bevacizumab (Avastin®) is an IgG1 monoclonal antibody to VEGF-1. It is a vascular endothelial growth factor-specific angiogenesis inhibitor indicated for the treatment of metastatic colorectal cancer, non-squamous non-small cell lung cancer, metastatic breast cancer, glioblastoma, and metastatic renal cell carcinoma.

2.2.2.1. Rationale for Adding TRC105 to Bevacizumab

TRC105 is a novel angiogenesis inhibitor that complements bevacizumab in preclinical models. Together, these antibodies may result in more effective angiogenesis inhibition in a patient with choriocarcinoma, given the vascular nature of this tumor and direct expression of CD105 on the cancer cells.

2.3. Patient Background

The patient that will be treated as part of this protocol is a 38 year old woman initially treated with single agent methotrexate for gestational trophoblastic neoplasia following a molar pregnancy in 2007. She then had a subsequent pregnancy in March, 2013 which resulted in a miscarriage, but was followed by the development of a uterine mass and persistently elevated β-hCG suspicious for recurrent gestational trophoblastic neoplasia. Given this diagnosis she was treated with two cycles of single agent methotrexate and then two rounds of pulsed actinomycin-D, both of which failed.

As per standard therapy, she then initiated EMA-CO (etoposide, methotrexate, actinomycin-D, cyclophosphamide, oncovorin) and had a hysterectomy, which confirmed a diagnosis of choriocarcinoma. Despite this, her β-hCG marker continued to rise. She was subsequently switched to EMA-EP (same as above but cisplatin instead of oncovorin) and went into remission in October 2013 after 7 cycles, followed by 3 cycles of consolidation chemotherapy.

In December, 2013 she recurred with multiple pulmonary metastases. She had 3 cycles of TP/TE (Taxol, cisplatin/Taxol, etoposide) but progressed, then received 2 cycles ICE (ifosfamide, carboplatin, etoposide).

She failed to go into remission, so in May, 2014 underwent high dose chemotherapy with stem cell rescue. She initially went into remission with normalization of her β-hCG, then relapsed in June, 2014 with multiple pulmonary metastases. In July, 2014, she had thorascopic resection of 10 pulmonary nodules, but continued to have a rising β-hCG.

She was subsequently treated with Xeloda. She had a good initial response, but now is progressing after 5 cycles. She developed isolated brain metastases that were treated with stereotactic brain radiation on 11/25/ 2014. Subsequent brain MRI on 12/17 showed treatment effect and no new lesions. Her current measurable disease consists of multiple pulmonary nodules up to 2 cm in diameter on last scan.

As of the writing of this protocol there are no proven therapies for this disease.

2.4. Potential Risks and Benefits to Human Patients

2.4.1. Potential Risks

TRC105

Grade 3 anemia has occurred with TRC105 therapy at the recommended phase 2 dose. All patients treated with TRC105 should be monitored closely for anemia and treated appropriately, including the possibility of TRC105 dose reductions. Anemia may be caused by correctable mineral or vitamin deficiency. The anemia related to TRC105 is hypoproductive in nature and is reversible with interruption of treatment, transfusion, erythropoietin, and other interventions as appropriate.

Gastrointestinal hemorrhage has occurred with TRC105 therapy. Patients with active ulcer disease or risk factors for ulcer disease are excluded from this study.

Grade 1 and 2 cutaneous telangiectasia related to TRC105 occur early in the course of therapy and have been the source of gingival bleeding and epistaxis. Telangiectasia 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.

Premedication including the use of glucocorticoids is required prior to infusion of TRC105 to reduce the frequency and severity of infusion reactions. Infusion reactions following TRC105 dosing generally occur with the first TRC105 dose and include a grade 4 vasovagal reaction that resolved without sequellae. Signs and symptoms of TRC105 infusion reactions include hypertension, hypotension, dyspnea, bronchospasm, chills/rigors, chills, sweats, fever, nausea, tachycardia, bradycardia, EKG changes, flushing, urticaria, pruritus, and headache, generally of grade 1 and 2 severity. 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.

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 CHO-produced TRC105 are rare. 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 for anti-product antibody concentrations to further characterize the immunogenicity of TRC105 and potential clinical implications.

Grade 3 cerebrovascular hemorrhage resulting in hemiparesis occurred in one patient with hepatocellular cancer who was thrombocytopenic (who entered the study with a platelet count of 60,000/uL) in a study of TRC105 with sorafenib. Patients must have a platelet count of > 100,000/uL to enter this study (see inclusion criteria). A grade 2 transient ischemic attack was reported in a study of TRC105 and pazopanib. Transient Grade 3 hepatic encephalopathy occurred in one patient with cirrhosis and hepatocellular carcinoma who received TRC105 in combination with sorafenib. Grade 3 pancreatitis was also observed in this study. Grade 5 intracranial hemorrhage occurred in one glioblastoma patient with markedly abnormal blood clotting parameters in a study of TRC105 with bevacizumab. A patient with glioblastoma developed temporary confusion and slurred speech following treatment with TRC105 and bevacizumab that required hospitalization for observation. Another patient with glioblastoma, who underwent resection and had a history of an abnormal collection of cerebral spinal fluid, developed a grade 2 cerebral spinal fluid leak. Another patient with glioblastoma with a history of recurrent meningitis developed recurrent grade 3 bacterial meningitis while treated with bevacizumab and TRC105.

Grade 3 myocardial infarction (non-Q wave infarct associated with hypertension following an infusion reaction) was observed in a patient with hepatocellular cancer following treatment with TRC105 that resolved without sequelae. In addition, a Grade 5 myocardial infarction occurred in a patient with coronary artery disease who received TRC105 in combination with sorafenib. Patients with evidence of active coronary artery disease are excluded from participation in this trial (see exclusion criteria).

Adult respiratory distress syndrome that required temporary intubation occurred in one patient who received TRC105 with pazopanib, from which the patient recovered. Of note, interstitial lung disease has been added as an adverse drug reaction and warning/precaution to the core safety information for pazopanib. Pneumothorax (collapsed lung) has been observed in trials of TRC105 administered with a VEGFR TKI in patients with lung metastases.

A patient with renal cell carcinoma treated with TRC105 and axitinib developed grade 3 localized perforation of the large intestine at the site of an intraabdominal tumor metastasis that required percutaneous drainage and diverting colostomy.

Infections have been observed rarely. Grade 3 infected lipoma/cyst was observed in a Phase 2 study of TRC105 as a single agent in patients with metastatic bladder cancer. Grade 3 orbital cellulitis and grade 3 brain abscess were observed in patients treated with TRC105 and bevacizumab and considered possibly related to TRC105. Grade 1 and 2 gingivitis including infection and ulceration has also been observed. Overall, infections have been observed in fewer

than 5% of patients and have largely been considered unrelated to treatment with TRC105. Reversible grade 3 colitis was reported in a patient treated with TRC105 and pazopanib.

Grade 1-3 headaches have been observed following TRC105 treatment, generally within hours following completion of the initial infusion. Headaches are throbbing in nature, are not associated with radiographic abnormalities, and have responded to treatment with non-steroidal anti-inflammatory agents and to triptans. Headaches were particularly common when TRC105 and bevacizumab were initially dosed on the same day and were ameliorated when TRC105 was dosed one week following bevacizumab dosing and given over two days during the initial week of dosing.

Nasal congestion and periorbital edema have been observed with TRC105 dosing, particularly when dosed in combination with bevacizumab. The edema has been transient in nature and treated with corticosteroids.

Fatigue of grade 1- 3 severity has been reported following dosing with TRC105. Maculopapular rash and skin flushing of grade 1 and grade 2 severity have also been reported. A patient receiving treatment with TRC105 and sorafenib developed self-limited pancreatitis of grade 2 severity.

Bevacizumab

Side effects associated with the use of bevacizumab include gastrointestinal perforation, hypertension, impaired wound healing, an increased incidence of arterial thromboembolic events, venous thromboembolic events (including pulmonary embolism), hemorrhage (including tumor-associated hemorrhage, mucocutaneous hemorrhage, and pulmonary hemorrhage or hemoptysis), proteinuria, rare reports of Reversible Posterior Leukoencephalopathy Syndrome (RPLS), congestive heart failure, fistulae, hypothyroidism, hypersensitivity reactions, headache and infusion reactions. Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone.

No specific studies in animals have been performed to evaluate the effect of bevacizumab on fertility. There are no adequate and well-controlled studies in pregnant women. Immunoglobulins are excreted in milk, although there are no data specifically for bevacizumab excretion in milk. Since bevacizumab could harm infant growth and development, women should be advised to discontinue breastfeeding during bevacizumab therapy and not to breast feed for at least 6 months following the last dose of bevacizumab.

Computed Tomography (CT) Scans

Patients will be exposed to a small amount of radiation as a result of the CT scans required in this study. This degree of exposure has not been associated with harmful health effects. In addition, the frequency of CT scans performed in this study is similar to the standard of care frequency.

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 patient has had a hysterectomy so any concerns to unborn children are not an issue for this study.

2.4.2. Potential Benefits

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

2.5. Conduct

This clinical trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirements.

3. TRIAL OBJECTIVES AND PURPOSE

3.1. Primary:

- To determine PFS, and ORR of one patient with metastatic and refractory choriocarcinoma by RECIST 1.1 including measurement of serum β-hCG

3.2. Secondary:

- To determine the frequency and severity of adverse events as assessed by NCI CTCAE (Version 4.0)
- To explore the effects of TRC105 and bevacizumab on circulating angiogenic protein biomarkers

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan: Description

4.1.1. Trial Overview

This is a single patient study of TRC105 in combination with standard dose bevacizumab in one patient with metastatic and refractory choriocarcinoma for whom curative therapy is unavailable. TRC105 will be administered weekly in combination with bevacizumab. The patient will receive bevacizumab on days 1 and 15 of each 28 day cycle and will receive TRC105 on days 8, 11, 15 and 22 of cycle 1 and on days 1, 8, 15 and 22 of subsequent cycles. The first weekly dose of TRC105 should be split with 3 mg/kg administered on cycle 1 day 8 and the balance of the weekly TRC105 dose administered on cycle 1 day 11, and then the full dose given on cycle 1 day 15 and weekly thereafter.

If the patient achieves complete remission (normalization of β-hCG on consecutive measurements separated by at least two weeks), she will be treated with at least 4 consolidation cycles of study treatment. If the patient achieves a CR following at least 4 cycles of consolidation therapy she can remain off study treatment for ≤ 6 months and subsequently re-initiate study treatment should she start to relapse (i.e. β-hCG increase on consecutive measurements separated by at least two weeks or increase in overall tumor burden) during the 6 months.

4.1.2. Trial Procedures

All on-study procedures are permitted within the time window indicated in the Schedule of Assessments (Table 3).

4.1.2.1. Screening

The following screening procedures must be performed within 28 days prior to the first day of study therapy. 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 3).

- Patient signature on current Institutional Review Board (IRB) approved informed consent form. Prior to undergoing any study-specific procedure, the patient must read and sign the current Institutional Review Board (IRB) approved informed consent form. The patients may sign consent prior to the 30 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, ECOG performance status, and vital signs.
- Hematology, coagulation (PT or INR) and serum chemistry to be performed locally.
- Urinalysis to be performed locally.

- CT or MRI scans of chest, abdomen and pelvis in addition to any other applicable sites of disease. Brain and bone scans to be performed if metastasis is suspected prior to starting the study.
- Single tracing 12-Lead ECG (QT, PR and QRS intervals and heart rate will be captured).
- Assessment of Adverse Events (serious and nonserious) from the date of informed consent.
- Assessment of concomitant medications from 30 days prior to the start of study treatment.

4.1.2.2. Trial Period

Hematology, blood chemistry, urinalysis, and physical examination 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 the combination of TRC105 and bevacizumab unless otherwise indicated in the Schedule of Assessments. The patients will initially receive 2 cycles (approximately 8 weeks) of treatment. If the patient demonstrates a response of CR, PR or SD, she 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 3).

- Physical examination including examination of all major body systems, ECOG performance status, and vital signs.
    - Assessment of vital signs during TRC105 infusion: Vital signs are to be assessed pre-infusion (within 30 minutes of starting TRC105 infusions) 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 should be performed as clinically indicated.
- Blood sampling for tumor markers (e.g. β-hCG), to be analyzed locally.
- Blood sampling for angiogenic protein biomarkers. Samples will be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).
- CT or MRI scans of chest, abdomen and/or pelvis in addition to any other applicable sites of disease. Scan of the chest, abdomen, and pelvis to be performed on-study as outlined in the assessment table. Known areas of disease should be consistently followed throughout the study. Assessments should be performed whenever disease progression is suspected. Allowable window for tumor imaging studies is +/- 7 days. Brain and bone scans are to be performed if metastasis is suspected.

- Administration of TRC105. TRC105 diluted in normal saline will be administered according to the schedule of assessments as a 1 to 4 hour infusion (+/- 15 minutes) following premedication (see Section 6.7 and Table 3). 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. The allowable dosing window is +/- 2 days.
- Administration of bevacizumab on day 1 and 15 of each 28-day cycle as described in the bevacizumab package insert.
- Assessment of TRC105 and bevacizumab drug accountability.
- Assessment of adverse events.
- Assessment of concomitant medications and concomitant treatments.

4.1.3. Complete Response Discontinuation of Therapy Visit

Assessments need to be completed if they were not completed during the previous 2 weeks if the patient discontinues study therapy due to CR following at least 4 cycles of consolidation therapy. The following will be performed according to the Schedule of Assessments (Table 3).

- Physical examination including examination of all major body systems, ECOG performance status, and vital signs.
- Hematology, coagulation (PT or INR) and serum chemistry to be performed locally.
- Urinalysis to be performed locally. Microscopic analysis should be performed as clinically indicated.
- Blood sampling for tumor markers (e.g. serum β-hCG), to be analyzed locally.
- Blood sampling for angiogenic protein biomarkers. Samples will be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).
- CT or MRI scans of chest, abdomen and pelvis in addition to any other applicable sites of disease.
- Assessment of adverse events.
- Assessment of concomitant medications and concomitant treatments.

4.1.4. End of Study Assessments

Assessments need to be completed if they were not completed during the previous 2 weeks on study. The following will be performed according to the Schedule of Assessments (Table 3).

- Physical examination including examination of all major body systems, ECOG performance status, and vital signs.
- Hematology, coagulation (PT or INR) and serum chemistry to be performed locally.

- Urinalysis to be performed locally. Microscopic analysis should be performed as clinically indicated.
- Blood sampling for tumor markers (e.g. serum β-hCG), to be analyzed locally.
- Blood sampling for angiogenic protein biomarkers. Samples will be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).
- CT or MRI scans of chest, abdomen and pelvis in addition to any other applicable sites of disease.
- Assessment of adverse events.
- Assessment of concomitant medications and concomitant treatments.

4.1.5. Post Treatment Follow-up

The following will be performed according to the Schedule of Assessments (Table 3). Adverse events should be followed for 28 days after completion of study protocol. The total follow-up period will be two years after the CR Discontinuation of Therapy Visit or EOS Visit.

- 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.
- Assessment of concomitant medications and concomitant treatments.
- If the patient has a CR and comes off study treatment following consolidation therapy she will have β-hCG levels measured every month for 6 months or until resumption of study therapy; after 6 months, the patient is no longer eligible for study therapy and will have β-hCG levels measured every month until disease progression, start of new therapy, or for a maximum of 18 months. If the patient comes off study with measurable β-hCG for reasons other than CR she will have β-hCG levels measured at least every 2 weeks from last measurement until start of new therapy.
- Long term survival telephone call every 2 months for 2 years following discontinuation.

Table 3: Schedule of Assessments

Protocol Activities	Screening	*Cycle 1					*Cycle 2				*Cycle 3+ Responding Patients [19]				CR DC Therapy Visit [3]	End of Study [4]	**Post Treatment Follow-up [20]		
	Day -30	Day 1 [1,2]	Day 8 [1]	Day 11 [1]	Day 15 [1]	Day 22 [1]	Day 1 [1]	Day 8 [1]	Day 15 [1]	Day 22 [1]	Day 1 [1]	Day 8 [1]	Day 15 [1]	Day 22 [1]			28 Days after EOS Visit	Every Month up to 2 Yrs	Every 2 Months up to 2 Yrs
Baseline Documentation																			
Informed Consent [5]	X																		
Medical/Oncology History [6]	X																		
Physical Examination [7]	X	X					X				X				X	X			
Vital Signs [8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Laboratory Studies																			
Hematology [9]	X	X	X		X	X	X	X	X	X	X				X	X			
Coagulation [9]	X	X					X								X	X			
Blood Chemistry [9]	X	X	X		X	X	X				X				X	X			
Thyroid Stimulating Hormone [9]	X	X					X				X				X	X			
Urinalysis [10]	X	X					X				X				X	X			
Treatment w/ Study Drug																			
TRC105 Dosing [11]			X	X	X	X	X	X	X	X	X	X	X	X					
Bevacizumab Dosing [12]		X			X		X		X		X		X						
Tumor Assessments																			
CT or MRI Scans [13]	X									X				Cycles 4, 6, 8 etc.	X	X			
Other Clinical Assessments																			
12-Lead ECG [14]	X																		
Concomitant Medications/Treatments [15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Baseline Signs and Symptoms [16]	X																		
Adverse Events [16]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Special Laboratory Assessments																			
Protein Biomarkers [17]		X	X				X								X	X			
Tumor Markers [18]		X					X				X				X	X	X	X	
Long Term Follow-Up																			
Phone Call Long Term Follow-Up																			X

*Allowable window for each visit within the cycle is +/- 2 day unless otherwise stated

**Allowable window for Post Treatment Follow-up is +/- 1 week

Schedule of Assessments Footnotes

1. **Days of Treatment with TRC105:** All assessments should be performed prior to dosing with TRC105/bevacizumab unless otherwise indicated. Each cycle is 28 days in duration.
2. **Cycle 1 day 1:** Hematology, blood chemistry, urinalysis, and physical examination not required if acceptable screening assessment is performed within 7 days prior to the start of treatment on cycle 1 day 1.
3. **CR Discontinuation of Therapy Visit:** Assessments need to be completed if they were not completed during the previous 2 weeks on study therapy (previous 4 weeks for radiologic tumor assessments) if the patient discontinues therapy due to CR following at least 4 cycles of consolidation therapy.
4. **End of Study Visit:** Assessments need to be completed if they were not completed during the previous 2 weeks (previous 4 weeks for radiologic tumor assessments) if the patient permanently discontinues all study therapy due to AE, patient decision, investigator decision, or any other reason. If the patient completed a "CR Discontinuation of Therapy Visit" and subsequently permanently discontinues the trial due to (1) continued CR, the "End of Study Visit" does not need to be completed and the "CR Discontinuation of Therapy Visit" will be the end of study visit, or (2) progression, adverse event, or any other reason except continued CR, the "End of Study Visit" should be completed.
5. **Informed Consent:** Must be obtained prior to undergoing any study specific procedure and may occur prior to the 30-day screening period.
6. **Medical/Oncologic History and Demographics:** To include information on prior anticancer therapy.
7. **Physical Examination:** Examination of major body systems and ECOG performance status.
8. **Vital Signs:** Heart rate, temperature, blood pressure, respiratory rate, weight. Assessment of Vital Signs during TRC105 Infusion: Vital signs are to be assessed pre-infusion (within 30 min of starting TRC105 infusions) 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).
9. **Hematology, Chemistry, Coagulation, & TSH:** Testing to be performed locally. Patients who have Monday visits may complete safety lab assessments on the Friday prior to the visit. In addition to the assessments scheduled for the clinical trial, patients should undergo assessment as appropriate to ensure safe treatment. Thyroid stimulating hormone (TSH) is to be collected at screening and on study as clinically indicated. See Section 8.1.1.1 for specific assessments to be performed.
10. **Urinalysis:** To be performed locally. Microscopic analysis should be performed as clinically indicated.
11. **TRC105 Administration:** IV TRC105 diluted in normal saline will be administered as outlined in the schedule of assessments. If TRC105 is reintroduced, the initial dose will be split such that 3 mg/kg is given initially and the balance is given three days later (i.e. 3 mg/kg if the total dose is 6 mg/kg).
12. **Bevacizumab Administration:** Commercially available bevacizumab will be administered per the package insert in this study. Patients will receive 10 mg/kg as outlined in the schedule of assessments.
13. **CT or MRI Tumor Imaging:** Images of chest, abdomen, and pelvis to be performed at screening and on-study as outlined in the assessment table. Known areas of disease should be consistently followed throughout the study. Assessments should be performed whenever disease progression is suspected. Allowable window for tumor imaging studies is +/- 7 days. Brain and bone scans are to be performed if metastasis is suspected prior to starting the study and during study conduct.
14. **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.

15. **Concomitant Medications and Treatments:** Concomitant medications and treatments will be recorded from 30 days prior to the start of study treatment and up to 28 days following the last dose of study treatment.
16. **Baseline Signs and Symptoms and 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-Signs and Symptoms" and will be recorded on "Medical History and Baseline Signs and Symptoms" case report forms. Events that occur from the time the patient has taken the first dose of bevacizumab and/or TRC105 study drug through 28 days after the last dose of bevacizumab and/or TRC105 study drug (whichever is later) 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.
17. **Protein biomarkers:** 5 mL of plasma (K_3EDTA) will be collected as indicated in the schedule of assessments and stored at approximately -70°C to be analysed by a central laboratory. Samples will be batch shipped every 3 months to a third-party laboratory for analysis. See separate laboratory guide for further collection and shipment information.
18. **Tumor markers:** Will be collected and analysed locally as indicated in the schedule of events (e.g.: β-hCG)
19. **Cycle 3+ Treatment:** Patients who demonstrate a response of CR, PR or SD will be eligible for additional treatment until progression as long as TRC105 drug supply is available.
20. **Follow-up:** If the patient has a CR and comes off study treatment following consolidation therapy, β-hCG levels will be measured every month for 6 months or until resumption of study therapy. The 28 day follow-up visit (occurring 28 days after the CR DC Visit or EOS Visit if applicable) should include Concomitant Medications and Adverse Events. After 6 months, the patient is no longer eligible for study therapy and will have β-hCG levels measured every month until disease progression, start of new therapy, or for a maximum of 18 months. If the patient has measurable β-hCG and comes off study therapy for reasons other than CR, β-hCG levels should be measured at least every 2 weeks from last measurement until start of new therapy. The patient will also be contacted by phone every 2 months for 2 years. The allowable visit window for follow-up assessments is +/- 7 days.

5. SELECTION AND WITHDRAWAL OF PATIENTS

5.1. Patient Inclusion Criteria

1. Willingness and ability to consent for self to participate in study
2. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures
3. Measurable disease by RECIST 1.1 and elevated serum β-hCG
4. Histologically proven choriocarcinoma that has progressed despite all described lines of chemotherapy for this condition

5.2. Exclusion Criteria

1. Prior treatment with TRC105
2. Serious dose-limiting toxicity related to prior bevacizumab
3. Current treatment on another therapeutic clinical trial
4. Uncontrolled chronic hypertension defined as systolic > 140 or diastolic > 90 despite optimal therapy (initiation or adjustment of BP medication prior to study entry is allowed provided that the average of 3 BP readings at a visit prior to enrollment is < 140/90 mm Hg)
5. Symptomatic pericardial or pleural effusions
6. Uncontrolled peritoneal effusions requiring paracentesis more frequently than every 2 weeks
7. Active bleeding or pathologic condition that carries a high risk of bleeding (i.e. hereditary hemorrhagic telangiectasia)
8. Thrombolytic or anticoagulant use (except to maintain i.v. catheters) within 10 days prior to first day of study therapy
9. Cardiac dysrhythmias of NCI CTCAE grade ≥ 2 within the last 28 days
10. Known active viral or nonviral hepatitis
11. Open wounds or unhealed fractures within 28 days of starting study treatment
12. History of peptic ulcer disease or erosive gastritis within the past 6 months, unless treated for the condition and complete resolution has been documented by esophagogastroduodenoscopy (EGD) within 28 days of starting study treatment
13. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness
14. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the

interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for this study

5.3. Patient Withdrawal Criteria

The patient will 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 the patient does not return for a scheduled visit, every effort should be made to contact her. 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 3). The patient 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, the patient will be withdrawn from treatment in the case of:

1. Disease Progression. Progressive Disease as defined in RECIST 1.1 or rise in serum β-hCG on 2 consecutive cycles. Disease progression may also be based unequivocal evidence of progressive disease sufficient to require a change in therapy.
2. There is a need for anticancer therapy not specified in the protocol including cancer surgery or radiation therapy.
3. The patient is lost to follow-up or noncompliant.
4. Patient has a TRC105 dose delay ≥ 8 weeks OR discontinuation of study therapy for > 6 months following CR.
5. Arterial thrombosis of any grade (including cerebrovascular ischemia, cardiac ischemia/infarction, or peripheral or visceral arterial ischemia) or grade 4 thromboembolism. For grade 3 venous thromboembolism hold bevacizumab treated. If the planned duration of full dose anticoagulation is < 2 weeks, bevacizumab should be held until the full dose anticoagulation period is over. If the planned duration of full dose anticoagulation is > 2 weeks, bevacizumab may be resumed during full dose anticoagulation IF all the following criteria are met. 1. Subject does not have a pathologic condition that carries high risk of bleeding (i.e. tumor involving major vessels). 2. Subject has not had any hemorrhagic events on study. 3. The subject has a stable dose of heparin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab. 4. If thromboembolism worsens/recurs upon resumption of bevacizumab, despite anticoagulation, bevacizumab should be discontinued.

6. TREATMENT OF PATIENTS

6.1. 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.

6.2. 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.

6.3. TRC105 Dose Levels

The patient will receive 10 mg/kg TRC105 weekly in combination with 10 mg/kg bevacizumab every other week on a q 28 day cycle.

6.4. TRC105 Packaging and Labeling

TRC105 may be provided in one or more of the following presentations.

Phosphate Buffered Saline Formulation (7 mg TRC105/mL)

210 mg TRC105/30 mL single-use vial

20 mM L-Histidine/L-Histidine Monohydrochloride, 240 mM Trehalose,

0.01% Polysorbate 20 Formulation (25 mg TRC105/mL)

100 mg TRC105/4 mL single-use vial

200 mg TRC105/8 mL single-use vial

400 mg TRC105/16 mL single-use vial

6.5. TRC105 Storage and Shipping

TRC105 must be stored upright between 2 °C and 8 °C (36 °F to 46 °F) and protected from light.

6.6. TRC105 Preparation

TRC105 will be prepared in the pharmacy and diluted into normal saline using appropriate aseptic technique. TRC105 will be administered using an in-line 0.2 micron filter. No incompatibilities between TRC105 and polyvinyl chloride or polyolefin bags have been observed. 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) × dose level (mg/kg) divided by TRC105 concentration (mg/mL) = 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 1.0 mL; in the case of an increment of 0.5 mL the volume should be rounded up. **The maximum weight that should be used for dose calculation in this study is 85 kg (note: there is not a**

weight restriction for enrollment purposes). The patient weight will be assessed on the day of treatment and used for calculation of each 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 0.6 mg/mL and 10 mg/mL. The prepared TRC105 must be gently inverted several times in order to ensure a homogeneous solution. The diluted infusion solution of TRC105 should be used within 8 hours of preparation if stored at room temperature, or within 24 hours of dilution if stored at 2° to 8°C (36º to 46ºF). The expiration time should be labeled on the bag. If the diluted infusion solution of TRC105 cannot be infused within 8 hours of preparation (i.e.: the prepared infusion is at room temperature for more than 8 hours), a second bag will be prepared that contains the balance of the planned dose that was not already delivered. The prepared solution should not be frozen.

6.7. TRC105 Administration

Patients should be encouraged to drink abundant fluid (e.g. two eight ounce glasses of water or juice) prior to the first treatment. Intravenous hydration prior to and during therapy is left to the discretion of the Investigator, but should be considered if the patient is thought to 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
- Methylprednisolone 100 mg i.v. will be given prior to the Cycle 1 Day 8 and Cycle 1 Day 11 infusions only. In addition, methylprednisolone will be given in the case of a delay of ≥ 10 days between any two doses or if the patient develops an infusion reaction ≥ grade 2 during the immediate prior infusion.
- Famotidine 20 mg i.v. or p.o. (or similar H2 blocker) x 1. Famotidine (or similar H2 blocker) may be discontinued starting with Cycle 2 in the absence of infusion reactions with the prior dose.
- Cetirizine 10 mg i.v. or p.o. x 1 (or similar oral or intravenous antihistamine). Cetirizine (or similar oral or intravenous antihistimine) may be discontinued starting with Cycle 2 in the absence of infusion reactions with the prior dose.

TRC105 premedication, including the methylprednisolone infusion, should be administered 2 hours to 30 minutes prior to initiating TRC105 infusions.

TRC105 will be administered intravenously utilizing an infusion pump. TRC105 has been demonstrated to be compatible with polyethylene lined, non-DEHP infusion sets and polyvinyl chloride, non-DEHP infusion sets. TRC105 is required to be administered 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.

Following the appropriate premedication regimen, the patient will receive TRC105 on days 8, 11, 15 and 22 of cycle 1 and on days 1, 8, 15 and 22 of subsequent cycles. The first weekly dose

of TRC105 will be split with 3 mg/kg administered on cycle 1 day 8 and infused over 4 hours (+/- 15 minutes) and 7 mg/kg administered on cycle 1 day 11 and infused over 2 hours (+/- 15 minutes), and then the full dose of 10 mg/kg given on cycle 1 day 15 and weekly thereafter and will be administered over 1 hour (+/- 15 minutes). The patient must complete at least one 4 hour infusion (+/- 15 minutes) without the development of any infusion reactions, in order to reduce the subsequent TRC105 infusion to 2 hours (+/- 15 minutes) and complete a 2 hour infusion (+/- 15 minutes) without the development of any infusion reactions in order to reduce subsequent TRC105 infusions to 1 hour (+/- 15 minutes). If the patient develops infusion reactions of any kind they should be managed appropriately (see Section 6.7.2) and the patient is not permitted to reduce the duration of the next planned infusion.

The rate of TRC105 infusion must not exceed 25 mg/min. When the i.v. bag containing TRC105 is empty, flush the i.v. line with a 20 mL normal saline. 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 the patient misses a weekly TRC105 dose (i.e., ≥ 10 days between doses), the methylprednisolone dose should be reinstituted as per the initial infusion and first TRC105 dose should be administered over two days as was done for the initial dose.

6.7.1. TRC105 Dose Modification/Dose Interruptions

TRC105 dose reductions are allowed for grade 3 or 4 related adverse events that resolve to grade 1 or baseline (including anemia). Treatment dose delays cannot exceed 8 consecutive weeks (i.e., both TRC105 and bevacizumab dosing held). However, if the patient cannot tolerate bevacizumab or TRC105 therapy, demonstrates a response of complete response (CR), partial response (PR) or stable disease (SD) with the combination and is thought to benefit from continued single agent therapy, the patient may continue on study on TRC105 or bevacizumab alone.

TRC105 and bevacizumab should be held for two weeks prior and for two weeks following surgical procedures.

Table 4: Allowable TRC105 Dose Modifications

Toxicity Attributed to TRC105	**Dose Adjustment for Next Dose of TRC105 (% of Starting Dose)**
Grade 1 or 2	Maintain Dose Level
Grade 3 or 4	
• 1st appearance	80%
• 2nd appearance	60%
• 3rd appearance	Discontinue treatment permanently

Note: if the patient is dose reduced and subsequently misses a dose whereby the first dose of TRC105 following the break needs to be split into two doses, 3 mg/kg should be given on the first day and the remainder of the dose (i.e., 5 mg/kg in the case of a dose reduction to 8 mg/kg) will be given 3 days later.

If the patient develops an arterial thrombosis or grade 4 venous thrombosis she will be removed from study. If she develops a grade 1, 2 or 3 venous thrombosis that requires anticoagulation she

will have her TRC105 therapy interrupted. TRC105 therapy may resume once the following criteria are met:

- The patient is on a stable dose of heparin, low molecular weight heparin, coumadin, or other anticoagulant.
- If on coumadin, the patient has an in range INR for therapeutic anticoagulation (usually between 2 and 3).
- The patient has a platelet count > 50,000 or baseline.
- The patient has not had a hemorrhagic event of grade 2 or higher while on study.
- The patient does not have a pathological condition that carries a high risk of bleeding (e.g., tumor involving major vessels).
- The patient is benefiting from TRC105 therapy (no evidence of disease progression).

The INR should be monitored weekly before each dose of TRC105 for the first 4 weeks, and then once per cycle thereafter (or more often as clinically indicated). Patients with an INR > 3 should not receive TRC105 until the INR is ≤ 3.

6.7.2. Management of TRC105 Infusion Reactions

If the 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, and then increased per patient tolerance to a maximum of 25 mg/min. 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 5: Management of TRC105 Infusion Reactions

Infusion Reaction Severity	**Recommended Management**
Grade 1 (mild)	**1.** No intervention **2.** Continue infusion unless symptoms worsen
Grade 2 (moderate)	**1.** Interrupt infusion **2.** Treat with symptomatic medications[a] **3.** Resume infusion at half the previous rate when infusion-related symptoms improve to grade 1 or less.

Infusion Reaction Severity	Recommended Management
Grade 3 (severe)	**1.** Interrupt infusion **2.** Treat with symptomatic medications[a] **3.** Monitor patient until infusion-related symptoms resolve, including hospitalization if necessary **4.** Withdraw patient from study unless other factors that contributed to the infusion reaction are identified and corrected
Grade 4 (life-threatening)	**1.** Discontinue infusion **2.** Treat with symptomatic medications[a] **3.** Hospitalize patient **4.** Withdraw from study

[a]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).

6.7.3. 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.

6.7.4. 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. Disposal of TRC105 should occur in accordance with institutional policy. The Site Pharmacist will be responsible for documenting the destruction (according to institutional requirements) of used or expired vials.

6.8. Bevacizumab Packaging

Bevacizumab is available as 100 mg pack containing one 4 mL single-dose vial and 400 mg pack containing one 16 mL single-dose vial.

6.9. Bevacizumab Preparation

Commercially available bevacizumab will be utilized in this study. The patient will receive 10 mg/kg on day 1 and day 15 of each 28-day cycle. Bevacizumab should be prepared according to institutional policy and using aseptic technique. Withdraw the necessary amount of bevacizumab and dilute to the required administration volume with 0.9% sodium chloride solution. The concentration of the final bevacizumab solution should be kept within the range of 1.4-16.5 mg/mL as described in the Avastin PI (Appendices – Appendix 3).

6.10. Bevacizumab Administration

The patient will receive 10 mg/kg on day 1 and day 15 of each 4-week cycle. Bevacizumab should be administered as a 90 minute infusion on cycle 1 day 1. Subsequent infusion times can be reduced by 30 minutes down to a minimum infusion time of 30 minutes if tolerated (Appendices – Appendix 3). Patient weight will be assessed on the day of treatment and used for the calculation of each Bevacizumab dose.

6.10.1. Bevacizumab Dose Modification

Dose reduction of bevacizumab for adverse reactions is not recommended. If indicated, bevacizumab should either be discontinued or temporarily suspended, see bevacizumab package insert for specific information related to different adverse events. If discontinuation of bevacizumab is clinically indicated, patients who demonstrate a response of complete response (CR), partial response (PR) or stable disease (SD) will be eligible for additional treatment with TRC105 alone until progression as long as TRC105 drug supply is available.

6.11. Bevacizumab Drug Accountability

Commercial bevacizumab will be utilized in this study, thus the site will follow institutional guidelines regarding drug accountability for commercial product.

6.12. Bevacizumab Handling and Disposal

Bevacizumab vials [100 mg (NDC 50242-060-01) and 400 mg (NDC 50242-061-01)] are stable at 2−8°C (36−46°F). Bevacizumab vials should be protected from light. Do not freeze or shake.

Diluted bevacizumab solutions may be stored at 2−8°C (36−46°F) for up to 8 hours. Bevacizumab vials should be stored in their original carton until time of use. No incompatibilities between bevacizumab and polyvinylchloride or polyolefin bags have been observed. Partially used vials should be properly destroyed according to institution guidelines.

6.13. Concomitant Medications

No other approved or investigational anticancer treatment will be permitted during the study period, including chemotherapy, biological response modifiers, immunotherapy, or radiotherapy.

If the patient is on low dose aspirin at baseline she may continue it if medically indicated. If the patient is on NSAIDs on study should also receive peptic ulcer disease (PUD) prophylaxis with an H2 or proton pump blocker.

Narcotic analgesics, nonsteroidals, 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.

6.14. Treatment Compliance

6.14.1. TRC105

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

6.14.2. Bevacizumab

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

6.15. Patient Enrollment

This is a single patient trial. She will be consented and enrolled at DFCI and followed by her treating physicians

7. ASSESSMENT OF EFFICACY

7.1. Radiological Tumor Assessment

The primary efficacy assessment will be best overall response as defined in Section 7.2.1. The determination of antitumor efficacy will be based on objective tumor assessments made by the Investigator according to RECIST version 1.1 [54] and by monitoring her serum β-hCG. Investigators will make treatment decisions based on these assessments. All lesions will be classified as Target or Nontarget lesions at the Screening visit. Each lesion designation will be maintained through the course of the study.

The same method and technique should be used to characterize each identified and reported lesion at Screening, during the study treatment period, and at the End of Study visit. Imaging-based evaluation over clinical examination is the required technique when both could be used to assess the antitumor effect of the treatment. Clinical Oncology review of all tumor measurements is desired.

Whenever possible, clinical evaluation of superficial lesions should not be used as the sole form of measurement. However, when necessary, color photograph with metric caliber is acceptable. Tumor evaluation by positron emission tomography (PET) scan or by ultrasound may not substitute for CT or MRI scans.

Radiological tumor assessments and serum tumor marker (serum β-hCG) measurements will be performed at screening, as outlined in the Schedule of Assessments (Table 3), 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. If the patient has an objective response of PR or CR she must have the response confirmed at least 4 weeks after the initial documentation of response.

Measurability of Tumor Lesions

At Screening, individual tumor lesions will be categorized by the Investigator as either target or non-target according to the RECIST 1.1 criteria described below.

- **Measurable:** Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with spiral CT scan. Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes) and ≥ 10 mm. Clinical lesions must be measured with calipers.
- **Non-Measurable:** All other lesions, including small lesions and bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusions, lymphangitis of the skin or lung, abdominal masses that are not confirmed and followed by imaging techniques, previously irradiated lesions, and disease documented by indirect evidence only (e.g. by laboratory tests such as alkaline phosphatase).

7.2. Recording Tumor Measurements

Measurable lesions up to a maximum of 5 lesions representative of all involved organs (with a maximum of 2 lesions per organ) should be identified as target lesions and measured and recorded at Screening and at the stipulated intervals during treatment. Target lesions should be

selected on the basis of their size (lesion with the longest diameters) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). Target lesions may include lymph nodes with a short axis ≥ 15 mm.

The longest diameter will be recorded for each target lesion (with the exception of lymph nodes, where the short axis will be used). The sum of the diameter for all target lesions at Screening will be calculated and recorded as the baseline sum diameter to be used as reference to further characterize the objective tumor response of the measurable dimension of the disease during treatment. All measurements should be performed using a caliper or ruler and should be recorded in metric notation in millimeters.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present", "stable", "absent", "increased" or "decreased".

7.2.1. Definitions of Tumor Response

7.2.1.1. Target Lesions

- **Complete response (CR)** is defined as the disappearance of all target lesions and normalization of her serum β-hCG.
- **Partial response (PR)** is defined as a ≥ 30% decrease in the sum of the dimensions of the target lesions taking as a reference the baseline sum dimensions.
- **Progressive disease (PD)** is defined as a ≥ 20% relative increase and ≥ 5 mm absolute increase in the sum of the dimensions of the target lesions taking as a reference the smallest sum of the dimensions recorded since the treatment started, or the appearance of one or more new lesions and rise of her serum β-hCG.
- **Stable disease (SD)** is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as a reference the smallest sum of the dimensions since the treatment started.

7.2.1.2. Non-Target Lesions

- **Complete response (CR)** is defined as the disappearance of all non-target lesions and normalization of tumor marker levels to ≤ ULN.
- **non-CR/non-PD** is defined as a persistence of ≥ 1 non-target lesions and/or maintenance of tumor marker levels > ULN.
- **Progressive disease (PD)** is defined as unequivocal progression of existing non-target lesions, or the appearance of ≥ 1 new lesions.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease and progressive disease.

7.2.1.3. Determination of Overall Response by the RECIST Criteria

When both target and non-target lesions are present, individual assessments will be recorded separately. The overall assessment of response will involve all parameters as depicted in Table 6 below. Per RECIST 1.1, a modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

Table 6: Response Evaluation Criteria in Solid Tumors

Target Lesions[a]	Non-target Lesions[b]	New Lesions[c]	Overall Response
CR	CR	No	CR
CR	non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Any Response	Yes or No	Not Evaluable
PD	Any Response	Yes or No	PD
Any Response	PD	Yes or No	PD
Any Response	Any Response	Yes	PD

[a]Measurable lesions only.
[b]May include measurable lesions not followed as target lesions or non-measurable lesions.
[c]Measurable or nonmeasurable lesions.

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

NOTE: If the patients has a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time her best response should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

8. ASSESSMENT OF SAFETY

8.1. 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 ECOG 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, and coagulation profile. In addition, an ECG will be recorded at baseline and as clinically indicated throughout the study.

8.1.1. Laboratory Safety Assessments

Abnormal and clinically significant laboratory tests should be recorded as adverse events.

8.1.1.1. Hematology, Serum Chemistry, Coagulation

Assessments will be performed at the time points indicated in the Schedule of Assessments (Table 3) 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, thyroid stimulating hormone (TSH), and glucose

8.1.1.2. Urinalysis

Urine analysis will be performed at time points indicated in the Schedule of Assessments (Table 3) and analyzed by local laboratories. Microscopic analysis should be performed as clinically indicated.

8.1.2. Other Safety Assessments

8.1.2.1. 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 3). The physical examination will include examination of known and suspected sites of disease.

8.1.2.2. Vital Signs

Heart rate, temperature, blood pressure, respiratory rate and weight will be assessed at time points indicated within the Schedule of Assessments (Table 3). 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).

8.1.2.3. Performance Status

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

8.1.2.4. 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 3) and as clinically indicated throughout the study.

8.2. Adverse Events

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

8.2.1. 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 *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

8.2.2. 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 serious adverse events 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 serious adverse events. 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 a serious adverse event 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).

8.2.2.1. 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).

8.3. Reporting Adverse Events

8.3.1. 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?"

8.3.2. 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-signs and symptoms" 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 bevacizumab and/or TRC105 study drug and ends 28 days after the last dose of bevacizumab and/or TRC105 study drug is administered whichever is later. 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.

8.3.3. 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 a serious adverse event 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:

Ronald Shazer, MD, MBA

TRACON Pharmaceuticals Inc.

8910 University Center Lane, Suite 700

San Diego, California 92122

Direct Phone: (858) 550-0780 x230

Cell Phone: (310) 922-8039

Email: rshazer@traconpharma.com

Following this 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 does not become aware of the occurrence of a serious adverse event immediately (for example, if a patient initially seeks treatment elsewhere), the

Investigator is to report the event **immediately upon learning of it** and document his/her first awareness of the serious adverse event.

TRACON Pharmaceuticals Inc. may also be contacted via telephone 24 hours a day at (858) 344-9400.

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.

8.3.4. 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 8.2.1 are to be recorded on patient source documents and on the CRFs. Adverse events should be reported using concise medical terminology.

8.3.5. 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 CTCAE 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 7: Adverse Event Grading

Grade	Non-CTCAE Severity	Definition
1	Mild	Does not interfere with patient's usual function
2	Moderate	Interferes to some extent with patient's usual function
3	Severe	Interferes significantly with patient's usual function
4	Life-Threatening	Results in immediate risk of patient's death
5	Fatal	Results in patient's death

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.

8.3.6. Relationship to TRC105 Study Drug

In this study, TRC105 study drug is given in combination with bevacizumab. 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.

AEs related to TRC105 study drug or bevacizumab are considered Adverse Drug Reactions (ADR).

8.3.7. 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.

8.3.8. Exposure in Utero

This patient is status post a hysterectomy so no exposure in utero is possible.

8.3.9. 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.

8.4. 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.

9. OTHER ASSESSMENTS

9.1. Other Laboratory Assessments

9.1.1. Protein Biomarker

A 5 mL K_3EDTA plasma blood sample will be collected on the days indicated within the Schedule of Assessments (Table 3). Samples will be stored at approximately -70 °C and batch shipped to Fisher BioServices Inc. (10 Forge Park, Franklin, MA 02038) for storage until the time of analysis. Duke University Medical Center will analyze plasma for several biomarkers including but not limited to VEGF, PDGF, and TGFβ. Please see the separate laboratory guide for further collection and shipment information.

10. STATISTICS

10.1. Data Analysis

Due to the exploratory nature of this study, no inferential analyses are planned, and no imputation of missing data will be done.

10.1.1. Analysis of Primary Objective

PFS and ORR will be calculated form the time of cycle 1 day 1 until the time of progression from cancer, if the patient remains on trial at the time of cancer progression. Stable disease will be defined as lack of tumor progression lasting for 2 cycles or longer.

10.1.2. Analysis of Secondary Objectives

The secondary objectives including the assessments of frequency and severity of toxicities, efficacy, and angiogenic protein biomarkers will be evaluated as described below.

10.1.2.1. Protein Biomarkers

Angiogenic protein biomarker data if the patient received at least one dose of study drug will be listed by cohort and tumor type.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

All data entered on CRFs/eCRFs must be verifiable within the patients' source documents (written or electronic record). The Investigator/institution guarantees TRACON representatives and appropriate regulatory authorities direct access to the original source records for the duration of the agreed study record retention period. Printouts of source records that are electronically obtained and stored will not be acceptable for audit/inspection unless provided as certified exact copies and the data remains as meaningful and useful as in its original electronic state.

Legally protected subject identification and other personal health information must be securely stored with limited access by the participating institutions. Unless secure provisions are established by the institution to allow TRACON (or designee) to perform remote monitoring of electronic source records, TRACON (or designee) will review source records/data on site and will not remove any such protected health information.

12. QUALITY CONTROL AND QUALITY ASSURANCE

Monitoring visits to clinical investigator sites will be made by TRACON or its representatives periodically during the trial to ensure that GCPs and all aspects of the protocol are being followed.

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

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

TRACON and its representatives will be governed by applicable regulations, good clinical practice standards, and internal SOPs for the conduct of monitoring visits and QA audits.

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 and other evidence of appropriate and timely communications 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, applicable local regulatory requirements and laws, and the International Conference on Harmonization Guideline on Good Clinical Practice, which supports the application of ethical principles that have their origin in the Declaration of Helsinki (see ICH E6, §2.1).

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 the 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. The patient must be informed about her right to withdraw from the trial at any time. Furthermore, it is the responsibility of the Investigator to ensure the patient is appropriately informed before obtaining her signed and dated consent. Signatures from the investigator conducting the informed consent discussion should also be obtained prior to undertaking any trial-related procedure. Consent by a legally authorized representative is not permitted. Should an impartial witness be needed, ICHE6 requirements for impartial witnesses will apply.

The Investigator will retain the original the patient's signed consent form in the Investigator/site files.

13.4. Patient Compensation

The patient will not be compensated for participation in this trial; this will be outlined to 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. Nevertheless, records of potential patients identified and screened shall be retained on site screening logs. 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 CRF data. The investigator will sign off on his/her data per patient. These signatures serve to attest that the investigator has reviewed and approved the information contained on the case report forms and that the information is complete, accurate, and 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.

The use of electronic CRFs (eCRFs) to capture study data using automated computerized data capture systems does not change the principles and requirements for collecting study data. The investigator still retains final personal responsibility for eCRF data and any associated data pertaining to it (e.g. metadata including any record of change to the originally recorded data). The investigator's signed approval of the eCRF data serves to attest that the electronic data and all of its associated metadata (including changes) has been reviewed and accepted as complete, accurate, and true for each patient in the study.

All CRF/eCRF data must be verifiable in the patient's source records by TRACON or its designee. TRACON will review CRF data as compared to source records in an attempt to identify missing and spurious data and notify the investigator of findings so that proper corrections can be made. TRACON representatives (monitors and auditors), and regulatory inspectors shall have direct access to the original source records in its original recorded format: electronic or hardcopy.

TRACON (or its designee) will perform all data management functions associated with the study. Data will be captured electronically. Automated data verification ("edit checks") will be used to ensure that the data are logical and consistent. Any inconsistencies will be queried for clarification or correction as appropriate by the clinical site.

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 inform TRACON of any such transfer of responsibilities and properly identify the person or institution assuming the responsibility. The responsible investigator/institution must obtain TRACON's written permission before disposing of any records.

15. DEFINITION OF END OF TRIAL

15.1. End of Trial

End of trial in all participating countries is defined as the time at which the patient enrolled in the study has completed treatment on study.

15.2. TRACON Discontinuation Criteria

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 the participating patient 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: 105CC201 AMENDMENT #3

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

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20. APPENDICES

20.1. Appendix 1: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

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

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

20.2. Appendix 2: ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

20.3. Appendix 3: Avastin Package Insert

The FDA approved bevacizumab package insert should be referenced and may be reviewed on-line at the following FDA website:

http://www.gene.com/gene/products/information/pdf/avastin-prescribing.pdf

CLINICAL PROTOCOL	
Title:	A SINGLE PATIENT PROTOCOL OF TRC105 COMBINED WITH STANDARD-DOSE BEVACIZUMAB FOR A PATIENT WITH METASTATIC AND REFRACTORY CHORIOCARCINOMA
Protocol Number:	105CC201B
Study Sponsor:	TRACON Pharmaceuticals, Inc. 8910 University Center Lane, Suite 700 San Diego, CA 92122 Phone: (858) 550-0780 Facsimile: (858) 550-0786
Medical Monitor:	Charles Theuer, MD, PhD 8910 University Center Lane, Suite 700 San Diego, CA 92122 Direct Phone: (858) 550-0780 x233 Fax: (858) 550-0786 Cell Phone: (858) 344-9400 Email: ctheuer@traconpharma.com
Signature & Date:	Signed: _____ Dated: 6 OCT 2015
Version Date:	Original Protocol: October 6th, 2015

Statement of Confidentiality:

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PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone number
Medical Monitor	Charles Theuer MD PhD	8910 University Center Lane, Suite 700 San Diego, CA 92122 Office: (858) 550-0780 x233 Mobile Phone: (858) 344-9400 Email: ctheuer@traconpharma.com

1. SYNOPSIS

Name of Sponsor/Company: TRACON Pharmaceuticals, Inc.	
Name of Investigational Product: TRC105	
Name of Active Ingredient: TRC105	
Title of Study: **A SINGLE PATIENT PROTOCOL OF TRC105 COMBINED WITH STANDARD-DOSE BEVACIZUMAB FOR A SINGLE PATIENT WITH METASTATIC AND REFRACTORY CHORIOCARCINOMA**	
Study center(s): This study will be performed at one US center in one patient.	
Investigator: Neil Horowitz, MD	
Studied period (years): Estimated date patient enrolled: October 2015	**Phase of development:** 2
Rationale: Bevacizumab is a monoclonal antibody to vascular endothelial growth factor (VEGF) that inhibits angiogenesis and extends survival in patients with a wide variety of solid tumor types. TRC105, a monoclonal antibody to endoglin, an angiogenic target highly expressed on the tumor vessels and the tumor cells in choriocarcinoma. TRC105 has been well tolerated when dosed with bevacizumab in more than 50 patients with advanced cancer. Together, these antibodies may be efficacious in metastatic and refractory choriocarcinoma, a tumor type that is highly vascular and expresses endoglin.	
Objectives Primary: • To determine PFS and ORR of one patient with metastatic and refractory choriocarcinoma by measurement of serum β- hCG Secondary: • To determine PFS and ORR of one patient with metastatic and refractory choriocarcinoma by RECIST 1.1 • To determine the frequency and severity of adverse events as assessed by NCI CTCAE (Version 4.0) • To explore the effects of TRC105 and bevacizumab on circulating angiogenic protein biomarkers	
Methodology: This is a feasibility study of TRC105 in combination with standard dose bevacizumab in a patient with metastatic and refractory choriocarcinoma for whom curative therapy is unavailable. TRC105 will be administered weekly in combination with bevacizumab. The patient will receive bevacizumab on days 1 and 15 of each 28 day cycle and will receive	

TRC105 on days 8, 11, 15 and 22 of cycle 1 and on days 1, 8, 15 and 22 of subsequent cycles. The first weekly dose of TRC105 will be split with 3 mg/kg administered on cycle 1 day 8 and 7 mg/kg administered on cycle 1 day 11, and then the full dose of 10 mg/kg given on cycle 1 day 15 and weekly thereafter.

Number of patients (planned):

One patient

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

1. Willingness and ability to consent for self to participate in study
2. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures
3. Measurable disease by RECIST 1.1 and elevated serum β-hCG
4. Histologically proven gestational trophoblastic disease that has progressed despite all described lines of chemotherapy for this condition

Exclusion Criteria:

1. Prior treatment with TRC105
2. Serious dose-limiting toxicity related to prior bevacizumab
3. Current treatment on another therapeutic clinical trial
4. Uncontrolled chronic hypertension defined as systolic > 140 or diastolic > 90 despite optimal therapy (initiation or adjustment of BP medication prior to study entry is allowed provided that the average of 3 BP readings at a visit prior to enrollment is < 140/90 mm Hg)
5. Symptomatic pericardial or pleural effusions
6. Uncontrolled peritoneal effusions requiring paracentesis more frequently than every 2 weeks
7. Active bleeding or pathologic condition that carries a high risk of bleeding (i.e. hereditary hemorrhagic telangiectasia)
8. Thrombolytic or anticoagulant use (except to maintain i.v. catheters) within 10 days prior to first day of study therapy
9. Cardiac dysrhythmias of NCI CTCAE grade ≥ 2 within the last 28 days
10. Known active viral or nonviral hepatitis
11. Open wounds or unhealed fractures within 28 days of starting study treatment
12. History of peptic ulcer disease or erosive gastritis within the past 6 months, unless treated for the condition and complete resolution has been documented by esophagogastroduodenoscopy (EGD) within 28 days of starting study treatment

13. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness
14. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for this study

Investigational product dose and mode of administration:

Following the appropriate premedication regiment, TRC105 is to be administered intravenously over 1 to 4 hours (+/- 15 minutes) on days 8, 11, 15, and 22 of cycle 1 and on days 1, 8, 15 and 22 of all subsequent cycles. There is a +/- 15 minute window for all infusions.

Duration of treatment:

The patient may continue on treatment until disease progression, unacceptable toxicity or withdrawal of consent, or other reasons.

The 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, the patient will be withdrawn from treatment in the case of:

1. Disease Progression. Progressive Disease as defined by a rise of more than 10% above baseline or nadir in serum β- hCG on 2 consecutive cycles. Disease progression may also 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 ≥ 8 weeks.
5. Arterial thrombosis of any grade (including cerebrovascular ischemia, cardiac ischemia/infarction, or peripheral or visceral arterial ischemia) or grade 4 thromboembolism. For grade 3 venous thromboembolism hold bevacizumab treatment. IF the planned duration of full dose anticoagulation is < 2 weeks, bevacizumab should be held until the full dose anticoagulation period is over. If the planned duration of full dose anticoagulation is > 2 weeks, bevacizumab may be resumed during full dose anticoagulation IF all the following criteria are met. 1. Subject does not have a pathologic condition that carries high risk of bleeding (i.e. tumor involving major vessels). 2. Subject has not had any hemorrhagic events on study. 3. The subject has a stable dose of heparin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab. 4. If thromboembolism worsens/recurs upon resumption of bevacizumab, despite anticoagulation, bevacizumab should be discontinued.

Reference therapy, dosage and mode of administration: Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab will be administered intravenously at a dose of 10 mg/kg on day 1 and 15 of each 28-day cycle prior to TRC105 (except on cycle 1 day 1 when TRC105 is not to be administered). The initial bevacizumab dose should be delivered over 90 minutes. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. Following bevacizumab, the line should be flushed with normal saline before TRC105 administration 30 minutes later.
Criteria for evaluation: Safety: A formally chartered in-house TRACON Safety Review Team will review safety data. Safety assessments include adverse events (AEs), physical exams, performance status, laboratory results (complete blood counts and serum chemistry) and 12-lead ECG's (if the patient develops an arrhythmia). Efficacy: Preliminary evidence of antitumor activity will be assessed by regression in β-hCG tumor marker.
Statistical methods: No statistical analyses are planned

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Table 2: Abbreviations and Specialist Terms

Abbreviation or specialist term	Explanation
ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
AE	Adverse Event
AFP	Alpha Fetoprotein
AIDS	Acquired Immunodeficiency Syndrome
ALKs	Activin receptor-Like Kinases
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AUC_{last}	Time of Last Measurable Concentration of Area Under the Curve
BALB/c mice	Mouse Strain
BUN	Blood Urea Nitrogen
β-hCG	Beta human chorionic gonadotropin
CA-125	Cancer Antigen-125
CABG	Coronary Artery Bypass Graft
CBC	Complete Blood Count
CEA	Carcinoembryonic Antigen
CHOP	Cyclophosphamide Hydroxydaunomycin Oncovin® Prednisone
CL	Clearance
C_{max}	Maximum Serum Concentration
CPA	Cyclophosphamide
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CTC	Common Terminology Criteria
dL	Deciliter

DLT	Dose Limiting Toxicity
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECM	Extracellular Matrix
EGFR	Epidermal Growth Factor Receptor
ELISA	Enzyme-Linked ImmunoSorbent Assay
EMA-CO	Etoposide, methotrexate, actinomycin, cyclophosphamide, vincristine
EMA-EP	Etoposide, methotrexate, actinomycin, etoposide, cisplatin
EOS	End of Study
FDA	Food and Drug Administration
G	Gram
GCP	Good Clinical Practice
GTD	Gestational Trophoblastic Disease
GTN	Gestational Trophoblastic Neoplasia
HACA	Human Anti-Chimeric Antibodies
HAMA	Human Anti-Murine Antibodies
Her-2	Human epidermal growth factor receptor 2
HHT-1	Hereditary Hemorrhagic Telangiectasia Type 1
HIF-1-α	Hypoxia-Inducible Factor-1-α
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HRA	Health Regulatory Authority
HUVECs	Human Umbilical Vein Endothelial Cells
ICE	Ifosfamide, carboplatin, etoposide
ICH	International Conference on Harmonization
ID	Identification
IEC	Independent Ethics Committee
IgG	Immunoglobulin G

IgM	Immunoglobulin M
INR	International Normalized Ratio
IP	Intraperitoneal
IRB	Institutional Review Board
i.v.	Intravenous
K_d	Avidity Binding Constant
Kg	Kilogram
L	Liter
LDH	Lactate Dehydrogenase
LOQ	Limit of Quantification
µL	Microliter
Mg	Milligram
mL	Milliliter
MAC	Methotrexate, actinomycin, cyclophosphamide
MACA	Monkey Anti-Chimeric Antibody
MAMA	Monkey Anti-Murine Antibody
MI	Myocardial Infarction
Mm	Millimeter
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCIC	National Cancer Institute of Canada
Ng	Nanogram
NHP	Nonhuman Primate
NOAEL	No Adverse Effect Level
PBS	Phosphate-Buffered Saline
PD	Progressive Disease
PDGF	Platelet Derived Growth Factor
PlGF	Placental Growth Factor

pM	Picomolar
PR	Partial Response
PSA	Prostate Specific Antigen
PT	Prothrombin Time
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTT	Partial Thromboplastin Time
qAM	Every Morning
qPM	Every Evening
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
sCD105	Soluble CD105/endoglin
SCID	Severe Combined Immunodeficient
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SN6j	Murine parent antibody of TRC105
sVEGFR2	Soluble VEGF Receptor 2
TGF-β	Transforming Growth Factor
TP/TE	Paclitaxel, cisplatin/paclitaxel, etoposide
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
US	United States of America
VEGF	Vascular Endothelial Growth Factor

2. INTRODUCTION

2.1. Background

2.1.1. Angiogenesis and Cancer

Angiogenesis is required for the survival and growth of solid cancers [1, 2]. It is generally accepted that solid cancers have two phases, an avascular phase and a vascular phase [2]. 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 that are 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 [3, 4]. Bevacizumab is also indicated for renal cell cancer, breast cancer and malignant glioma [5-7] with published evidence of clinical benefit in other solid tumor types. 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].

2.1.2. CD105 and Angiogenesis

CD105 (endoglin) is a homodimeric cell membrane glycoprotein that was initially identified as a human leukemia-associated antigen [12] and later also found on endothelial cells [13, 14]. The expression pattern of CD105 is relatively restricted and CD105 is mainly expressed on immature B-lineage/myeloid leukemia cells and endothelial cells [12, 13]. CD105 is a TGF-β coreceptor that is essential for angiogenesis [15, 16]. CD105 is strongly expressed on the proliferating vascular endothelium of solid tumors [14, 17]. All of these properties make CD105 a good target for the antiangiogenic therapy of cancer [18]. Vascular targeted therapy may be more effective for destroying large established tumors than conventional antiangiogenic therapy such as anti-VEGF therapy [19]. In animal models, CD105 targeted therapy has demonstrated both vascular

targeting effects and antiangiogenic effects by inducing regression of established tumors as well as by preventing new tumor formation and inhibiting expansion of existing tumors [14, 20-23]. Therefore, CD105 offers a novel alternative target relative to the VEGF inhibitors currently available for antiangiogenesis therapy. 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) [24, 25]. CD105 has also been show to protect hypoxic cells from apoptosis [26].

CD105 acts to modulate signaling of multiple kinase receptor complexes of the TGF-β superfamily, including TGF-β receptors, activin receptor-like kinases (ALKs) and activin receptors [27]. In the absence of CD105, activation of TGF-β receptors results in phosphorylation of SMAD proteins that inhibit endothelial cell growth. However, activation of CD105 by TGF-β modulates SMAD protein phosphorylation. The end result is release of the growth inhibitory effects of TGF-β receptor activation on endothelial. Not surprisingly, prevention of CD105 activation by anti-CD105 antibody acts synergistically with TGF-β to inhibit endothelial cell growth [28].

The expression of CD105 by endothelial cells is essential for the development of new vasculature. 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 [16].

CD105 is critical for normal human blood vessel development [29]. CD105 haplotype insufficiency causes a well-described syndrome known as hereditary hemorrhagic telangiectasia type 1 (HHT-1 or Osler-Weber-Rendu 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 [30]. 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 [31].

CD105 is highly expressed on the proliferating endothelial cells of tumor vessels including lung, breast, colorectal, gastric, liver, endometrial, renal cell, head and neck, and ovarian cancers. In adults, CD105 expression can be measured on activated monocytes and endothelial cells, and expression levels on endothelial cells exceed those on activated monocytes by approximately 10-fold [32, 33].

Importantly, CD105 expression is increased following inhibition of the VEGF pathway. CD105 expression increased more than two-fold in human pancreatic cancers grown in mice treated with an antibody that binds VEGF [34]. 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 [35].

CD105 expression is a prognostic factor in solid tumor patients. Higher numbers of tumor vessels expressing CD105 have been correlated with poor prognosis in clinical studies of breast cancer [36, 37], lung cancer [38], prostate cancer [39, 40], colorectal cancer [41, 42], gastric cancer [43], endometrial cancer [44], astrocytic brain tumors [45], hepatocellular carcinoma [46], ovarian cancer [47, 48], esophageal adenocarcinoma [49], and head and neck cancer [50, 51].

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 4-fold higher than the mean value in 40 healthy subjects without cancer [41]. In the study, a positive correlation was observed between CD105 concentration and stage of disease. For example, patients with advanced cancer had higher plasma CD105 levels than those with early-stage disease (r=0.20, p=0.0470). 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 [52]. 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 [37]. These sCD105 concentrations are relatively low compared to TRC105 concentrations > 100,000 ng/mL that were safely achieved in cancer patients treated with TRC105 monotherapy on Study 105ST101.

CD105 is expressed directly on certain cancers in addition to its expression on the tumor vessels. Choriocarcinoma is a vascular cancer that arises from trophoblast tissue that densely expresses CD105. CD105 has been shown to induce trophoblastic outgrowth and migration. Hence, patients with choriocarcinoma are viewed as excellent candidates for treatment with angiogenesis inhibitors, especially a therapy that directly targets CD105 expressed on choriocarcinoma.

2.2. TRC105 Background

TRC105 is a genetically engineered human/murine chimeric monoclonal antibody directed against human CD105 [53], a growth proliferation receptor found on the surface of normal and proliferating endothelial cells.

The antibody is an IgG1 kappa immunoglobulin containing murine variable region sequences and human constant region sequences [53]. TRC105 has an approximate molecular weight of 148 kDa. TRC105 has a binding avidity for human CD105 of approximately 5 pM.

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 and to inhibit the growth of tumor xenografts [21]. Reactivity with tumor tissues is restricted to the tumor endothelium, as CD105 is not generally expressed on epithelial tumor cells [20]. TRC105 induces ADCC on proliferating HUVECs at low conentrations and induces apoptosis and growth inhibition at higher concentrations.

In trophoblastic cell line TRC105 was shown to directly inhibit growth in a dose dependent and methotrexate independent manner.

2.2.1. Studies with TRC105

Several studies with TRC105 are underway or have been completed. An open-label, phase 1, multicenter study of TRC105 (Study 105ST101) enrolled fifty patients, who were treated until disease progression with TRC105 at 0.01-15 mg/kg/q2wk or 10-15 mg/kg/wk. Studies of TRC105 in prostate, bladder, and ovarian cancer and a phase 1b study of TRC105 in combination with bevacizumab have also been completed. Ongoing studies include a phase 1b

study of TRC105 in combination with capecitabine in breast cancer, a phase 1b study of TRC105 in combination with sorafenib in liver cancer, a phase 1b study of TRC105 in combination with axitinib in renal cell carcinoma, and phase 2 studies of TRC105 monotherapy in liver cancer and in combination with bevacizumab in glioblastoma multiforme (2 studies) and renal cell carcinoma.

2.2.1.1. 105ST101 Phase 1 Monotherapy

2.2.1.1.1. 105ST101 Phase 1 Monotherapy 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.

2.2.1.1.2. 105ST101 Phase 1 Monotherapy Immunogenicity

In Study 105ST101, serum samples for evaluation of TRC105 immunogenicity, including HAMA and HACA, were collected pre-dose 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.

2.2.1.1.3. 105ST101 Phase 1 Monotherapy 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. Dose escalation proceeded stepwise until the top dose was reached. The maximum tolerated dose was exceeded at 15 mg/kg weekly and the recommended phase 2 dose of TRC105 was therefore determined to be 10 mg/kg weekly. Three of 4 patients at 15 mg/kg weekly developed grade 3 hypoproliferative anemia (without leucopenia or thrombocytopenia) in cycle 2, and one of the three progressed to grade 4 in cycle 3. Anemia was associated with accumulation of TRC105 and characterized by a low reticulocyte production index. Additional laboratory and clinical evaluations excluded common causes of anemia including blood loss, hemolysis, plasma volume expansion, inadequate erythropoietin, iron deficiency, and vitamin B-12 or folate deficiency. The anemia is believed to result from TRC105-mediated suppression of proerythroblasts, the only cells in the bone marrow known to express substantial levels of CD105 [54]. Anemia was reversible and manageable with dose reduction and standard supportive measures including erythropoietin and blood transfusion.

Infusion reactions, anemia, fatigue, epistaxis and headache were the most frequently observed adverse events considered related to TRC105. The majority of treatment-related adverse events were grade 1 or 2.

Infusion reactions, among the most common adverse events, were usually with the initial TRC105 dose and included one or more of the following signs or symptoms: rigors, bronchospasm, urticaria, hypertension, hypotension, tachycardia or bradycardia. Infusion reactions were initially reported at 1 mg/kg every 2 weeks for patients receiving TRC105 produced in NS0 cells without premedication. TRC105 produced in CHO cells was known to more potently engage ADCC *in vitro* than TRC105 produced in NS0 cells. Because of this, the initial dose level for patients receiving CHO-produced TRC105 was de-escalated to 0.3 mg/kg. Despite dose de-escalation, the first two patients at 0.3 mg/kg treated with CHO-produced TRC105 experienced grade 2 and grade 3 infusion reactions with the first dose in the absence of premedication. The protocol was therefore amended to require a glucocorticoids -based premedication regimen and extend the initial infusion duration from 1 to 4 hours.

The amendment mandating premedication and extended initial infusion duration successfully reduced the frequency and severity of infusion reactions and allowed dose escalation to continue. One additional patient who received CHO-produced TRC105 at 1 mg/kg developed a grade 3 infusion reaction with the third dose given over 2 hours. This patient had experienced a grade 2 infusion reaction when the dose was administered over 4 hours. In all three patients with grade 3 infusion reactions, TRC105 was not detectable in serum at the time of dosing, which allowed *de novo* binding of TRC105 to CD105 expressing endothelium within the vasculature. Grade 3 infusion reactions were not observed in patients dosed at 10 or 15 mg/kg who maintained TRC105 serum levels known to saturate CD105 binding sites for the full dosing interval. At dose levels where continuous TRC105 serum levels were achieved, glucocorticoids were safely discontinued and the infusion duration reduced to 1 hour.

Three patients developed grade 1 cutaneous telangiectasia on the trunk early in the course of therapy, all at dose levels of 10 or 15 mg/kg weekly that resulted in continuous serum levels of TRC105 known to saturate CD105 sites on human endothelium. Grade 1 or 2 hemorrhage was reported, including intermittent postcoital vaginal bleeding (that also occurred prior to TRC105 treatment), epistaxis, and superficial gingival bleeding.

Grade 1 or 2 headaches were observed, mainly in patients treated at doses of TRC105 above 3 mg/kg. Headaches began the day following infusion and were generally manageable with acetaminophen. However, grade 2 headache in one patient at 15 mg/kg weekly prompted discontinuation prior to completion of the dose-limiting toxicity evaluation period. Fatigue was one of the more common adverse events attributable to TRC105 and was more prevalent at doses above 3 mg/kg.

One patient developed dose-limiting toxicity of grade 4 hemorrhage presenting as melena from a gastric ulcer within 5 days of the initial TRC105 infusion at 0.1 mg/kg. He discontinued TRC105 treatment, was transfused 2 units of packed red blood cells and the bleeding resolved with nonsurgical management by the time of upper endoscopy. Serious bleeding was not observed following protocol amendment to exclude patients with a history of peptic ulcer disease (unless healing was documented) and patients on ulcerogenic medications including non-steroidal anti-inflammatory drugs.

Classic toxicities associated with VEGF inhibition, including hypertension, proteinuria and thrombosis were not prominent. One patient with recurrent anal cancer treated at 0.1 mg/kg developed proteinuria considered possibly related to TRC105, but proteinuria was also noted

prior to TRC105 dosing. Transient hypertension (156/112) without QT changes occurred in a single patient one day following infusion of 15 mg/kg, and was controlled by a single dose of oral antihypertensive medication. There were no arterial or venous thromboembolic events, nor gastrointestinal or other perforations in these patients.

2.2.1.1.4. 105ST101 Phase 1 Monotherapy Efficacy

In study 105ST101 stable disease ≥ 2 months was observed in 21 of 45 patients (47%) and stable disease ≥ 4 months in 6 of 44 patients (14%). Decreases in CEA, PSA, or CA-125 were noted in 7 of 21 patients (33%) and a global decrease in key angiogenic biomarkers was observed with treatment. One patient with castrate-refractory prostate cancer remains on TRC105 treatment after 6 years at a TRC105 dose of 0.01 mg/kg every 2 weeks. He has an ongoing complete PSA response, with resolution of bone pain and bone scan normalization. One patient with metastatic carcinosarcoma, manifested decreased tumor burden on computerized tomographic scanning and maintained stable disease for 20 months on therapy. The latter is especially notable when one considers that this patient had received three prior treatments -- carboplatin + paclitaxel for 4 months, anastrozole for 8 months, and ifosfamide for 2 months -- and had manifested tumor progression on each. In effect, TRC105 provided the most favorable clinical outcome and did so as a fourth-line therapy.

2.2.1.2. Phase 1b 105ST102 Study with Bevacizumab

2.2.1.2.1. 105ST102 Summary of Safety

Administration of TRC105 at a dose of 3 mg/kg weekly in combination with bevacizumab was well tolerated by three patients without the development of dose limiting toxicity (DLT) and dose escalation occurred per the protocol to cohort 2 (6 mg/kg TR105 weekly). However, the concurrent administration of 6 mg/kg TRC105 and bevacizumab on day 1 resulted in the development of moderate or severe headaches (including two grade 3 headaches) in four of five treated patients. The 6 mg/kg dose of TRC105 was tolerated when the initial TRC105 dose was delayed one week following bevacizumab dosing at 10 mg/kg every two weeks. Tolerability was further improved when the initial dose of TRC105 was given over two days during the first week of TRC105 dosing, and dose escalation proceeded to the recommended phase 2 dose of 10 mg/kg TRC105 weekly. At the recommended phase 2 dose of both drugs (10 mg/kg), TRC105 serum concentration were present above target concentration continuously and immunogenicity was rarely observed.

A total of 38 patients were dosed on study across six cohorts and four dose levels. Other than headaches that were mitigated by adjusting the dosing schedule of TRC105, the combination of TRC105 and bevacizumab was well tolerated. Two patients experienced grade 3 serious adverse suspected events as described below. Most adverse events were graded as 1 or 2 and Grade 4 and 5 suspected adverse events were not observed. Grade 3 suspected adverse reactions included anemia (the dose limiting toxicity of TRC105 established as a single agent; 9 patients), headache (4 patients; three of which occurred prior to adjusting the schedule of TRC105), fatigue (2 patients), brain abscess (1 patient), infusion reaction (in a patient dosed at 6 mg/kg), and decreased appetite (1 patient). Headache was the most common suspected adverse event and

occurred in 31 patients (86.1%); three patients (7.9%) experienced migraine headaches (two of grade 1 and one of grade 2 severity). Headaches were treated with triptans and NSAIDs.

Two patients experienced serious adverse suspected events as described below. One of the grade 3 headaches (in a patient dosed at 8 mg/kg without splitting the initial TRC105 dose over two days) resulted in hospitalization and patient discontinuation. One patient dosed at 10 mg/kg of TRC105 experienced a serious suspected event of grade 3 brain abscess. Serious adverse events, considered unrelated to TRC105 treatment, included: grade 3 pneumonia and subsequent grade 4 MRSA sepsis that was complicated by a non Q-wave myocardial infarction during a period of hemodynamic instability while hospitalized; grade 3 ileus at the time of symptomatic disease progression; grade 5 disease progression; grade 3 left foot cellulitis; grade 3 recurrent pneumothorax; grade 3 small bowel obstruction; grade 4 urosepsis.

At least one sign of the triad of epistaxis, gingival bleeding and telangiectasia, reflecting vascular ectasia characteristic of the Osler-Weber-Rendu syndrome of endoglin haplotype insufficiency (i.e., an autosomal dominant genetic disorder of heterozygous endoglin expression) was observed frequently. One of these signs or symptoms (of grade 1 or 2 severity) was noted in one of three patients treated at 3 mg/kg, four of eight patients treated at 6 mg/kg, four of eight patients treated at 8 mg/kg and in all nineteen patients treated at 10 mg/kg of TRC105, generally within the first month of dosing. These signs and symptoms are an expected pharmacologic effects of TRC105 binding to the endoglin receptor (i.e., they are characteristic of the Osler-Weber-Rendu syndrome, that is caused by endoglin haploinsufficiency), and were also observed routinely within the first month of dosing of 10 mg/kg weekly in the single agent TRC105 dose escalation study.

Infusion reactions were, as expected, more notable at lower doses, and were rare at the MTD of TRC105 of 10 mg/kg, when TRC105 serum concentrations were maintained continuously. Two of nineteen patients (10%) dosed with 10 mg/kg of TRC105 each experienced a single infusion reaction of grade 2 severity, both with the initial dose of TRC105, that required a brief interruption of the infusion prior to completion of the scheduled dose.

Clinically significant anemia was not reported in patients dosed with 3 mg/kg or 6 mg/kg of TRC105, was reported in three of seven patients (43%; all grade 3) dosed with 8 mg/kg of TRC105, and was observed in nine of 19 (47%; three of grade 2 and six of grade 3 severity) of patients dosed with 10 mg/kg of TRC105. Anemia prompted transfusion of packed red blood cells in 10 patients and growth factors were used in five patients.

Other, less frequent, suspected adverse reactions included hypothyroidism, periorbital edema (which was generally noted prior to splitting the initial dose of TRC105), gingival pain, nausea, oral pain, vomiting, edema, decreased appetite, dyspnea, nasal congestion, rash and flushing.

Other adverse events characteristic of each individual drug were not increased in frequency or severity when the two drugs were administered together. Of note, the concurrent administration of bevacizumab and TRC105 did not potentiate the known toxicities of bevacizumab of hypertension, hemorrhage (including tumor-associated hemorrhage, and pulmonary hemorrhage or hemoptysis), or proteinuria. Reversible posterior leukoencephalopathy syndrome (RPLS), congestive heart failure, fistulae, gastrointestinal perforation impaired wound healing, and arterial thromboembolic events, were not observed.

Notably, hypertension and proteinuria, known adverse events of bevacizumab, were rarely observed when bevacizumab was given with TRC105. Mild and transient clinically significant hypertension or blood pressure increases were observed in five patients (13%; grade 3 in one case (prior to dosing with study drugs) and grade 2 in four cases) and mild transient proteinuria was observed in two patients (5%; both grade 2).

2.2.1.2.2. 105ST102 Summary of Efficacy

The combination of TRC105 and bevacizumab was active in patients with advanced refractory cancer who had progressed on prior bevacizumab or other VEGF inhibitor treatment. Thirty-three patients had measurable disease (31 patients) or evaluable disease (2 patients) at baseline and received at least one follow up scan and were evaluable for the primary efficacy outcome of ORR by RECIST 1.1. Eighteen patients with measureable disease (58%) had a best response of stable disease or partial response. Two patients (6%), both of whom had been treated with bevacizumab and chemotherapy prior to study entry and were then treated at the top dose level of TRC105 and bevacizumab, had RECIST 1.1- defined partial responses, including one patient with colorectal cancer remained on treatment for more than 28 months. A total of 14 patients (45%) had decreases in overall tumor burden, of whom 10 received prior VEGF inhibitor treatment (usually bevacizumab with chemotherapy). Notably, the duration of treatment with TRC105 and bevacizumab of six patients (20% of those with measureable disease) exceeded the duration of treatment of the most recent treatment regimen containing a VEGF inhibitor (i.e., VEGFR TKI or bevacizumab), received prior to study entry. These six patients had decreases in tumor burden and several were responders by Choi criteria or RECIST. Time to progression ranged from 0 to 861 days. Reductions in tumor markers ranging from 5% to 85% were observed in 15 of 28 (54%) patients with relevant tumor markers. Three patients demonstrated clinical benefit throughout the study (patient 10038102 at cycle 12 day 22, patient 10018106 at cycle 7 day 22 and patient 10028101 at cycle 17 day 1); two of them continue to receive treatment under a continuation protocol (105CON101).

2.2.1.3. Phase 2 105CC201 Single Patient Study of TRC105 with Bevacizumab

A patient with metastatic and refractory gestational trophoblastic neoplasia was previously treated with a laparoscopic hysterectomy and the following chemotherapy regimens: EMA-CO, EMA-EP, TE-TP, ICE, autologous stem cell, and capecitabine. Despite this she had persistent unresectable disease. She was enrolled on a single patient trial of TRC105 plus bevacizumab (protocol 105CC201). The patient experienced a complete response with normalization of her β-hCG after 4 cycles of therapy and remains in remission after 7 months of treatment. TRC105 and bevacizumab treatments were well tolerated. Toxicities have included grade 1 epistaxis, fatigue, and bloody gums, grade 2 headache and gingivitis, and grade 3 hypertension. A TRC105 dose reduction to 8 mg/m^2 was required with the 4th cycle secondary to gingivitis. Consolidation therapy is ongoing.

2.2.1.3.1. Background on Choriocarcinoma

Gestational trophoblastic disease (GTD) is the term used to describe a group of rare diseases that originate in the placenta and have the potential to locally invade the uterus and metastasize. The pathogenesis of GTD is unique because the maternal tumor arises from gestational rather than

maternal tissue. The major histologic entities for this disease include complete molar pregnancy, partial molar pregnancy, invasive mole, and choriocarcinoma. Molar pregnancies although benign are considered to be premalignant because they have the capability of developing into a malignancy. The term gestational trophoblastic neoplasia (GTN) is used when molar and non-molar pregnancies become malignant, and comprise the morphologic entities of invasive mole and choriocarcinoma. Choriocarcinoma consists of invasive, highly vascular and anaplastic trophoblastic tissue made up of cytotrophoblasts and syncytiotrophoblasts without villi. Choriocarcinoma metastasizes hematogenously and can follow any type of pregnancy, but most commonly develops after complete hydatidiform mole. The most common metastatic site is the lungs which are involved in over 80 percent of patients with metastases. Staging for GTN is based on a number of unique criteria that differs from the usual staging procedures and prognosis is dependent upon factors that are not reflected in the anatomic extent of disease such as age, type of antecedent pregnancy, interval between the antecedent pregnancy and the persistent disease and serum β-hCG level. These risk factors are used to establish a WHO Risk score.

Almost all trophoblastic malignancies develop from the cyto-and syncytial cells of the villous trophoblast and produce abundant amounts of β-hCG, the measurement of which serves as a reliable tumor marker for diagnosis, monitoring treatment response and follow-up to detect recurrence. Currently, with sensitive quantitative assays for β-hCG and highly effective chemotherapy, most women with GTN can be cured and their reproductive function preserved providing they are managed according to well-established guidelines.

GTN is uniquely sensitive to chemotherapy which is the major treatment modality. Selection of an appropriate regimen should take into account the FIGO Stage and WHO Prognostic Score as defined above. Despite the success of chemotherapy, other modalities such as surgery and radiation therapy should also be utilized where indicated, particularly in the patients with high-risk scores. Most patients with low risk disease are cured with single agent chemotherapy with the most active agents being methotrexate and actinomycin D. For those that present with high risk disease or have relapse/resistance to monotherapy, multiagent chemotherapy regimens are used. These regimens include EMA-CO, EMA-EP, TE-TP and are often able to produce cure for these women. Rarely, if standard chemotherapy options have been ineffective there are reports of salvage with use of 5-FU or stem cell transplant.

2.2.2. Description of Bevacizumab

Bevacizumab (Avastin®) is an IgG1 monoclonal antibody to VEGF-1. It is a vascular endothelial growth factor-specific angiogenesis inhibitor indicated for the treatment of metastatic colorectal cancer, non-squamous non-small cell lung cancer, metastatic breast cancer, glioblastoma, and metastatic renal cell carcinoma.

2.2.2.1. Rationale for Adding TRC105 to Bevacizumab

TRC105 is a novel angiogenesis inhibitor that complements bevacizumab in preclinical models. Together, these antibodies may result in more effective angiogenesis inhibition in a patient with choriocarcinoma, given the vascular nature of this tumor and direct expression of CD105 on the cancer cells.

2.3. Patient Background

The patient is a 33 year old woman with the following history and no standard chemotherapy options available:

- In February of 2013 the patient was diagnosed with post abortal choriocarcinoma. Pelvic ultrasound on 13Feb2013 showed a 4.5 cm vascular mass in the uterus. A chest radiograph was negative; CT showed > 20 pulmonary nodules. β-hCG was 667 and dilation and curettage confirmed choriocarcinoma. β-hCG increased to 1,946.
- The patient received 4 cycles of MAC with her first cycle given from 1Mar2013-9June2013. β-hCG dropped to 99 after her first cycle. Pulmonary lesions improved but the vascular uterine mass persisted.
- Laparoscopic hysterectomy was completed on 26July2013
- The patient received EMA-CO x 4 cycles, First cycle given from 23July2013 until 29Aug2013. β-hCG normalized after the first cycle.
- On 9Jan2014, β-hCG increased to 8.1. Chest CT showed left upper lobe lesion. Video assisted thoracoscopic resection revealed pathology consistent with choriocarcinoma. β-hCG was 38.3 on 23Jan2014.
- The patient received EMA-EP from 30Jan2014 through 20Mar2014. B-hCG normalized at cycle 2, and she received 4 cycles of consolidation.
- By June2014 β-hCG increased from 1.4 to 90. PET/CT was negative.
- The patient received TP/TE from 7July2014 through 25Sept2014. On 7July2014, β-hCG was 178.5 and decreased to a minimum value of 6.9 on 18Aug2014, and then started increasing.
- The patient was admitted to hospital 28July2014 - 1Aug2014 for cough and fever. New pulmonary changes were seen on CT (new ill-defined pulmonary nodules that were indeterminant and may have represented inflammation or malignant disease), β-hCG had decreased to 18.8 during that admission.
- β-hCG was relatively stable on 9Sept2014, but increased to 33 on 23Oct2014.
- On 16Sept2014, MRI revealed no convincing evidence of metastatic disease in the abdomen and a 1.1 cm right adrenal hemorrhagic nodule without convincing enhancement.
- On 19Sept2014, PET/CT was negative.
- On 24Oct2014 the patient initiated treatment with carboplatin AUC 4 and gemcitabine 800mg/m^2. β-hCG was 57.2
- On 13Nov2014 (C2D1 of carbo/gem), β-hCG was 33.4; On C2D8, β-hCG was 6.7.
- On 4Dec2014 (C3D1 of carbo/gem) β-hCG was 2.9.
- On 11Dec2014 (C3D8 of carbo/gem), β-hCG was 6.9

- On 18Dec2014, β-hCG was 6.3.
- On 24Dec2014 (C4D1 of carbo/gem), β-hCG was 5.8
- On 31Dec2014 (C4D8 of carbo/gem), β-hCG was 9.2.
- On 8Jan2015 (Off treatment week), β-hCG was 9.6. Subsequent β-hCGs noted to increase to 32 and then 76.
- The patient began ICE treatment on 23Jan2015. β-hCG was 106.
- The second cycle of ICE began on 12Feb2015. β-hCG was 79.
- The third cycle of ICE began on 5Mar2015. β-hCG was 55.2.
- On 26Mar2015, β-hCG was 57
- On 2Apr2015 β-hCG was 197, and the patient began treatment with capecitabine at 2500mg/m2 divided twice daily (2500 mg qAM, 2000 mg qPM).
- On 7May2015, β-hCG was 351.5. PET/CT showed enlarging and PET enhancing right adrenal lesion. Percutaneous biopsy revealed choriocarcinoma.
- On 28May2015 the patient underwent laparoscopic right adrenalectomy. Pathology confirmed choriocarcinoma with positive margin. Plan had been for re-resection. However, repeat imaging on 6/19/15 showed new bilateral pulmonary nodules too small to be FDG avid but concerning for metastatic disease.
- On 25June2015 the patient started on Olaparib 400 mg twice daily and progression was noted after 2 cycles.
- On 24Aug2015 the patient started single agent carboplatin for palliation and remains with persistent disease.

2.4. Potential Risks and Benefits to Human Patients

2.4.1. Potential Risks

TRC105

Grade 3 anemia has occurred with TRC105 therapy at the recommended phase 2 dose. All patients treated with TRC105 should be monitored closely for anemia and treated appropriately, including the possibility of TRC105 dose reductions. Anemia may be caused by correctable mineral or vitamin deficiency. The anemia related to TRC105 is hypoproductive in nature and is reversible with interruption of treatment, transfusion, erythropoietin, and other interventions as appropriate.

Gastrointestinal hemorrhage has occurred with TRC105 therapy. Patients with active ulcer disease or risk factors for ulcer disease are excluded from this study.

Grade 1 and 2 cutaneous telangiectasia related to TRC105 occur early in the course of therapy and have been the source of gingival bleeding and epistaxis. Telangiectasia 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.

Premedication including the use of glucocorticoids is required prior to infusion of TRC105 to reduce the frequency and severity of infusion reactions. Infusion reactions following TRC105 dosing generally occur with the first TRC105 dose and include a grade 4 vasovagal reaction that resolved without sequellae. Signs and symptoms of TRC105 infusion reactions include hypertension, hypotension, dyspnea, bronchospasm, chills/rigors, chills, sweats, fever, nausea, tachycardia, bradycardia, EKG changes, flushing, urticaria, pruritus, and headache, generally of grade 1 and 2 severity. 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.

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 CHO-produced TRC105 are rare. 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 for anti-product antibody concentrations to further characterize the immunogenicity of TRC105 and potential clinical implications.

Grade 3 cerebrovascular hemorrhage resulting in hemiparesis occurred in one patient with hepatocellular cancer who was thrombocytopenic (who entered the study with a platelet count of 60,000/uL) in a study of TRC105 with sorafenib. A grade 2 transient ischemic attached was reported in a study of TRC105 and pazopanib. Transient Grade 3 hepatic encephalopathy occurred in one patient with cirrhosis and hepatocellular carcinoma who received TRC105 in combination with sorafenib. Grade 3 pancreatitis was also observed in this study. Grade 5 intracranial hemorrhage occurred in one glioblastoma patient with markedly abnormal blood clotting parameters in a study of TRC105 with bevacizumab. A patient with glioblastoma developed temporary confusion and slurred speech following treatment with TRC105 and bevacizumab that required hospitalization for observation. Another patient with glioblastoma who underwent resection and had a history of an abnormal collection of cerebral spinal fluid developed a grade 2 cerebral spinal fluid leak.

Grade 3 myocardial infarction (non-Q wave infarct associated with hypertension following an infusion reaction) was observed in a patient with hepatocellular cancer following treatment with TRC105 that resolved without sequelae. In addition, a Grade 5 myocardial infarction occurred in a patient with coronary artery disease who received TRC105 in combination with sorafenib. Patients with evidence of active coronary artery disease are excluded from participation in this trial (see exclusion criteria).

Adult respiratory distress syndrome that required temporary intubation occurred in one patient who received TRC105 with pazopanib, from which the patient recovered. Of note, interstitial lung disease has been added as an adverse drug reaction and warning/precaution to the core

safety information for pazopanib. Pneumothorax (collapsed lung) has been observed in trials of TRC105 administered with a VEGFR TKI in patients with lung metastases.

A patient with renal cell carcinoma treated with TRC105 and axitinib developed grade 3 localized perforation of the large intestine at the site of an intraabdominal tumor metastasis that required percutaneous drainage and diverting colostomy. Infections have been observed rarely. Grade 3 infected lipoma/cyst was observed in a Phase 2 study of TRC105 as a single agent in patients with metastatic bladder cancer. Grade 3 orbital cellulitis and grade 3 brain abscess were observed in patients treated with TRC105 and bevacizumab and considered possibly related to TRC105. Grade 1 and 2 gingivitis including infection and ulceration has also been observed. Overall, infections have been observed in fewer than 5% of patients and have largely been considered unrelated to treatment with TRC105.

Grade 1-3 headaches have been observed following TRC105 treatment, generally within hours following completion of the initial infusion. Headaches are throbbing in nature, are not associated with radiographic abnormalities, and have responded to treatment with non-steroidal anti-inflammatory agents and to triptans. Headaches were particularly common when TRC105 and bevacizumab were initially dosed on the same day and were ameliorated when TRC105 was dosed one week following bevacizumab dosing and given over two days during the initial week of dosing.

Nasal congestion and periorbital edema have been observed with TRC105 dosing, particularly when dosed in combination with bevacizumab. The edema has been transient in nature and treated with corticosteroids.

Fatigue of grade 1- 3 severity has been reported following dosing with TRC105. Maculopapular rash and skin flushing of grade 1 and grade 2 severity have also been reported. A patient receiving treatment with TRC105 and sorafenib developed self-limited pancreatitis of grade 2 severity.

Bevacizumab

Side effects associated with the use of bevacizumab include gastrointestinal perforation, hypertension, impaired wound healing, an increased incidence of arterial thromboembolic events, venous thromboembolic events (including pulmonary embolism), hemorrhage (including tumor-associated hemorrhage, mucocutaneous hemorrhage, and pulmonary hemorrhage or hemoptysis), proteinuria, rare reports of Reversible Posterior Leukoencephalopathy Syndrome (RPLS), congestive heart failure, fistulae, hypothyroidism, hypersensitivity reactions, headache and infusion reactions. Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone.

No specific studies in animals have been performed to evaluate the effect of bevacizumab on fertility. There are no adequate and well-controlled studies in pregnant women. Immunoglobulins are excreted in milk, although there are no data specifically for bevacizumab excretion in milk. Since bevacizumab could harm infant growth and development, women should

be advised to discontinue breastfeeding during bevacizumab therapy and not to breast feed for at least 6 months following the last dose of bevacizumab.

Computed Tomography (CT) Scans

The patient will be exposed to a small amount of radiation as a result of the CT scans required in this study. This degree of exposure has not been associated with harmful health effects. In addition, the frequency of CT scans performed in this study is similar to the standard of care frequency.

Venipuncture

The patient 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 patient has had a hysterectomy so any concerns to unborn children are not an issue for this study.

2.4.2. Potential Benefits

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

2.5. Conduct

This clinical trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirements.

3. TRIAL OBJECTIVES AND PURPOSE

3.1. Primary:

- To determine PFS, and ORR of one patient with metastatic and refractory choriocarcinoma by measurement of serum β-hCG

3.2. Secondary:

- To assess To determine PFS and ORR of one patient with metastatic and refractory choriocarcinoma by RECIST 1.1
- To determine the frequency and severity of adverse events as assessed by NCI CTCAE (Version 4.0)
- To explore the effects of TRC105 and bevacizumab on circulating angiogenic protein biomarkers

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan: Description

4.1.1. Trial Overview

This is a single patient protocol of TRC105 in combination with standard dose bevacizumab in one patient with metastatic and refractory choriocarcinoma for whom curative therapy is unavailable. TRC105 will be administered weekly in combination with bevacizumab. The patient will receive bevacizumab on days 1 and 15 of each 28 day cycle and will receive TRC105 on days 8, 11, 15 and 22 of cycle 1 and on days 1, 8, 15 and 22 of subsequent cycles. The first weekly dose of TRC105 should be split with 3 mg/kg administered on cycle 1 day 8 and the balance of the weekly TRC105 dose administered on cycle 1 day 11, and then the full dose given on cycle 1 day 15 and weekly thereafter.

4.1.2. Trial Procedures

All on-study procedures are permitted within the time window indicated in the Schedule of Assessments (Table 3).

4.1.2.1. Screening

The following screening procedures must be performed within 28 days prior to the first day of study therapy. 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 3).

- Patient signature on current Institutional Review Board (IRB) approved informed consent form. Prior to undergoing any study-specific procedure, the patient must read and sign the current Institutional Review Board (IRB) approved informed consent form. The patient may sign consent prior to the 30 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, ECOG performance status, and vital signs.
- Hematology, coagulation (PT or INR) and serum chemistry to be performed locally.
- Urinalysis to be performed locally.
- CT or MRI scans of chest, abdomen and pelvis in addition to any other applicable sites of disease. Brain and bone scans to be performed if metastasis is suspected prior to starting the study.
- Single tracing 12-Lead ECG (QT, PR and QRS intervals and heart rate will be captured).
- Assessment of Adverse Events (serious and nonserious) from the date of informed consent.

- Assessment of concomitant medications from 30 days prior to the start of study treatment.

4.1.2.2. Trial Period

Hematology, blood chemistry, urinalysis, and physical examination 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 the combination of TRC105 and bevacizumab unless otherwise indicated in the Schedule of Assessments. The patient will initially receive 2 cycles (approximately 8 weeks) of treatment. If the patient demonstrates a response of CR, PR or SD, she 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 3).

- Physical examination including examination of all major body systems, ECOG performance status, and vital signs.
    - Assessment of vital signs during TRC105 infusion: Vital signs are to be assessed pre-infusion (within 30 minutes of starting TRC105 infusions) 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 should be performed as clinically indicated.
- Blood sampling for tumor markers (e.g. β-hCG), to be analyzed locally.
- Blood sampling for angiogenic protein biomarkers. Samples will be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).
- CT or MRI scans of chest, abdomen and/or pelvis in addition to any other applicable sites of disease. Scan of the chest, abdomen, and pelvis to be performed on-study as outlined in the assessment table. Known areas of disease should be consistently followed throughout the study. Assessments should be performed whenever disease progression is suspected. Allowable window for tumor imaging studies is +/- 7 days. Brain and bone scans are to be performed if metastasis is suspected.
- Administration of TRC105. TRC105 diluted in normal saline will be administered according to the schedule of assessments as a 1 to 4 hour infusion (+/- 15 minutes) following premedication (see Section 6.7 and Table 3). 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. The allowable dosing window is +/- 2 days.
- Administration of bevacizumab on day 1 and 15 of each 28-day cycle as described in the bevacizumab package insert.

- Assessment of TRC105 and bevacizumab drug accountability.
- Assessment of adverse events.
- Assessment of concomitant medications and concomitant treatments.

4.1.3. End of Study Assessments

Assessments need to be completed if they were not completed during the previous 2 weeks on study. The following will be performed according to the Schedule of Assessments (Table 3).

- Physical examination including examination of all major body systems, ECOG performance status, and vital signs.
- Hematology, coagulation (PT or INR) and serum chemistry to be performed locally.
- Urinalysis to be performed locally. Microscopic analysis should be performed as clinically indicated.
- Blood sampling for tumor markers (e.g. serum β-hCG), to be analyzed locally.
- Blood sampling for angiogenic protein biomarkers. Samples will be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).
- CT or MRI scans of chest, abdomen and pelvis in addition to any other applicable sites of disease.
- Assessment of adverse events.
- Assessment of concomitant medications and concomitant treatments.

4.1.4. Post Treatment Follow-up

The following will be performed according to the Schedule of Assessments (Table 3). Adverse events should be followed for 28 days after completion of study protocol

- 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.
- Assessment of concomitant medications and concomitant treatments.
- Long term survival telephone call every 2 months for 2 years following discontinuation.

Table 3: Schedule of Assessments

Protocol Activities	Screening	*Cycle 1					*Cycle 2				*Cycle 3+ Responding Patients [18]				End of Study [3]	**Post Treatment Follow-up [19]	
	Day -30	Day 1 [1,2]	Day 8 [1]	Day 11 [1]	Day 15 [1]	Day 22 [1]	Day 1 [1]	Day 8 [1]	Day 15 [1]	Day 22 [1]	Day 1 [1]	Day 8 [1]	Day 15 [1]	Day 22 [1]		28 Days	Every 2 Months
Baseline Documentation																	
Informed Consent [4]	X																
Medical/Oncology History [5]	X																
Physical Examination [6]	X	X					X				X				X		
Vital Signs [7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Laboratory Studies																	
Hematology [8]	X	X	X		X	X	X	X	X	X	X				X		
Coagulation [8]	X	X					X								X		
Blood Chemistry [8]	X	X	X		X	X	X				X				X		
Thyroid Stimulating Hormone [8]	X	X					X				X				X		
Urinalysis [9]	X	X					X				X				X		
Treatment w/ Study Drug																	
TRC105 Dosing [10]			X	X	X	X	X	X	X	X	X	X	X	X			
Bevacizumab Dosing [11]		X			X		X		X		X		X				
Tumor Assessments																	
CT or MRI Scans [12]	X									X				Cycles 4, 6, 8 etc.	X		
Other Clinical Assessments																	
12-Lead ECG [13]	X																
Concomitant Medications/Treatments [14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Baseline Signs and Symptoms [15]	X																
Adverse Events [15]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Special Laboratory Assessments																	
Protein Biomarkers [16]		X	X				X								X		
Tumor Markers [17]		X	X				X				X				X		
Long Term Follow-Up																	
Phone Call Long Term Follow-Up																	X

*Allowable window for each visit within the cycle is +/- 2 day unless otherwise stated

**Allowable window for Post Treatment Follow-up is +/- 1 week

Schedule of Assessments Footnotes

1. **Days of Treatment with TRC105:** All assessments should be performed prior to dosing with TRC105/bevacizumab unless otherwise indicated. Each cycle is 28 days in duration. .
2. **Cycle 1 day 1:** Hematology, blood chemistry, urinalysis, and physical examination not required if acceptable screening assessment is performed within 7 days prior to the start of treatment on cycle 1 day 1.
3. **End of Study:** Assessments do not need to be repeated if performed within the previous 2 weeks (previous 4 weeks for radiologic tumor assessments). Follow-up visits should occur 28 days following the last dose of TRC105 study drug 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 30-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 ECOG performance status.
7. **Vital Signs:** Heart rate, temperature, blood pressure, respiratory rate, weight. Assessment of Vital Signs during TRC105 Infusion: Vital signs are to be assessed pre-infusion (within 30 min of starting TRC105 infusions) 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. If the patient has a Monday visit she may complete safety lab assessments on the Friday prior to the visit. In addition to the assessments scheduled for the clinical trial, patients should undergo assessment as appropriate to ensure safe treatment. Thyroid stimulating hormone (TSH) is to be collected at screening and on day 1 of each cycle.
9. **Urinalysis:** To be performed locally. Microscopic analysis should be performed as clinically indicated.
10. **TRC105 Administration:** IV TRC105 diluted in normal saline will be administered as outlined in the schedule of assessments.
11. **Bevacizumab Administration:** Commercially available bevacizumab will be administered per the package insert in this study. The patient will receive 10 mg/kg as outlined in the schedule of assessments.
12. **CT or MRI Tumor Imaging:** Images of chest, abdomen, and pelvis to be performed at screening and on-study as outlined in the assessment table. Known areas of disease should be consistently followed throughout the study. Assessments should be performed whenever disease progression is suspected. Allowable window for tumor imaging studies is +/- 7 days. Brain and bone scans are to be performed if metastasis is suspected prior to starting the study and during study conduct.
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 30 days prior to the start of study treatment and up to 28 days following the last dose of study treatment.

15. **Baseline Signs and Symptoms and Adverse Events:** The patient 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-Signs and Symptoms” and will be recorded on “Medical History and Baseline Signs and Symptoms” case report forms. Events that occur from the time the patient has taken the first dose of bevacizumab and/or TRC105 study drug through 28 days after the last dose of bevacizumab and/or TRC105 study drug (whichever is later) 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. **Protein biomarkers:** 5 mL of plasma (K_3EDTA) will be collected as indicated in the schedule of assessments and stored at approximately -70°C to be analysed by a central laboratory. Samples will be batch shipped every 3 months to a third-party laboratory for analysis. See separate laboratory guide for further collection and shipment information.
17. **Tumor markers:** Will be collected and analysed locally as indicated in the schedule of events (e.g.: β-hCG)
18. **Cycle 3+ Treatment:** If the patient demonstrates a response of CR, PR or SD will be eligible for additional treatment until progression as long as TRC105 drug supply is available.
19. **Follow-up:** The initial follow-up visit should occur 28 days following the last dose of TRC105. Phone calls for long term follow-up to be conducted every 2 months for 2 years following the end of study visit.

5. SELECTION AND WITHDRAWAL OF THE PATIENT

5.1. Patient Inclusion Criteria

1. Willingness and ability to consent for self to participate in study
2. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures
3. Measurable disease by RECIST 1.1 and elevated serum β-hCG
4. Histologically proven choriocarcinoma that has progressed despite all described lines of chemotherapy for this condition

5.2. Exclusion Criteria:

1. Prior treatment with TRC105
2. Serious dose-limiting toxicity related to prior bevacizumab
3. Current treatment on another therapeutic clinical trial
4. Uncontrolled chronic hypertension defined as systolic > 140 or diastolic > 90 despite optimal therapy (initiation or adjustment of BP medication prior to study entry is allowed provided that the average of 3 BP readings at a visit prior to enrollment is < 140/90 mm Hg)
5. Symptomatic pericardial or pleural effusions
6. Uncontrolled peritoneal effusions requiring paracentesis more frequently than every 2 weeks
7. Active bleeding or pathologic condition that carries a high risk of bleeding (i.e. hereditary hemorrhagic telangiectasia)
8. Thrombolytic or anticoagulant use (except to maintain i.v. catheters) within 10 days prior to first day of study therapy
9. Cardiac dysrhythmias of NCI CTCAE grade ≥ 2 within the last 28 days
10. Known active viral or nonviral hepatitis
11. Open wounds or unhealed fractures within 28 days of starting study treatment
12. History of peptic ulcer disease or erosive gastritis within the past 6 months, unless treated for the condition and complete resolution has been documented by esophagogastroduodenoscopy (EGD) within 28 days of starting study treatment
13. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness
14. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the

interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for this study

5.3. Patient Withdrawal Criteria

Patient will 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 the patient does not return for a scheduled visit, every effort should be made to contact them. In any circumstance, every effort should be made to document patient outcomes. Data to be collected at the end of study visit are described in the Schedule of Assessments (Table 3). Patient 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, the patient will be withdrawn from treatment in the case of:

1. Disease Progression. Progressive Disease as defined as a rise in serum β-hCG of more than 10% above baseline or nadir on 2 consecutive cycles. Disease progression may also be based unequivocal evidence of progressive disease sufficient to require a change in therapy.
2. There is a need for anticancer therapy not specified in the protocol including cancer surgery or radiation therapy.
3. The patient is lost to follow-up or noncompliant.
4. Patient has a TRC105 dose delay ≥ 8 weeks.
5. Arterial thrombosis of any grade (including cerebrovascular ischemia, cardiac ischemia/infarction, or peripheral or visceral arterial ischemia) or grade 4 thromboembolism. For grade 3 venous thromboembolism hold bevacizumab treated. If the planned duration of full dose anticoagulation is < 2 weeks, bevacizumab should be held until the full dose anticoagulation period is over. If the planned duration of full dose anticoagulation is > 2 weeks, bevacizumab may be resumed during full dose anticoagulation IF all the following criteria are met. 1. Subject does not have a pathologic condition that carries high risk of bleeding (i.e. tumor involving major vessels). 2. Subject has not had any hemorrhagic events on study. 3. The subject has a stable dose of heparin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab. 4. If thromboembolism worsens/recurs upon resumption of bevacizumab, despite anticoagulation, bevacizumab should be discontinued.

6. TREATMENT OF THE PATIENT

6.1. 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.

6.2. 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.

6.3. TRC105 Dose Levels

The patient will receive 10 mg/kg TRC105 weekly in combination with 10 mg/kg bevacizumab every other week on a q 28 day cycle.

6.4. TRC105 Packaging and Labeling

TRC105 may be provided in one or more of the following presentations:

Phosphate Buffered Saline Formulation (7 mg TRC105/mL)

- 210 mg TRC105/30 mL single-use vial

or

20 mM L-Histidine/L-Histidine Monohydrochloride, 240 mM Trehalose, 0.01% Polysorbate 20 Formulation (25 mg TRC105/mL)

- 100 mg TRC105/4 mL single-use vial
- 400 mg TRC105/16 mL single-use vial

6.5. TRC105 Storage and Shipping

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

6.6. TRC105 Preparation

TRC105 will be prepared in the pharmacy and diluted into normal saline using appropriate aseptic technique. TRC105 will be administered using an in-line 0.2 micron filter. No incompatibilities between TRC105 and polyvinyl chloride or polyolefin bags have been observed. 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) × dose level (mg/kg) divided by TRC105 concentration (mg/mL) = 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 1.0 mL; in the case of an increment of 0.5 mL the volume should be rounded up. **The maximum**

weight that should be used for dose calculation in this study is 85 kg (note: there is not a weight restriction for enrollment purposes). The patient weight will be assessed on the day of treatment and used for calculation of each 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 0.3 mg/mL and 10 mg/mL. The prepared TRC105 must be gently inverted several times in order to ensure a homogeneous solution. The diluted infusion solution of TRC105 should be used within 8 hours of preparation if stored at room temperature, or within 24 hours of dilution if stored at 2° to 8°C (36º to 46ºF). The expiration time should be labeled on the bag. If the diluted infusion solution of TRC105 cannot be infused within 8 hours of preparation (i.e.: the prepared infusion is at room temperature for more than 8 hours), a second bag will be prepared that contains the balance of the planned dose that was not already delivered. The prepared solution should not be frozen.

6.7. TRC105 Administration

The patient should be encouraged to drink abundant fluid (e.g. two eight ounce glasses of juice) prior to the first treatment. Intravenous hydration prior to and during therapy is left to the discretion of the Investigator, but should be considered if the patient is thought to 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
- Methylprednisolone 100 mg i.v. will be given prior to the Cycle 1 Day 8 and Cycle 1 Day 11 infusions only. In addition, methylprednisolone will be given in the case of a delay of ≥ 10 days between any two doses or if the patient develops an infusion reaction ≥ grade 2 during the immediate prior infusion.
- Famotidine 20 mg i.v. or p.o. (or similar H2 blocker) x 1. Famotidine (or similar H2 blocker) may be discontinued starting with Cycle 2 in the absence of infusion reactions with the prior dose.
- Cetirizine 10 mg i.v. or p.o. x 1 (or similar oral or intravenous antihistamine). Cetirizine (or similar oral or intravenous antihistimine) may be discontinued starting with Cycle 2 in the absence of infusion reactions with the prior dose.

TRC105 premedication, including the methylprednisolone infusion, should be administered 2 hours to 30 minutes prior to initiating TRC105 infusions.

TRC105 will be administered intravenously utilizing an infusion pump. TRC105 has been demonstrated to be compatible with polyethylene lined, non-DEHP infusion sets and polyvinyl chloride, non-DEHP infusion sets. TRC105 is required to be administered 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.

Following the appropriate premedication regimen, the patient will receive TRC105 on days 8, 11, 15 and 22 of cycle 1 and on days 1, 8, 15 and 22 of subsequent cycles. The first weekly dose of TRC105 will be split with 3 mg/kg administered on cycle 1 day 8 and infused over 4 hours (+/- 15 minutes) and 7 mg/kg administered on cycle 1 day 11 and infused over 2 hours (+/- 15 minutes), and then the full dose of 10 mg/kg given on cycle 1 day 15 and weekly thereafter and will be administered over 1 hour (+/- 15 minutes). The patient must complete at least one 4 hour infusion (+/- 15 minutes) without the development of any infusion reactions, in order to reduce the subsequent TRC105 infusion to 2 hours (+/- 15 minutes) and complete a 2 hour infusion (+/- 15 minutes) without the development of any infusion reactions in order to reduce subsequent TRC105 infusions to 1 hour (+/- 15 minutes). If the patient develops infusion reactions of any kind they should be managed appropriately (see Section 6.7.2) and the patient is not permitted to reduce the duration of the next planned infusion. In the event a dose cannot be completed on a given day, the balance of the planned dose may be administered the following day with premedication at the rate of infusion planned for the prior day.

The rate of TRC105 infusion must not exceed 25 mg/min. When the i.v. bag containing TRC105 is empty, flush the i.v. line with a 20 mL normal saline. 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 the patient misses a weekly TRC105 dose (i.e., ≥ 10 days between doses), the methylprednisolone dose should be reinstituted as per the initial infusion and first TRC105 dose should be administered over two days as was done for the initial dose.

6.7.1. TRC105 Dose Modification/Dose Interruptions

TRC105 dose reductions are allowed for grade 3 or 4 related adverse events that resolve to grade 1 or baseline (including anemia). Treatment dose delays cannot exceed 8 consecutive weeks (i.e., both TRC105 and bevacizumab dosing held). However, if the patient cannot tolerate bevacizumab or TRC105 therapy, demonstrates a response of complete response (CR), partial response (PR) or stable disease (SD) with the combination and is thought to benefit from continued single agent therapy, the patient may continue on study on TRC105 or bevacizumab alone.

TRC105 and bevacizumab should be held for two weeks prior and for two weeks following surgical procedures.

Table 4: Allowable TRC105 Dose Modifications

Toxicity Attributed to TRC105	Dose Adjustment for Next Dose of TRC105 (% of Starting Dose)
Grade 1 or 2	Maintain Dose Level
Grade 3 or 4	
• 1st appearance	80%
• 2nd appearance	60%
• 3rd appearance	Discontinue treatment permanently

Note: If the patient is dose reduced and subsequently misses a dose whereby the first dose of TRC105 following the break needs to be split into two doses, 3 mg/kg should be given on the first day and the remainder of the dose (i.e., 5 mg/kg in the case of a dose reduction to 8 mg/kg) will be given 3 days later.

If the patient develops an arterial thrombosis or grade 4 venous thrombosis she will be removed from study. If she develops a grade 1, 2 or 3 venous thrombosis that requires anticoagulation she will have her TRC105 therapy interrupted. TRC105 therapy may resume once the following criteria are met:

- The patient is on a stable dose of heparin, low molecular weight heparin, coumadin, or other anticoagulant.
- If on coumadin, the patient has an in range INR for therapeutic anticoagulation (usually between 2 and 3).
- The patient has a platelet count > 50,000 or baseline.
- The patient has not had a hemorrhagic event of grade 2 or higher while on study.
- The patient does not have a pathological condition that carries a high risk of bleeding (e.g., tumor involving major vessels).
- The patient is benefiting from TRC105 therapy (no evidence of disease progression).

The INR should be monitored weekly before each dose of TRC105 for the first 4 weeks, and then once per cycle thereafter (or more often as clinically indicated). The patient should not receive TRC105 until the INR is ≤ 3.

6.7.2. Management of TRC105 Infusion Reactions

If the 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 (i.e., the same day) at half of the previous rate if and when the infusion reaction has resolved, and then increased per patient tolerance to a maximum of 25 mg/min. 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 5: Management of TRC105 Infusion Reactions

Infusion Reaction Severity	Recommended Management
Grade 1 (mild)	**1.** No intervention **2.** Continue infusion unless symptoms worsen
Grade 2 (moderate)	**1.** Interrupt infusion **2.** Treat with symptomatic medications[a] **3.** Resume infusion at half the previous rate when infusion-related symptoms improve to grade 1 or less.
Grade 3 (severe)	**1.** Interrupt infusion **2.** Treat with symptomatic medications[a] **3.** Monitor patient until infusion-related symptoms resolve, including hospitalization if necessary **4.** Withdraw patient from study unless other factors that contributed to the infusion reaction are identified and corrected
Grade 4 (life-threatening)	**1.** Discontinue infusion **2.** Treat with symptomatic medications[a] **3.** Hospitalize patient **4.** Withdraw from study

[a]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).

6.7.3. 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.

6.7.4. 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. Disposal of TRC105 should occur in accordance with institutional policy. The Site Pharmacist will be responsible for documenting the destruction (according to institutional requirements) of used or expired vials.

6.8. Bevacizumab Packaging

Bevacizumab is available as 100 mg pack containing one 4 mL single-dose vial and 400 mg pack containing one 16 mL single-dose vial.

6.9. Bevacizumab Preparation

Commercially available bevacizumab will be utilized in this study. The patient will receive 10 mg/kg on day 1 and day 15 of each 28-day cycle. Bevacizumab should be prepared according to institutional policy and using aseptic technique. Withdraw the necessary amount of bevacizumab and dilute to the required administration volume with 0.9% sodium chloride solution. The concentration of the final bevacizumab solution should be kept within the range of 1.4-16.5 mg/mL as described in the Avastin PI (Appendices – Appendix 3).

6.10. Bevacizumab Administration

The patient will receive 10 mg/kg on day 1 and day 15 of each 4-week cycle. Bevacizumab should be administered as a 90 minute infusion on cycle 1 day 1. Subsequent infusion times can be reduced by 30 minutes down to a minimum infusion time of 30 minutes if tolerated (Appendices – Appendix 3). Bevacizumab will be administered according to institutional guidelines.

6.10.1. Bevacizumab Dose Modification

Dose reduction of bevacizumab for adverse reactions is not recommended. If indicated, bevacizumab should either be discontinued or temporarily suspended, see bevacizumab package insert for specific information related to different adverse events. If discontinuation of bevacizumab is clinically indicated, and the patient demonstrated a response of complete response (CR), partial response (PR) or stable disease (SD), she will be eligible for additional treatment with TRC105 alone until progression as long as TRC105 drug supply is available.

6.11. Bevacizumab Drug Accountability

Commercial bevacizumab will be utilized in this study, thus the site will follow institutional guidelines regarding drug accountability for commercial product.

6.12. Bevacizumab Handling and Disposal

Bevacizumab vials [100 mg (NDC 50242-060-01) and 400 mg (NDC 50242-061-01)] are stable at 2−8°C (36−46°F). Bevacizumab vials should be protected from light. Do not freeze or shake.

Diluted bevacizumab solutions may be stored at 2−8°C (36−46°F) for up to 8 hours. Bevacizumab vials should be stored in their original carton until time of use. No incompatibilities between bevacizumab and polyvinylchloride or polyolefin bags have been observed. Partially used vials should be properly destroyed according to institution guidelines.

6.13. Concomitant Medications

No other approved or investigational anticancer treatment will be permitted during the study period, including chemotherapy, biological response modifiers, immunotherapy, or radiotherapy.

If the patient is on low dose aspirin at baseline she may continue it if medically indicated. If the patient is on NSAIDs on study for more than three consecutive days should also receive peptic ulcer disease (PUD) prophylaxis with an H2 or proton pump blocker.

Narcotic analgesics, nonsteroidals, anti-inflammatory drugs, and triptans (e.g. sumatriptan) may be offered as needed for relief of pain or headaches. Triptans are recommended for patients who experience a migraine headache following dosing, and may be taken prior to the occurrence of headache, as a prophylactic medication. 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.

6.14. Treatment Compliance

6.14.1. TRC105

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

6.14.2. Bevacizumab

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

6.15. Patient Enrollment

This is a single patient trial. She will be consented and enrolled at DFCI and followed by her treating physicians

7. ASSESSMENT OF EFFICACY

7.1. Tumor Assessment by β-hCG

The primary efficacy assessment will be best overall response as defined in Section 7.3.1. Determination of antitumor efficacy will be based on serum β-hCG measurements and investigators will make treatment decisions based on these assessments.

Serum tumor marker (β-hCG) assessments will be performed at screening, and as outlined in the Schedule of Assessments (Table 3).

7.1.1. Definition of Tumor Response

- **Complete response (CR)** is defined as normalization of serum β-hCG on two consecutive measurements separated by at least two weeks
- **Partial response (PR)** is defined as ≥ 50% decrease of serum β-hCG from baseline on consecutive measurements separated by at least two weeks.
- **Progressive disease (PD)** is defined as a rise in β-hCG of >10% above the starting value or prior nadir on consecutive measurements separated by at least two weeks.
- **Stable disease (SD)** is defined as absence of response or progression on three consecutive β-hCG measurements separated by at least two weeks

7.2. Radiological Tumor Assessment

A secondary efficacy assessment will be best overall response as defined in Section 7.3.1. The determination of radiologic antitumor efficacy will be based on objective tumor assessments made by the Investigator according to RECIST version 1.1 [55]. All lesions will be classified as Target or Nontarget lesions at the Screening visit. Each lesion designation will be maintained through the course of the study.

The same method and technique should be used to characterize each identified and reported lesion at Screening, during the study treatment period, and at the End of Study visit. Imaging-based evaluation over clinical examination is the required technique when both could be used to assess the antitumor effect of the treatment. Clinical Oncology review of all tumor measurements is desired.

Whenever possible, clinical evaluation of superficial lesions should not be used as the sole form of measurement. However, when necessary, color photograph with metric caliber is acceptable. Tumor evaluation by positron emission tomography (PET) scan or by ultrasound may not substitute for CT or MRI scans.

Radiological tumor assessments will be performed at screening, as outlined in the Schedule of Assessments (Table 3), 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. If the patient has an objective response of PR or CR she must have the response confirmed at least 4 weeks after the initial documentation of response.

Measurability of Tumor Lesions

At Screening, individual tumor lesions will be categorized by the Investigator as either target or non-target according to the RECIST 1.1 criteria described below.

- **Measurable:** Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with spiral CT scan. Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes) and ≥ 10 mm. Clinical lesions must be measured with calipers.
- **Non-Measurable:** All other lesions, including small lesions and bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusions, lymphangitis of the skin or lung, abdominal masses that are not confirmed and followed by imaging techniques, previously irradiated lesions, and disease documented by indirect evidence only (e.g. by laboratory tests such as alkaline phosphatase).

7.3. Recording Radiologic Tumor Measurements

Measurable lesions up to a maximum of 5 lesions representative of all involved organs (with a maximum of 2 lesions per organ) should be identified as target lesions and measured and recorded at Screening and at the stipulated intervals during treatment. Target lesions should be selected on the basis of their size (lesion with the longest diameters) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). Target lesions may include lymph nodes with a short axis ≥ 15 mm.

The longest diameter will be recorded for each target lesion (with the exception of lymph nodes, where the short axis will be used). The sum of the diameter for all target lesions at Screening will be calculated and recorded as the baseline sum diameter to be used as reference to further characterize the objective tumor response of the measurable dimension of the disease during treatment. All measurements should be performed using a caliper or ruler and should be recorded in metric notation in millimeters.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present", "stable", "absent", "increased" or "decreased".

7.3.1. Definitions of Tumor Response by RECIST 1.1

7.3.1.1. Target Lesions

- **Complete response (CR)** is defined as the disappearance of all target lesions and normalization of her serum β-hCG.
- **Partial response (PR)** is defined as a ≥ 30% decrease in the sum of the dimensions of the target lesions taking as a reference the baseline sum dimensions.
- **Progressive disease (PD)** is defined as a ≥ 20% relative increase and ≥ 5 mm absolute increase in the sum of the dimensions of the target lesions taking as a reference the smallest sum of the dimensions recorded since the treatment started, or the appearance of one or more new lesions and rise of her serum β-hCG.

- **Stable disease (SD)** is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as a reference the smallest sum of the dimensions since the treatment started.

7.3.1.2. Non-Target Lesions

- **Complete response (CR)** is defined as the disappearance of all non-target lesions and normalization of tumor marker levels to ≤ ULN.
- **non-CR/non-PD** is defined as a persistence of ≥ 1 non-target lesions and/or maintenance of tumor marker levels > ULN.
- **Progressive disease (PD)** is defined as unequivocal progression of existing non-target lesions, or the appearance of ≥ 1 new lesions.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease and progressive disease.

7.3.1.3. Determination of Overall Response by RECIST 1.1

When both target and non-target lesions are present, individual assessments will be recorded separately. The overall assessment of response will involve all parameters as depicted in Table 6 below. Per RECIST 1.1, a modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

Table 6: Response Evaluation Criteria in Solid Tumors

Target Lesions[a]	Non-target Lesions[b]	New Lesions[c]	Overall Response
CR	CR	No	CR
CR	non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Any Response	Yes or No	Not Evaluable
PD	Any Response	Yes or No	PD
Any Response	PD	Yes or No	PD
Any Response	Any Response	Yes	PD

[a]Measurable lesions only.
[b]May include measurable lesions not followed as target lesions or non-measurable lesions.
[c]Measurable or nonmeasurable lesions.

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest

measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

NOTE: If the patient has a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time her best response should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

8. ASSESSMENT OF SAFETY

8.1. 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 ECOG 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, and coagulation profile. In addition, an ECG will be recorded at baseline and as clinically indicated throughout the study.

8.1.1. Laboratory Safety Assessments

Abnormal and clinically significant laboratory tests should be recorded as adverse events.

8.1.1.1. Hematology, Serum Chemistry, Coagulation

Assessments will be performed at the time points indicated in the Schedule of Assessments (Table 3) 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, thyroid stimulating hormone (TSH), and glucose

8.1.1.2. Urinalysis

Urine analysis will be performed at time points indicated in the Schedule of Assessments (Table 3) and analyzed by local laboratories. Microscopic analysis should be performed as clinically indicated.

8.1.2. Other Safety Assessments

8.1.2.1. 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 3). The physical examination will include examination of known and suspected sites of disease.

8.1.2.2. Vital Signs

Heart rate, temperature, blood pressure, respiratory rate and weight will be assessed at time points indicated within the Schedule of Assessments (Table 3). 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).

8.1.2.3. Performance Status

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

8.1.2.4. 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 3) and as clinically indicated throughout the study.

8.2. Adverse Events

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

8.2.1. 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 *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

8.2.2. 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 serious adverse events 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 serious adverse events. 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 a serious adverse event 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).

8.2.2.1. 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).

8.3. Reporting Adverse Events

8.3.1. 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?"

8.3.2. 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-signs and symptoms" and will be recorded on corresponding case report forms. The adverse event reporting period for this trial begins when the patient have taken the first dose of bevacizumab and/or TRC105 study drug and ends 28 days after the last dose of bevacizumab and/or TRC105 study drug is administered whichever is later. All adverse events that occur on trial for this patient 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.

8.3.3. 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 a serious adverse event 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:

Charles Theuer, MD, PhD

TRACON Pharmaceuticals Inc.

8910 University Center Lane, Suite 700

San Diego, California 92122

Direct Phone: (858) 550-0780 x233

Cell Phone: (858) 344-9400

Email: ctheuer@traconpharma.com

Following this 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 does not become aware of the occurrence of a serious adverse event immediately (for example, if a patient initially seeks treatment elsewhere), the Investigator is to report the event **immediately upon learning of it** and document his/her first awareness of the serious adverse event.

TRACON Pharmaceuticals Inc. may also be contacted via telephone 24 hours a day at (858) 344-9400.

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.

8.3.4. 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 8.2.1 are to be recorded on patient source documents and on the CRFs. Adverse events should be reported using concise medical terminology.

8.3.5. 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 CTCAE 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 7: Adverse Event Grading

Grade	Non-CTCAE Severity	Definition
1	Mild	Does not interfere with patient's usual function
2	Moderate	Interferes to some extent with patient's usual function
3	Severe	Interferes significantly with patient's usual function
4	Life-Threatening	Results in immediate risk of patient's death

Grade	Non-CTCAE Severity	Definition
5	Fatal	Results in patient's death

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.

8.3.6. Relationship to TRC105 Study Drug

In this study, TRC105 study drug is given in combination with bevacizumab. 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.

AEs related to TRC105 study drug or bevacizumab are considered Adverse Drug Reactions (ADR).

8.3.7. Exposure in Utero

This patient is status post a hysterectomy so no exposure in utero is possible.

8.3.8. 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.

8.3.9. 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.

8.4. 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 this patient on this study will be promptly communicated in writing to all participating clinical sites and institutions participating in this clinical trial.

9. OTHER ASSESSMENTS

9.1. Other Laboratory Assessments

9.1.1. Protein Biomarker

A 5 mL K_3EDTA plasma blood sample will be collected on the days indicated within the Schedule of Assessments (Table 3). Samples will be stored at approximately -70 °C and batch shipped to Fisher BioServices Inc. (10 Forge Park, Franklin, MA 02038) for storage until the time of analysis. Duke University Medical Center will analyze plasma for several biomarkers including but not limited to VEGF, PDGF, and TGFβ. Please see the separate laboratory guide for further collection and shipment information.

10. STATISTICS

10.1. Data Analysis

Due to the exploratory nature of this study, no inferential analyses are planned, and no imputation of missing data will be done.

10.1.1. Analysis of Primary Objective

PFS and ORR will be calculated form the time of cycle 1 day 1 until the time of progression from cancer, if the patient remains on trial at the time of cancer progression. Stable disease will be defined as lack of tumor progression lasting for 2 cycles or longer.

10.1.2. Analysis of Secondary Objectives

The secondary objectives including the assessments of efficacy by RECIST 1.1 and the frequency and severity of toxicities, efficacy, and angiogenic protein biomarkers will be evaluated as described below.

10.1.2.1. Protein Biomarkers

Angiogenic protein biomarker data if the patient received at least one dose of study drug will be listed by cohort and tumor type.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

All data entered on CRFs/eCRFs must be verifiable within the patient's' source documents (written or electronic record). The Investigator/institution guarantees TRACON representatives and appropriate regulatory authorities direct access to the original source records for the duration of the agreed study record retention period. Printouts of source records that are electronically obtained and stored will not be acceptable for audit/inspection unless provided as certified exact copies and the data remains as meaningful and useful as in its original electronic state.

Legally protected subject identification and other personal health information must be securely stored with limited access by the participating institutions. Unless secure provisions are established by the institution to allow TRACON (or designee) to perform remote monitoring of electronic source records, TRACON (or designee) will review source records/data on site and will not remove any such protected health information.

12. QUALITY CONTROL AND QUALITY ASSURANCE

Monitoring visits to clinical investigator sites will be made by TRACON or its representatives periodically during the trial to ensure that GCPs and all aspects of the protocol are being followed.

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

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

TRACON and its representatives will be governed by applicable regulations, good clinical practice standards, and internal SOPs for the conduct of monitoring visits and QA audits.

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 the patients is consented for participation on the trial. All correspondence and other evidence of appropriate and timely communications 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 patient. 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, applicable local regulatory requirements and laws, and the International Conference on Harmonization Guideline on Good Clinical Practice, which supports the application of ethical principles that have their origin in the Declaration of Helsinki (see ICH E6, §2.1).

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 the 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. The patient must be informed about her right to withdraw from the trial at any time. Furthermore, it is the responsibility of the Investigator to ensure the patient is appropriately informed before obtaining her signed and dated consent. Signatures from the investigator conducting the informed consent discussion should also be obtained prior to undertaking any trial-related procedure. Consent by a legally authorized representative is not permitted. Should an impartial witness be needed, ICHE6 requirements for impartial witnesses will apply.

The Investigator will retain the original the patient's signed consent form in the Investigator/site files.

13.4. Patient Compensation

The patient will not be compensated for participation in this trial; this will be outlined to the patient informed consent form.

14. DATA HANDLING AND RECORDKEEPING

14.1. Inspection of Records

CRF's are required and should be completed for the patient when she receives treatment with TRC105 and bevacizumab. 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 CRF data. The investigator will sign off on his/her data per patient. These signatures serve to attest that the investigator has reviewed and approved the information contained on the case report forms and that the information is complete, accurate, and 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.

The use of electronic CRFs (eCRFs) to capture study data using automated computerized data capture systems does not change the principles and requirements for collecting study data. The investigator still retains final personal responsibility for eCRF data and any associated data pertaining to it (e.g. metadata including any record of change to the originally recorded data). The investigator's signed approval of the eCRF data serves to attest that the electronic data and all of its associated metadata (including changes) has been reviewed and accepted as complete, accurate, and true for this patient.

All CRF/eCRF data must be verifiable in the patient's source records by TRACON or its designee. TRACON will review CRF data as compared to source records in an attempt to identify missing and spurious data and notify the investigator of findings so that proper corrections can be made. TRACON representatives (monitors and auditors), and regulatory inspectors shall have direct access to the original source records in its original recorded format: electronic or hardcopy.

TRACON (or its designee) will perform all data management functions associated with the study. Data will be captured electronically. Automated data verification ("edit checks") will be used to ensure that the data are logical and consistent. Any inconsistencies will be queried for clarification or correction as appropriate by the clinical site.

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 the patient (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 inform TRACON of any such transfer of responsibilities and properly identify the person or institution assuming the responsibility. The responsible investigator/institution must obtain TRACON's written permission before disposing of any records.

15. DEFINITION OF END OF TRIAL

15.1. End of Trial

End of trial in all participating countries is defined as the time at which the patient enrolled in the study has completed treatment on study.

15.2. TRACON Discontinuation Criteria

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,, but intends only to exercise this right for valid scientific or administrative reasons. If the trial is prematurely terminated or discontinued, TRACON will promptly notify the Investigator. After notification, the Investigator must contact the participating patient 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: 105CC201B

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

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20. APPENDICES

Appendix 1: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

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

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Appendix 2: ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix 3: Avastin Package Insert

The FDA approved bevacizumab package insert should be referenced and may be reviewed on-line at the following FDA website:

http://www.gene.com/gene/products/information/pdf/avastin-prescribing.pdf