CLINICAL PROTOCOL	
Title:	**A PHASE 2A STUDY OF TRC105 (WITH OPTION TO ADD BEVACIZUMAB) IN PATIENTS WITH REFRACTORY GESTATIONAL TROPHOBLASTIC NEOPLASIA (GTN)**
Protocol Number:	105GTN201 EudraCT 2015-005475-25
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Version Date:	Original Protocol: January 18th, 2016 Amendment #1: April 25th, 2016 Amendment #2: July 25th, 2016 Amendment #3: September 20th, 2016

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 PHASE 2A STUDY OF TRC105 (WITH OPTION TO ADD BEVACIZUMAB) IN PATIENTS WITH REFRACTORY GESTATIONAL TROPHOBLASTIC NEOPLASIA (GTN)**	
Study center(s): This study will be performed at multiple centers globally.	
Investigator: To be determined	
Studied period: Estimated date first patient enrolled: October 2016 Estimated date last patient enrolled: July 2018 Estimated date last patient completed: December 2018	**Phase of development:** 2A
Rationale: TRC105 is a monoclonal antibody that binds to endoglin, an angiogenic target highly expressed on the tumor vessels and tumor cells in gestational trophoblastic neoplasia (GTN). 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 has been well tolerated as a single agent and when combined with bevacizumab. These antibodies may be efficacious in refractory GTN, a tumor type that is highly vascular and has been shown to densely express endoglin. A single patient IND study of TRC105 and bevacizumab demonstrated a complete response to treatment as evidenced by normalization of hCG, a reliable marker highly correlated with disease burden, in a heavily treated and chemotherapy refractory patient with metastatic choriocarcinoma, an aggressive form of GTN. Given the limited experience treating patients with TRC105 and bevacizumab, this trial will limit toxicity and maximize the opportunity of each individual patient to respond to treatment with either TRC105 or bevacizumab, and if necessary, both agents, by employing a sequential treatment design per Figure 1 - Figure 4.	

Figure 1: Sequential Treatment Design

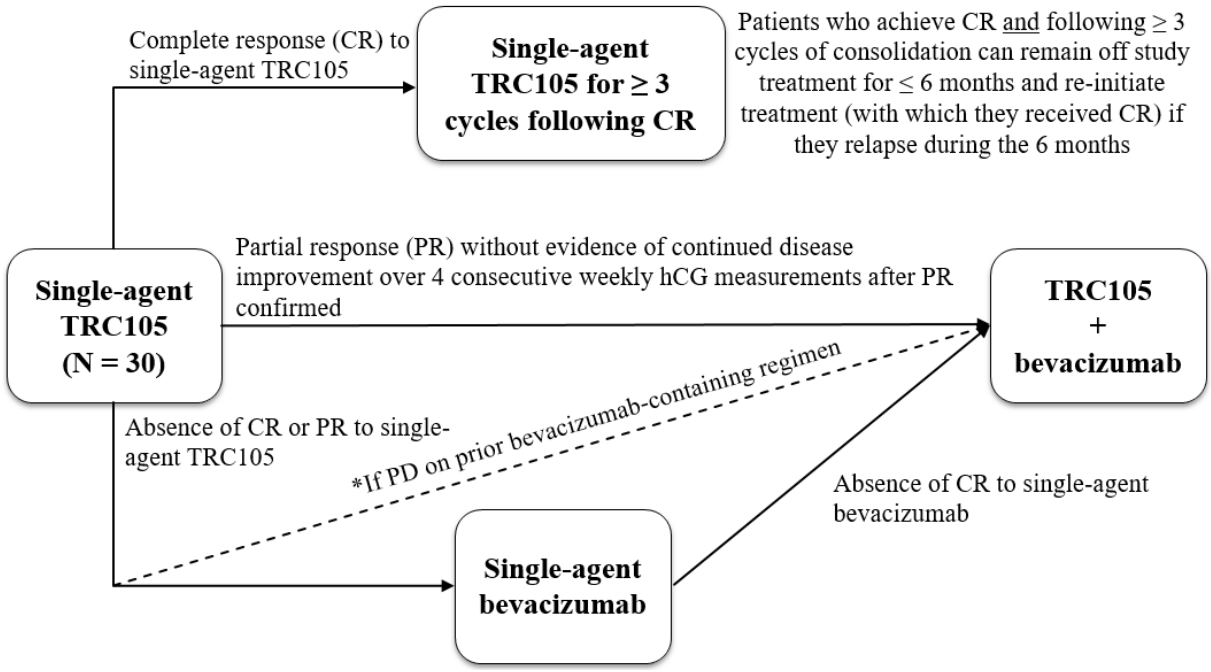


Figure 2: Treatment Algorithm After Single-Agent TRC105

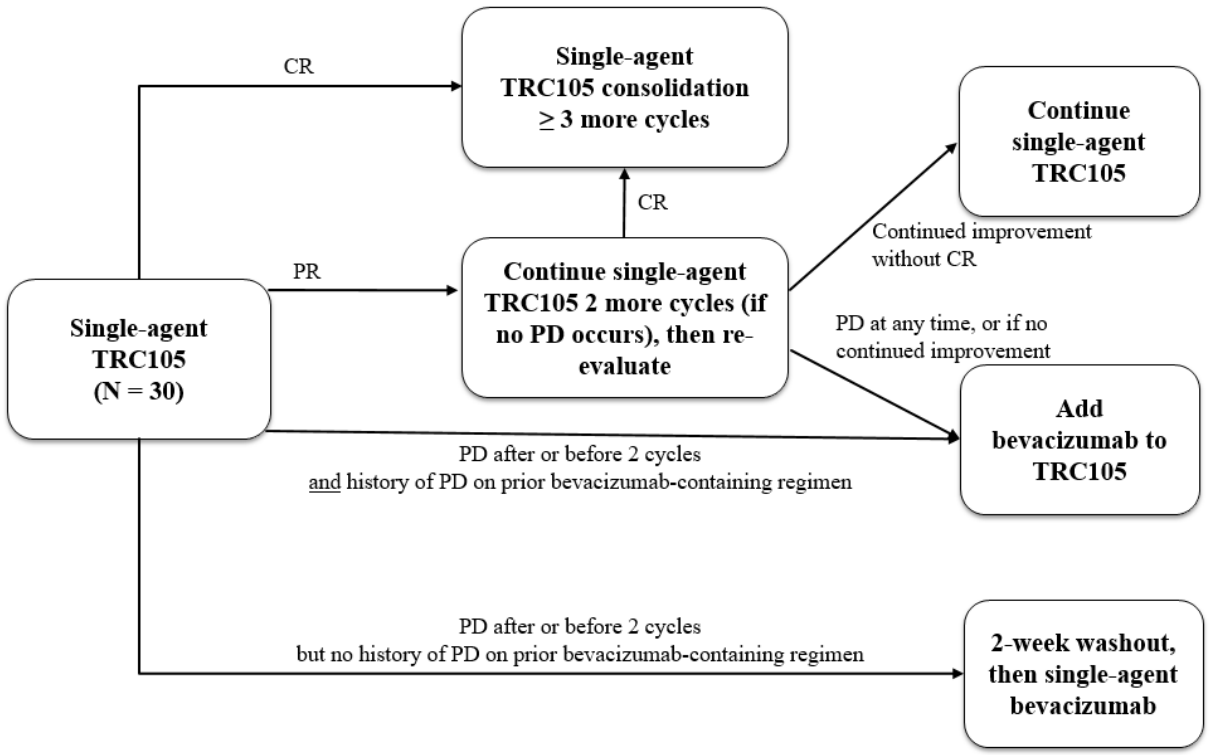


Figure 3: Treatment Algorithm After Single-Agent Bevacizumab

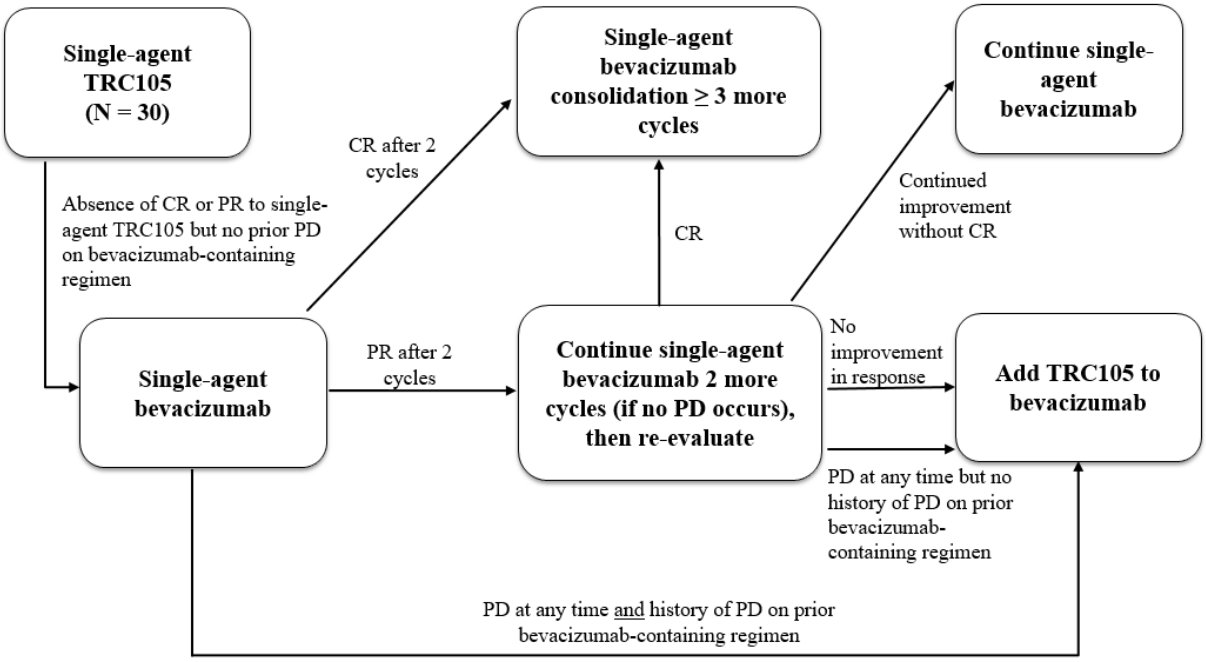
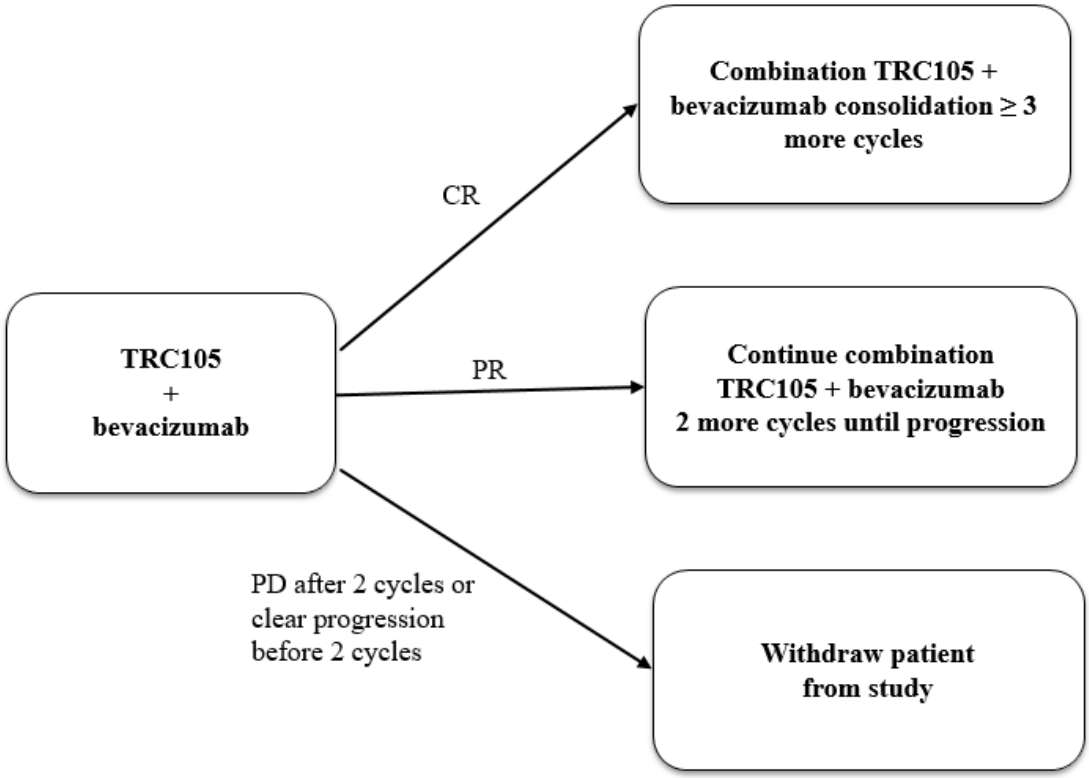


Figure 4: Treatment Algorithm After Combination Therapy (TRC105+Bevacizumab)



Objectives

Primary:

- To determine the objective response rate (ORR) of single agent TRC105 and of the combination of TRC105 and bevacizumab (in bevacizumab refractory patients) in patients with refractory GTN (including choriocarcinoma, placental site trophoblastic tumor [PSTT], and epithelioid trophoblastic tumor [ETT])

Secondary:

- To determine PFS
- To determine ORR of single agent bevacizumab in patients with refractory GTN (including choriocarcinoma, PSTT, and ETT)
- To evaluate the formation of TRC105 anti-product antibodies
- To evaluate PK of TRC105 and bevacizumab
- To determine the frequency and severity of adverse events as assessed by NCI CTCAE (Version 4.03)

Exploratory:

- To correlate efficacy endpoints with endoglin expression on tumor samples
- To explore the effects of TRC105 and bevacizumab on circulating angiogenic protein biomarkers
- To explore the effects of CD16 genotype on response to TRC105 therapy

Methodology:

This is a multicenter, open-label, nonrandomized, single-arm phase 2 study to assess the response rate to treatment with single agent TRC105 and the combination of TRC105 and bevacizumab (in bevacizumab refractory patients) in patients with GTN that has progressed following treatment with at least one chemotherapy regimen that included two or more chemotherapy agents.

As per Figure 1 - Figure 4, all patients will initially receive TRC105 as a single agent. Patients will receive TRC105 for two 28-day cycles at which time formal measurement for response will be made. The following scenarios are possible:

1. Single agent TRC105
    a. Complete response after 2 cycles: The patient will receive at least 3 cycles of consolidation therapy with single agent TRC105.
    b. Partial response after 2 cycles: The patient will continue single agent TRC105 for an additional 2 cycles and re-evaluate the response, unless the patient has clear progression any time after completing 2 cycles of treatment then add bevacizumab. If there is continued improvement in response after 4 cycles of treatment, continue single agent TRC105. If there is no improvement in response, add bevacizumab for combination therapy. If there is a complete response any time after completing 2 cycles of treatment, the patient will receive at least 3 cycles of consolidation therapy.
    c. Progression after 2 cycles or clear progression before 2 cycles: Transition to single agent bevacizumab after a 2 week washout period. Patients who have documented disease progression on a prior bevacizumab containing regimen will transition directly to TRC105 plus bevacizumab combination therapy.
2. Single agent bevacizumab
    a. Complete response after 2 cycles: The patient will receive at least 3 cycles of consolidation therapy with single agent bevacizumab.
    b. Partial response after 2 cycles: The patient will continue single agent bevacizumab for an additional 2 cycles are re-evaluate the response unless the patient has clear progression any time after completing 2 cycles of treatment then add TRC105. If there is continued improvement in response after 4 cycles of treatment, continue single agent bevacizumab. If there is no improvement in response, add TRC105 for combination therapy. If there is a complete response any time after completing 2 cycles of treatment, the patient will receive at least 3 cycles of consolidation therapy.
    c. Progression after 2 cycles or clear progression before 2 cycles: Add TRC105 and treat with combination therapy.
3. Combination therapy with TRC105 + bevacizumab
    a. Complete response after 2 cycles: The patient will receive at least 3 cycles of consolidation therapy with the combination.
    b. Partial response after 2 cycles: The patient will continue combination therapy for another 2 cycles to confirm partial response. Combination therapy will be continued until remission or progression.
    c. Progression after 2 cycles or clear progression before 2 cycles: The patient will come off study.

Improvement in response is defined as a continued decline in hCG and/or a continued decrease in tumor volume by RECIST 1.1 for patients with measurable disease. For patients with choriocarcinoma, efficacy will be assessed using weekly hCG central lab results, starting two weeks after initiation of treatment:

- Disease progression is defined as >20% increase (the absolute increase must be ≥10 IU/L) above nadir on consecutive measurements separated by at least two weeks;
- Partial response is defined as a hCG decrease of 50% or more from starting value on consecutive measurements separated by at least two weeks;
- Complete response is defined as normalization of hCG on consecutive measurements separated by at least two weeks;
- Stable disease is defined as the absence of response or progression on 3 consecutive measurements separated by at least two weeks.

Assessment of patients with PSTT and ETT will use standard RECIST 1.1 radiographic criteria integrated with weekly hCG assessment. Refer to Section 7.3.2.

Number of patients:

Up to 30 evaluable patients with refractory GTN

Diagnosis and main criteria for inclusion:

Note: If study therapy is resumed > 56 days after last dose of study drug for patients with a CR who come off study treatment following consolidation therapy, the investigator must confirm that the patient continues to be eligible to receive study therapy.

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. Elevated serum hCG (in cases of choriocarcinoma); elevated hCG or measurable disease (in cases of PSTT or ETT)
4. Histologically proven trophoblastic neoplasia, or clinically demonstrated trophoblastic neoplasia that has progressed following treatment with at least one chemotherapy regimen that included two or more chemotherapy agents.
5. Female age of 16 years or older
6. ECOG performance status ≤ 1
7. Resolution of all acute adverse events resulting from prior cancer therapies to NCI CTCAE grade ≤ 1 or baseline (except alopecia or neuropathy)
8. Adequate organ function as defined by the following criteria:
   - Serum aspartate transaminase (AST; serum glutamic oxaloacetic transaminase [SGOT]) and serum alanine transaminase (ALT; serum glutamic pyruvic transaminase [SGPT]) ≤ 2.5 x upper limit of normal (ULN) or ≤ 5 x ULN in cases of liver metastases
   - Total serum bilirubin ≤ 1.5 times the upper limit of normal
   - Absolute neutrophil count (ANC) ≥ 1500/μL
   - Platelets ≥ 100,000/μL without transfusion support within the past 28 days
   - Hemoglobin ≥ 9.0 g/dL without transfusion support within the past 14 days (erythropoietin or darbepoetin permitted)

- Serum creatinine ≤ 1.5 times the upper limit of normal or creatinine clearance > 30 mL/min by Cockcroft-Gault formula
- INR from 0.8 to 1.2

9. Woman of non-child bearing potential due to surgical sterilization (at least 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by medical history or menopause (i.e., no menstrual bleeding for more than 12 months in a woman aged 45 years or more), OR woman of child bearing potential who agrees to use at least two acceptable methods of birth control, one of which must be highly effective during the study and for at least 180 days after stopping TRC105 or bevacizumab (refer to Section 2.3.1). Women that enter the study with hCG > 100 IU/L and had maintained that level continuously after exclusion of pregnancy by a previous pelvic ultrasound are excluded from the birth control requirement unless their hCG decreases to ≤ 100 IU/L.
10. Women of child bearing potential **only**: ultrasound of pelvis to exclude pregnancy at screening except women that enter the study with a hCG > 100 IU/L and had maintained that level continuously after exclusion of pregnancy by a previous pelvic ultrasound.

Exclusion Criteria:

1. Males are excluded from the study
2. Prior treatment with TRC105
3. Current treatment on another therapeutic clinical trial
4. Uncontrolled chronic hypertension defined as systolic > 150 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 < 150/90 mm Hg)
5. Significant pericardial effusion, pleural effusion, or ascites
6. Active bleeding or pathologic condition that carries a high risk of bleeding (e.g., hereditary hemorrhagic telangiectasia)
7. Tumors located in the central chest or other location where bleeding is associated with high morbidity
8. Thrombolytic use (except to maintain i.v. catheters) within 10 days prior to first day of study therapy
9. Angina, MI, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack, arterial embolism, pulmonary embolism, percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) within the past 6 months. Deep venous thrombosis within 6 months unless the patient is therapeutically anti-coagulated without the use of warfarin for at least 2 weeks. In this situation, low molecular weight heparin is preferred.
10. Known active viral or nonviral hepatitis
11. Pregnant or actively breastfeeding without intention to discontinue prior to initiation of study
12. Open wounds or unhealed fractures within 28 days of starting study treatment

13. 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
14. History of gastrointestinal perforation or fistula in the past 6 months, or while previously on antiangiogenic therapy, unless underlying risk has been resolved (e.g., through surgical resection or repair)
15. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness
16. Other severe acute or chronic medical (including bone marrow suppressive diseases) 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
17. History of brain involvement with cancer, spinal cord compression, or carcinomatous meningitis, or new evidence of brain or leptomeningeal disease. Patients with radiated or resected lesions are permitted, provided the lesions are fully treated and inactive, patients are asymptomatic, and no steroids have been administered for brain edema for at least 28 days
18. Receipt of systemic anticancer therapy, or any investigational agents, within 28 days of starting study treatment. If anticancer therapy was given within 28 days of starting study treatment, patients may be included if 5 times the elimination half-life of the drug has passed
19. Patients who have received wide field radiotherapy ≤ 28 days (defined as > 50% of volume of pelvic bones or equivalent) or limited field radiation for palliation < 14 days prior to starting study treatment or those patients who have not recovered adequately from side effects of such therapy
20. Major surgical procedure or significant traumatic injury within 6 weeks prior to study registration or not fully recovered from any such procedure; date of surgery (if applicable) or the anticipated need for a major surgical procedure within the next six months. Note: the following are not considered to be major procedures and are permitted up to 7 days before therapy initiation: Thoracentesis, paracentesis, port placement, laparoscopy, thoracoscopy, tube thoracostomy, bronchoscopy, endoscopic ultrasonographic procedures, mediastinoscopy, skin biopsies, incisional biopsies, imaging-guided biopsy for diagnostic purposes, and routine dental procedures
21. Patients with known hypersensitivity to the active substance or any of the excipients, or Chinese hamster ovary products or other recombinant human, chimeric, or humanized antibodies
22. Patients with active infection that requires systemic therapy

Investigational products dose and mode of administration:

Following the appropriate premedication regimen, TRC105 will be dosed weekly with the first weekly dose of TRC105 split, with 3 mg/kg administered on cycle 1 day 1 and 7 mg/kg administered on cycle 1 day 4, and then the full dose of 10 mg/kg given on cycle 1 day 8 and weekly thereafter.

Patients who achieve CR on **single-agent** TRC105 and have received at least 2 cycles of weekly TRC105 may transition to TRC105 15 mg/kg administered every two weeks.

Bevacizumab will be dosed at 5 mg/kg every 2 weeks and will be administered according to the package insert. On days of combination dosing with TRC105 and bevacizumab, there will be at least 60 minutes between the completion of the bevacizumab infusion and the initiation of the TRC105 infusion.

Withdrawal Criteria:

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

Patients should be withdrawn from study treatment if, in the opinion of the Investigator, it is medically necessary, or if it is the wish of the patient. In addition, patients will be withdrawn from treatment in the case of:

1. Disease Progression while receiving TRC105 and bevacizumab as combination therapy.
2. There is a need for anticancer therapy not specified in the protocol including cancer surgery or radiation therapy.
3. Lost to follow-up or noncompliant.
4. 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 TRC105 and/or bevacizumab treatment. If the planned duration of full dose anticoagulation is < 2 weeks, TRC105 and/or bevacizumab should be held until the full dose anticoagulation period is over. If the planned duration of full dose anticoagulation is > 2 weeks, TRC105 and/or 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 > grade 1 on study. 3. The subject has a stable dose of heparin or a Factor X inhibitor or has an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting TRC105 and/or bevacizumab. 4. If thromboembolism worsens/recurs upon resumption of TRC105 and/or bevacizumab, despite anticoagulation, study drugs (TRC105 and/or bevacizumab) should be discontinued.
5. Missed study drug treatment (i.e., single agent TRC105, single agent bevacizumab, or BOTH TRC105 and bevacizumab if dosing with the combination regimen) for > 8 consecutive weeks without CR as defined in Section 7 OR discontinuation of study therapy (i.e., single agent TRC105, single agent bevacizumab or BOTH TRC105 and bevacizumab if dosing with the combination regimen) for > 6 months following CR.
6. Pregnancy. Pregnant patients should be followed for the duration of the pregnancy and the outcome of the pregnancy should be documented.
7. Discontinuation of bevacizumab treatment for other toxicities is at the discretion of the investigator, after considering the individual risk and benefit to the patient of continued treatment and per appropriate product labeling.

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 ECGs (if the patient develops an arrhythmia).

Efficacy:

The co-primary objectives are to determine the objective response rates (ORR) of single agent TRC105 and of the combination of TRC105 and bevacizumab (in bevacizumab refractory patients) in patients with refractory GTN. ORR will be assessed by hCG response and/or radiologic criteria in patients with measurable disease. Treatment decisions will be based on hCG testing in patients with choriocarcinoma and on radiographic criteria integrated with serum hCG assessment in patients with PSTT and ETT.

Statistical methods:

Efficacy analysis:

Point estimates and two-sided exact binomial 95% confidence intervals will be provided for the co-primary endpoints (ORR), as well as for all secondary endpoints defined as proportions. The estimates and confidence intervals for ORR will be calculated twice – once for each of the two co-primary populations. PFS will be estimated using the Kaplan-Meier method.

Sample size justification:

The sample size of 30 patients is not based on statistical considerations. If five or more responses to TRC105 given as a single agent or when combined with bevacizumab (in a bevacizumab refractory patient) are detected among 30 patients, then the lower limit of the two-sided exact binomial 95% confidence interval will be greater than 5%. For example, with five responses, the 95% confidence interval would be (5.64%, 34.72%).

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Abbreviation or specialist term	Explanation
5-FU	Fluorouracil
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
APA	Anti-Product Antibodies
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
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 D, Cyclophosphamide, and Vincristine
EMA-EP	Etoposide, Methotrexate, Actinomycin, and Cisplatinum
EOS	End of Study
ETT	Epithelioid Trophoblastic Tumor
FIGO	International Federation of Gynecology and Obstetrics
FDA	Food and Drug Administration
G	Gram
GCP	Good Clinical Practice

GTD	Gestational Trophoblastic Disease
GTN	Gestational Trophoblastic Neoplasia
hCG	Human chorionic gonadotropin
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
ORR	Overall Response Rate
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
PSTT	Placental Site Trophoblastic Tumor
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
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
WHO	World Health Organization

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, ovarian cancer [57], cervical cancer [58] 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 proliferating 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 was 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 soluble CD105 (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 sCD105 was determined to be 8.70 ng/mL, and patients with elevated sCD105 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 [56]. 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 [21]. TRC105 induces ADCC on proliferating HUVECs and cancer cells at low conentrations and induces apoptosis and growth inhibition at higher concentrations. In a 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, liver and ovarian cancer, a phase 1b study of TRC105 in combination with capecitabine in breast 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 sorafenib in liver cancer, a phase 1b/2 study of TRC105 in combination with axitinib in renal cell carcinoma, a phase 1b/2 study of TRC105 in combination

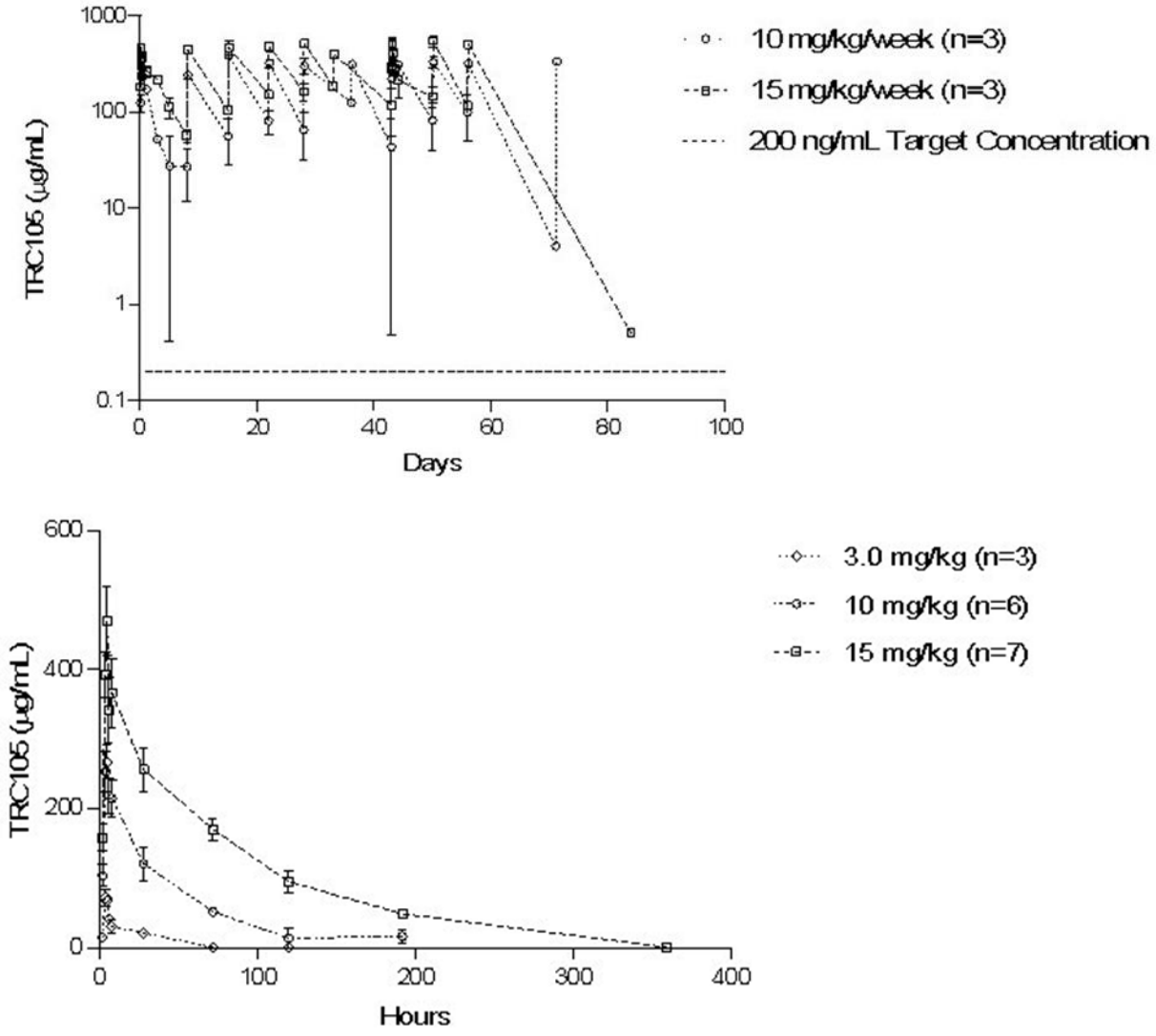
with pazopanib in sarcoma and phase 2 studies of TRC105 in combination with bevacizumab in glioblastoma multiforme and renal cell carcinoma.

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 (Figure 5).

Figure 5: Single-Dose and Multiple-Dose Pharmacokinetic Data from Study 105ST101



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 or 15 mg/kg every 2 weeks. Three of 4 patients at 15 mg/kg weekly developed grade 3 hypoproductive 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. 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 that 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.

2.2.2. Gestational Trophoblastic Neoplasia

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, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). Choriocarcinoma, the most common type of GTN, 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 hCG level. These risk factors are used to establish a WHO Risk score [56].

Almost all trophoblastic malignancies develop from the cyto-and syncytial cells of the villous trophoblast and produce abundant amounts of 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 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 below. 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.

Table 3: FIGO 2000 Scoring System for GTN [59]

Prognostic factor	Score			
	0	**1**	**2**	**4**
Age (years)	<40	≥40	–	–
Antecedent pregnancy (AP)	Mole	Abortion	Term	–
Interval (end of AP to chemotherapy in months)	<4	4 – 6	7 – 12	>12
hCG (IU/L)	$<10^3$	$10^3 – 10^4$	$10^4 – 10^5$	$>10^5$
Number of metastases	0	1 – 4	5 – 8	>8
Site of metastases	Lung	Spleen and kidney	GI tract	Brain and liver
Largest tumor mass	–	3 – 5 cm	>5 cm	–
Prior chemotherapy	–	–	Single drug	≥2 drugs

The total score for a patient is obtained by adding the individual scores for each prognostic factor. Low risk, 0 – 6; high risk, ≥7. PSTT should not be scored and instead requires staging. Stage I, disease confined to the uterus; stage II, disease extending into the pelvis; stage III, disease spread to lungs and/or vagina; stage IV, all other metastatic sites including liver, kidney, spleen, and brain.

2.2.3. Rationale for Sequential Single Agent Treatment and Combination Treatment with TRC105 and Bevacizumab

TRC105 is a monoclonal antibody that binds to endoglin, an angiogenic target highly expressed on the tumor vessels and tumor cells in GTN. Bevacizumab is an approved 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 has been well tolerated as a single agent and when dosed with bevacizumab. In a trophoblastic cell line, TRC105 was shown to directly inhibit growth in a dose dependent and methotrexate independent manner. Furthermore, bevacizumab complements TRC105 in preclinical models.

A single patient study of TRC105 and bevacizumab demonstrated significant activity, including a complete response to treatment as evidenced by normalization of hCG, a reliable marker highly correlated with disease burden, in a heavily treated and chemotherapy refractory patient with metastatic choriocarcinoma, an aggressive form of GTN. Given the limited experience treating patients with TRC105 and bevacizumab, this trial will limit toxicity and maximize the opportunity of each individual patient to respond to treatment with either TRC105 or bevacizumab, and if necessary, both agents, by employing a sequential treatment design (Figure 1 - Figure 4).

The patients enrolled in this trial will initially be treated with TRC105 as a single agent. In the case of progression on TRC105 (without a response to single agent TRC105), the patient will be

treated with bevacizumab alone to assess the activity of single agent bevacizumab. In the absence of response to bevacizumab dosed as a single agent, the patient will receive TRC105 in combination with bevacizumab. In the case that the patient has an objective, but incomplete, response to initial treatment with TRC105 as a single agent, bevacizumab will be added to TRC105 therapy (i.e., the patient will not be treated with bevacizumab alone).

2.2.4. Complete Response in a Single Patient Study of TRC105 and Bevacizumab in Metastatic and Refractory Choriocarcinoma

TRC105 is currently being studied in combination with bevacizumab in a 38 year old woman with metastatic choriocarcinoma who received 6 previous lines of therapy. She responded well to treatment, with normalization of serum hCG occurring after 4 months of treatment, with TRC105 in combination with bevacizumab; the complete response by hCG is ongoing as of April 2016 after more than 6 months off treatment. She also has an ongoing partial response by RECIST 1.1. Of note, hCG did not normalize following each of the six treatments prior to TRC105 and bevacizumab therapy, with the exception of stem cell transplant. After stem cell transplant, her hCG normalized for two weeks but had risen again when checked for confirmation.

2.3. Potential Risks and Benefits to Human Patients

2.3.1. 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, growth factors, 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 the Osler-Weber-Rendu syndrome, a disease of CD105 haplotype insufficiency. Patients with Osler-Weber-Rendu 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 sequelae. 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 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. Additionally, 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. A third 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.

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.

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. As the long term effects of bevacizumab treatment are unknown, patients should be advised to consider preservation of oocytes or ovarian tissue prior to study enrollment.

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. Patients with a medical contraindication to CT scans or known Iodinated contrast

allergies may undergo MRI. There is minimal risk of MRI imaging in patients able to undergo this type of exam including very rare reports of gadolinium-induced nephrogenic systemic fibrosis in patients with poor renal function.

Magnetic Resonance Imaging (MRI)

MRI is a noninvasive imaging test used to diagnose and evaluate medical conditions. MRI does not use radiation and there are no known harmful side-effects. However, MRI may cause anxiety for people due to the loud banging made by the machine and the confined space of the testing area. People with pacemakers, aneurysm clips, artificial heart valves, ear implants, or metal implants or foreign objects in their body are not permitted to have an MRI.

Bone Scans

A bone scan is a test that can find cancer that has spread to the bones. A bone scan can often find a problem days to months earlier than a regular X-ray test. During a bone scan, a radioactive substance called a tracer is injected into a vein in your arm. The tracer travels through your bloodstream and into your bones. Then a special camera takes pictures of the tracer in your bones. A bone scan poses no greater risk than do conventional X-ray procedures. The tracers used in a bone scan produce very little radiation exposure – less than half that of a CT scan.

Pelvic Ultrasound

A pelvic ultrasound is a diagnostic exam that uses sound waves to produce images that are used to assess organs and structures within the female pelvis. The ultrasound is safe, noninvasive and does not use ionizing radiation.

Venipuncture

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

Other Risks

This study treatment may involve risks to unbor children therefore patients should not become pregnant while participating in this study. Patients should not nurse while on this study. Women must be of non-child bearing potential due to surgical sterilization (at least 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by medical history or menopause; or must agree to use two acceptable methods of birth control, one of which must be highly effective (see below), at the same time during study treatment (including during temporary breaks from treatment), and for at least 180 days after stopping TRC105 or bevacizumab. Women that enter the study with a hCG > 100 IU/L and had maintained that level continuously after exclusion of pregnancy by a previous pelvic ultrasound are excluded from the birth control requirement unless their hCG decreases to ≤ 100 IU/L. The long term risk of infertility is unknown. Ovarian failure has been observed with other antiangiogenic agents.

Acceptable birth control methods considered highly effective:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - oral
  - injectable
  - implantable
- Bilateral tubal ligation
- Intrauterine device (IUD)
- Vasectomy of partner that has received medical assessment of surgical success
- Sexual abstinence*

* In the context of this protocol, sexual abstinence is considered a highly effective method of birth control only if refraining from heterosexual intercourse during the entire period of risk (i.e., during study treatment, including temporary breaks from treatment, and for at least 180 days after stopping TRC105 or bevacizumab). If sexual abstinence is the highly effective method of birth control used, a second acceptable method is not required.

Acceptable birth control methods **not** considered highly effective:

- Male or female condom with spermicide*
- Cap, diaphragm, or sponge with spermicide

* A female condom and a male condom should not be used together as friction between the two can result in either product failing.

2.3.2. Potential Benefits

TRC105 is an investigational product, and its efficacy has not been established. Bevacizumab is an approved anticancer agent that has not been approved in gestational trophoblastic disease. It is possible that the administration of TRC105 as a single agent, bevacizumab as a single agent, or the combination of TRC105 and bevacizumab may result in clinical benefit (i.e., tumor response or prolonged stable disease).

2.4. Conduct

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

3. TRIAL OBJECTIVES

3.1. Primary:

- To determine objective response rate (ORR) of single agent TRC105 and of the combination of TRC105 and bevacizumab (in bevacizumab refractory patients) in patients with refractory GTN (including choriocarcinoma, placental site trophoblastic tumor [PSTT], and epithelioid trophoblastic tumor [ETT])

3.2. Secondary:

- To determine PFS
- To determine ORR of single agent bevacizumab in patients with refractory GTN (including choriocarcinoma, PSTT, and ETT)
- To evaluate the formation of TRC105 anti-product antibodies
- To evaluate PK of TRC105 and bevacizumab
- To determine the frequency and severity of adverse events as assessed by NCI CTCAE (Version 4.03)

3.3. Exploratory:

- To correlate efficacy endpoints with endoglin expression on tumor samples
- To explore the effects of TRC105 and bevacizumab on circulating angiogenic protein biomarkers
- To explore the effects of CD16 genotype on response to TRC105 therapy

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan: Description

4.1.1. Trial Overview

This is a study of sequential treatment with single agent TRC105, with the option of treatment with single agent bevacizumab, and the combination of both TRC105 and bevacizumab in patients with GTN that has progressed following treatment with at least one chemotherapy regimen that included two or more agents (see Figures 1-4). TRC105 will be initially administered weekly at a dose of 10 mg/kg on days 1, 8, 15, and 22 of each 28-day cycle. The first weekly dose of TRC105 will be split with 3 mg/kg administered on cycle 1 day 1 and 7 mg/kg administered on cycle 1 day 4, and then the full dose of 10 mg/kg given on cycle 1 day 8 and weekly thereafter. Patients who achieve CR on **single-agent** TRC105 and have received at least 2 cycles of weekly TRC105 may transition to TRC105 15 mg/kg administered every two weeks.

All patients will initially receive TRC105 as a single agent for two 28-day cycles at which time formal measurement for response will be made. The following scenarios are possible:

1. Single agent TRC105
    a. Complete response after 2 cycles: The patient will receive at least 3 cycles of consolidation therapy with single agent TRC105.
    b. Partial response after 2 cycles: The patient will continue single agent TRC105 for an additional 2 cycles and re-evaluate the response, unless the patient has clear progression any time after completing 2 cycles of treatment then add bevacizumab. If there is continued improvement in response after 4 cycles of treatment, continue single agent TRC105. If there is no improvement in response, add bevacizumab for combination therapy. If there is a complete response any time after completing 2 cycles of treatment, the patient will receive at least 3 cycles of consolidation therapy.
    c. Progression after 2 cycles or clear progression before 2 cycles: Transition to single agent bevacizumab after a 2 week washout period. Patients who have documented disease progression on a prior bevacizumab containing regimen will transition directly to TRC105 plus bevacizumab combination therapy.
2. Single agent bevacizumab
    a. Complete response after 2 cycles: The patient will receive at least 3 cycles of consolidation therapy with single agent bevacizumab.
    b. Partial response after 2 cycles: The patient will continue single agent bevacizumab for an additional 2 cycles are re-evaluate the response unless the patient has clear progression any time after completing 2 cycles of treatment then add TRC105. If there is continued improvement in response after 4 cycles of treatment, continue single agent bevacizumab. If there is no improvement in response, add TRC105 for combination therapy. If there is a complete response any time after completing 2 cycles of treatment, the patient will receive at least 3 cycles of consolidation therapy.
    c. Progression after 2 cycles or clear progression before 2 cycles: Add TRC105 and treat with combination therapy.
3. Combination therapy with TRC105 + bevacizumab

a. Complete response after 2 cycles: The patient will receive at least 3 cycles of consolidation therapy with the combination.
b. Partial response after 2 cycles: The patient will continue combination therapy for another 2 cycles to confirm partial response. Combination therapy will be continued until remission or progression.
c. Progression after 2 cycles or clear progression before 2 cycles: The patient will come off study.

Bevacizumab will be dosed at 5 mg/kg every 2 weeks as a single agent or in combination with TRC105. Patients who achieve a complete response on single agent TRC105 or single agent bevacizumab and subsequently progress while receiving the single agent will receive TRC105 in combination with bevacizumab (e.g., patients who initially achieve a CR while on single agent TRC105 but subsequently progress during treatment will transition directly to the TRC105 + bevacizumab therapy regimen and will NOT dose with bevacizumab alone).

Improvement in response is defined as a continued decline in hCG and/or a continued decrease in tumor volume by RECIST 1.1 for patients with measurable disease. For patients with choriocarcinoma, disease progression, response and stable disease will be assessed using hCG central lab results, starting two weeks after initiation of treatment:

- Disease progression is defined as >20% increase (the absolute increase must be ≥10 IU/L) above the nadir on consecutive measurements separated by at least two weeks;
- Partial response is defined as a hCG decrease of 50% or more from starting value on consecutive measurements;
- Complete response will be defined as normalization of hCG on consecutive measurements separated by at least two weeks;
- Stable disease will be defined as the absence of response or progression on 3 consecutive measurements separated by at least two weeks.

Assessment of patients with PSTT and ETT will use radiographic criteria integrated with weekly hCG assessment (refer to Section 7.3.2).

If a patient achieves complete response they will be treated with at least 3 consolidation cycles of therapy that produced the response (single agent TRC105, single agent bevacizumab, or combination of TRC105 + bevacizumab). Patients who achieve a CR following at least 3 cycles of consolidation therapy can remain off study treatment for ≤ 6 months and subsequently re-initiate the treatment (whereby they achieved the CR) should they start to relapse (i.e. 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 4, Table 5 and Table 6).

4.1.2.1. Screening

The following screening procedures must be performed within 30 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 4, Table 5 and Table 6).

- Patient signature on current approved informed consent form. Prior to undergoing any study-specific procedure, each patient must read and sign the current approved informed consent form. 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 (including serum iron, ferritin, and total iron binding capacity), coagulation (PT or INR) and serum chemistry (including thyroid stimulating hormone (TSH)) to be performed locally.
- Urinalysis to be performed locally. Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated.
- Blood sampling for hCG (and other tumor markers if indicated), to be analyzed at a central lab.
- Urine sampling for hCG (per PI discretion only to rule out suspected false positives from blood hCG test), to be analyzed by local lab.
- CT or MRI scans of chest, abdomen and pelvis in addition to any other applicable sites of disease. Bone scans to be performed if metastasis is suspected prior to starting the study.
- CT or MRI of the brain with contrast
- Single tracing 12-Lead ECG (QT, PR and QRS intervals and heart rate will be captured).
- Assessment of baseline emergent Adverse Events (serious and nonserious) from the date of informed consent.
- Assessment of concomitant medications from 30 days prior to the start of study treatment.
- Archival Tumor Tissue Specimens: Archival specimens (formalin-fixed, paraffin-embedded) of the primary cancer specimen and/or metastatic cancer specimen for each study participant, if they are available. It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 10 unstained slides are requested for immunohistochemical analysis (sections of ~5 microns are preferred). Patients without available archival tumor tissue specimens are still eligible to participate in the study. See separate laboratory guide for further collection and shipment information.
- Pelvic ultrasound for patients of child bearing potential, except women that enter the study with serum hCG > 100 IU/L and had maintained that level continuously after exclusion of pregnancy by a previous pelvic ultrasound.

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 unless otherwise indicated in the Schedule of Assessments. Each cycle is 4 weeks in duration. The following will be performed according to the Schedule of Assessments (Table 4, Table 5 and Table 6).

- Physical examination including examination of all major body systems, ECOG performance status, and vital signs.
  - Assessment of vital signs during infusion of TRC105 and/or bevacizumab: Vital signs are to be assessed pre-infusion (within 30 minutes of starting TRC105 or bevacizumab 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 a patient experiences an infusion reaction that has not yet resolved).
- Hematology (including serum iron, ferritin, and total iron binding capacity), coagulation (PT or INR) and serum chemistry to be performed locally.
- Urinalysis to be performed locally. Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated.
- Blood sampling for TRC105 and bevacizumab pharmacokinetics will include trough and peak sample collections (see laboratory manual for specific instructions regarding collection times, procedures, processing, storage and shipment).
- Blood sampling for immunogenicity (APA concentrations) (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).
- Blood sampling for hCG tumor markers, to be analyzed at a central lab.
- Urine sampling for hCG (per PI discretion), to be analyzed by local lab.
- Blood sampling for angiogenic protein biomarkers (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).
- Blood sampling for CD16 genotype (see laboratory manual for specific instructions regarding collection, processing, storage and shipment). Patients who decline to provide a CD16 sample are still eligible to participate in the study.
- 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. Scans will be performed every 56 days from cycle 1 day 1. 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, Table 4 and Table 6). 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. TRC105 will be given 30 minutes following completion of bevacizumab when both agents are given on the same day.

- Administration of bevacizumab at 5 mg/kg every 2 weeks 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.
- Pelvic ultrasound every 8 weeks for patients of child bearing potential, except women not pregnant by pelvic ultrasound at study entry who enter the study with serum hCG > 100 IU/L and continuously maintain serum hCG > 100 IU/L

4.1.3. Complete Response Discontinuation of Therapy Visit and/or Change in Therapy Visit

Assessments need to be completed if they were not completed during the previous 2 weeks on a given therapy (1) prior to transitioning to another study therapy (e.g. transition from single agent TRC105 to single bevacizumab, etc.) or (2) if the patient discontinues study therapy due to CR following at least 3 cycles of consolidation therapy. The following will be performed according to the Schedule of Assessments (Table 4, Table 5 and Table 6).

- Physical examination including examination of all major body systems, ECOG performance status, and vital signs.
- Hematology (including serum iron, ferritin, and total iron binding capacity), 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 TRC105 and bevacizumab pharmacokinetics will include trough sample collections (see laboratory manual for specific instructions regarding collection times, procedures, processing, storage and shipment).
- Blood sampling for immunogenicity (APA concentrations) (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).
- Blood sampling for hCG tumor markers, to be analyzed at a central lab. Blood sampling for hCG should be repeated at this visit if not completed during the previous 7 days on a given therapy.
- Urine sampling for hCG (per PI discretion), to be analyzed by local lab.
- Blood sampling for angiogenic protein biomarkers (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. Scans should be repeated at this visit if not completed during the previous 7 days on a given therapy.
- Assessment of adverse events.
- Assessment of concomitant medications and concomitant treatments.

4.1.4. End of Study Visit Assessments

Assessments need to be completed if they were not completed during the previous 2 weeks on a given therapy if the patient permanently discontinues all study therapy due to AE, patient decision etc. 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 count as 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. The following will be performed according to the Schedule of Assessments (Table 4, Table 5 and Table 6).

- Physical examination including examination of all major body systems, ECOG performance status, and vital signs.
- Hematology (including serum iron, ferritin, and total iron binding capacity), 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 TRC105 and bevacizumab pharmacokinetics will include trough sample collections (see laboratory manual for specific instructions regarding collection times, procedures, processing, storage and shipment).
- Blood sampling for immunogenicity (APA concentrations) (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).
- Blood sampling for hCG tumor markers, to be analyzed at a central lab. Blood sampling for hCG should be repeated at this visit if not completed during the previous 7 days on a given therapy.
- Urine sampling for hCG (per PI discretion only to rule out suspected false positives from blood hCG test), to be analyzed by local lab.
- Blood sampling for angiogenic protein biomarkers (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. Scans should be repeated at this visit if not completed during the previous 7 days on a given therapy.
- Assessment of adverse events.
- Assessment of concomitant medications and concomitant treatments.

4.1.5. Post Treatment Follow-up

The total post treatment follow-up period is up to 2 years. The following will be performed according to the Schedule of Assessments (Table 4, Table 5 and Table 6).

- Assessment of adverse events. The Investigator should continue to report any related or possibly related adverse events that occur beyond adverse event reporting period if applicable (i.e. beyond the 28-day post treatment follow-up visit).
- Assessment of concomitant medications and concomitant treatments.
- Patients with a CR who come off study treatment following consolidation therapy will have hCG levels measured every 2 weeks for 6 months or until resumption of study therapy; after 6 months, patients are no longer eligible for study therapy and will have hCG levels measured every month until disease progression, start of new therapy, or for a maximum of 2 years total follow-up. Patients with measurable hCG who come off study therapy for reasons other than CR should have hCG levels measured at least every 2 weeks from last measurement until start of new therapy. The allowable time window for hCG sample collection is +/- 2 days.
- Long term survival telephone call every month following discontinuation of treatment for two years

Table 4: Single Agent TRC105 Schedule of Assessments

Protocol Activities	Screening	*Cycle 1					*Cycle 2				*Cycle 3+ Responding Patients [26]				CR Discontinuation of Therapy Visit OR Change in Therapy Visit [3]	End of Study [4]	**Post Treatment Follow-up [25] (Up to 2 years total)		
	Day -30	Day 1 [1,2]	Day 4 [1]	Day 8 [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]			Every 2 Weeks up to 6 Mo	28 Days after EOS Visit	Every Month 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			
Coagulation [9]	X	X					X				X				X	X			
Blood Chemistry [9]	X	X					X				X				X	X			
Thyroid Stimulating Hormone [9]	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	(X)					
Tumor Assessments																			
CT or MRI Scans [12]	X Including Brain	**Every 56 days from Cycle 1 Day 1**													X	X			
Serum hCG Tumor Biomarker [13]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X			
Urine hCG Tumor Biomarker [14]	**Per PI discretion to rule out suspected false positive values from serum hCG assessment**																		
Other Clinical Assessments																			
Pelvic Ultrasound [15]	X									(X) Even Cycles									
12-Lead ECG [16]	X																		
Concomitant Medications/Treatments [17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Baseline Signs and Symptoms [18]	X																		
Adverse Events [18]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Special Laboratory Assessments																			
TRC105 Pre-Dose PK [19]		X		X	X	X	X	X	X	X	X				X	X			
TRC105 Post-Dose PK [20]		X					X												
Anti-Product Antibody Testing [21]		X		X	X	X	X	X	X	X	X				X	X			
Protein Biomarkers [22]		X					X				X				X	X			
CD16 Genotype [23]		X																	
Archival Tumor Tissue [24]	X																		
Long Term Follow-Up																			
Serum hCG Tumor Biomarker [13]																	X		X
Phone Call [25]																			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

Single Agent TRC105 Dosing Schedule of Assessments Footnotes:

1. **Days of Treatment with TRC105:** All assessments should be performed prior to dosing with TRC105 unless otherwise indicated. Each cycle is 28 days in duration.
2. **Cycle 1 day 1:** Hematology, blood chemistry, urinalysis, coagulation, and physical examination are not required if acceptable screening assessment is performed within 7 days prior to the start of treatment on cycle 1 day 1.
3. **CR TRC105 Single Agent Therapy Discontinuation or Change in Study Therapy Visit:** Assessments need to be completed if they were not completed during the previous 2 weeks on single agent TRC105 (previous 7 days for radiologic tumor assessments) (1) prior to transitioning from single agent TRC105 to single agent bevacizumab and/or (2) if the patient discontinues therapy due to CR following at least 3 cycles of consolidation therapy. Note: patients are eligible for treatment on this trial until they progress on the combination portion of the study (i.e., treatment with TRC105 combined with bevacizumab).
4. **End of Study Visit:** Assessments need to be completed if they were not completed during the previous 2 weeks on a given study therapy (previous 7 days 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:** All information related to prior anticancer treatment should be recorded. Significant medical history and baseline signs and symptoms should be captured from the date of informed consent.
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 Infusions: Vital signs (except weight) are to be assessed pre-infusion (within 30 min of starting TRC105 infusions), every 30 minutes during the infusion (+/- 15 minutes), and at the end of infusion (within 30 minutes after completing infusion). Vital signs should be monitored more frequently and/or beyond the completion of the infusion if medically indicated (e.g. if a patient experiences an infusion reaction that has not yet resolved). For patients on bevacizumab alone, Vital Signs are only required on days of infusion.
9. **Hematology, Chemistry, Coagulation & TSH:** Testing to be performed locally. Lab assessments may be performed within 3 days prior to study drug dosing. In addition to the assessments scheduled for the clinical trial, patients should undergo assessment as appropriate to ensure safe treatment. Hematology to include serum ion, ferritin, and total iron binding capacity. Thyroid stimulating hormone (TSH) is to be tested 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:** 10 mg/kg IV TRC105 diluted in normal saline will be administered according to Section 6.7. The initial dose of TRC105 will be split such that 3 mg/kg is given on cycle 1 day 1 and 7 mg/kg is given on cycle 1 day 4. In addition, if TRC105 is reintroduced while the patient is receiving bevacizumab, the initial dose will be split such that 3 mg/kg is given initially and 7 mg/kg is given three days later. Patients who achieve CR on **single-agent** TRC105 and have received at least 2 cycles of weekly TRC105 may transition to TRC105 15 mg/kg administered every two weeks.
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. In addition, a brain MRI or CT with contrast to be performed at screening to ensure absence of CNS metastases and on study as needed if metastases are suspected. Known areas of disease should be consistently followed throughout the study with the same modality used at screening. Assessments should also be performed whenever disease progression is suspected. Allowable window for tumor imaging studies is +/- 7 days. Scans will be performed every 56 days from cycle 1 day 1. Brain scans are to be performed prior to starting the study and during study conduct if metastasis is suspected. **Bone scans:** to be performed at screening only if bone metastasis is suspected; while on study, if bone metastasis is detected at baseline, then bone scans should be repeated to confirm complete response or when progression in bone is suspected but not observed on CT/MRI. If metastasis was not detected at baseline, then bone scans should be performed only when progression in bone is suspected but not observed on CT/MRI.
13. **Serum hCG (Other Tumor markers if Indicated):** Will be collected and analysed by central lab as indicated in the schedule of events and will include other markers in addition to hCG if applicable. See laboratory manual for additional details.
14. **Urine hCG:** Will be collected and analysed by local lab per PI discretion to rule out suspected false positive values from the serum hCG assessment.
15. **Pelvic Ultrasound:** Women of child bearing potential **only**: ultrasound of pelvis to exclude pregnancy at screening and throughout the study, except women that enter the study with serum hCG > 100 IU/L and had maintained that level continuously after exclusion of pregnancy by a previous pelvic ultrasound. Women of childbearing potential must follow birth control guidance while on study therapy and for 180 days after discontinuing TRC105 or bevacizumab. Women of childbearing potential that restart study treatment due to rising hCG must have a pelvic ultrasound to exclude pregnancy. Pregnant patients are excluded from the study.
16. **12-Lead ECG:** Single tracing 12-lead ECG will be performed at screening. If patients develop an arrhythmia, the ECG should be repeated on day 1 of each subsequent cycle and as clinically indicated.
17. **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.
18. **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 a 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.

19. **TRC105 Pre-Dose PK (Trough):** A blood sample to be collected at the time-points indicated in the Schedule of Assessments, prior to starting the TRC105 infusion. Samples will be stored at approximately -70 °C. See separate laboratory guide for further collection and shipment information. Additional PK samples may also be collected at the time of unexpected clinical events.
20. **TRC105 Post-Dose PK (Peak):** A blood sample to be collected at the time-points indicated in the Schedule of Assessments, within 10 minutes of completion of the TRC105 infusion. Samples will be stored at approximately -70 °C. See separate laboratory guide for further collection and shipment information. Additional PK samples may also be collected at the time of unexpected clinical events.
21. **Anti-Product Antibody Testing:** A blood sample will be collected to assess APA at the time-points indicated in the Schedule of Assessments and stored at approximately -70°C. See separate laboratory guide for further collection and shipment information. Additional APA samples may also be collected at the time of unexpected clinical events.
22. **Protein Biomarkers:** A plasma sample (K_2EDTA tube) will be collected as indicated in the Schedule of Assessments and stored at approximately -70°C. See separate laboratory guide for further collection and shipment information.
23. **CD16 Genotype:** A blood sample will be collected on C1D1 to test for the CD16 genotype. See separate laboratory guide for further collection and shipment information. Patients who decline to provide a CD16 sample are still eligible to participate in the study.
24. **Archival Tumor Tissue:** Archival specimens (formalin-fixed, paraffin-embedded) are required of the primary cancer and/or metastatic cancer specimen for each study participant, if they are available. It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 10 unstained slides are requested for immunohistochemical analysis (sections of 5 microns are preferred). Patients without available archival tumor tissue specimens are still eligible to participate in the study. See separate laboratory guide for further collection and shipment information.
25. **Follow-up:** 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. Patients with a CR who come off study treatment following consolidation therapy will have hCG levels measured every 2 weeks for 6 months or until resumption of study therapy; after 6 months, patients are no longer eligible for study therapy and will have hCG levels measured every month until disease progression, start of new therapy, or for a maximum of 2 years. Patients with measurable hCG who come off study therapy for reasons other than CR should have hCG levels measured at least every 2 weeks from last measurement until start of new therapy. All patients will also be contacted by phone every month for long term follow-up for two years. The allowable visit window is +/- 7 days for follow-up assessments.
26. **Cycle 3+ Responding Patients:** Patients who achieve CR on **single-agent** TRC105 and have received at least 2 cycles of weekly TRC105 may transition to TRC105 15 mg/kg administered every two weeks.

Table 5: Single Agent Bevacizumab Schedule of Assessments

Protocol Activities	*Cycle X				*Cycle X+1				*Cycle X+2+ Responding Patients				CR Discontinuation of Therapy Visit OR Change in Therapy Visit [2]	End of Study [3]	**Post Treatment Follow-up [19] (Up to 2 years total)		
	Day 1 [1]	Day 8 [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]			Every 2 Weeks up to 6 Mo	28 Days after EOS Visit	Every Month up to 2 Yrs
Routine Exams																	
Physical Examination [4]	X				X				X				X	X			
Vital Signs [5]	X		X		X		X		X		X		X	X			
Laboratory Studies																	
Hematology [6]	X		X		X		X		X		X		X	X			
Coagulation [6]	X				X				X				X	X			
Blood Chemistry [6]	X				X				X				X	X			
Urinalysis [7]	X				X				X				X	X			
Treatment w/ Study Drug																	
Bevacizumab Dosing [8]	X		X		X		X		X		X						
Tumor Assessments																	
CT or MRI Scans [9]	**Every 56 days from Cycle 1 Day 1**												X	X			
Serum hCG Tumor Biomarker [10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Urine hCG Tumor Biomarker [11]	**Per PI discretion to rule out suspected false positive values from serum hCG assessment**																
Other Clinical Assessments																	
Pelvic Ultrasound [12]				(X) Even Cycles													
Concomitant Medications/Treatments [13]	X		X		X		X		X		X		X	X		X	
Adverse Events [14]	X		X		X		X		X		X		X	X		X	
Special Laboratory Assessments																	
Bevacizumab Pre-Dose PK [15]	X		X		X		X		X				X	X			
Bevacizumab Post-Dose PK [16]	X				X												
Protein Biomarkers [17]	X				X				X				X	X			
Anti-Product Antibody Testing [18]	X	X	X	X	X	X	X	X	X				X	X			
Long Term Follow-Up																	
Serum hCG Tumor Biomarker [10]															X		X
Phone Call [19]																	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

Single Agent Bevacizumab Schedule of Assessments Footnotes:

1. **Days of Treatment with Bevacizumab:** All assessments should be performed prior to dosing with bevacizumab unless otherwise indicated. Each cycle is 28 days in duration.
2. **CR Bevacizumab Single Agent Therapy Discontinuation or Change in Study Therapy Visit:** Assessments need to be completed if they were not completed during the previous 2 weeks on single agent bevacizumab (previous 7 days for radiologic tumor assessments) (1) prior to transitioning from single agent bevacizumab to combination bevacizumab + TRC105 therapy and/or (2) if the patient discontinues bevacizumab therapy due to CR following at least 3 cycles of consolidation therapy. Note: patients are eligible for treatment on this trial until they progress on the combination portion of the study (i.e., treatment with TRC105 combined with bevacizumab).
3. **End of Study Visit:** Assessments need to be completed if they were not completed during the previous 2 weeks on a given study therapy (previous 7 days 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 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.
4. **Physical Examination:** Examination of major body systems and ECOG performance status.
5. **Vital Signs:** Heart rate, temperature, blood pressure, respiratory rate, weight. Assessment of Vital Signs during TRC105 Infusions: Vital signs (except weight) are to be assessed pre-infusion (within 30 min of starting TRC105 infusions), every 30 minutes during the infusion (+/- 15 minutes), and at the end of infusion (within 30 minutes after completing infusion). Vital signs should be monitored more frequently and/or beyond the completion of the infusion if medically indicated (e.g. if a patient experiences an infusion reaction that has not yet resolved). For patients on bevacizumab alone, Vital Signs are only required on days of infusion.
6. **Hematology, Chemistry, Coagulation and TSH:** Testing to be performed locally. Lab assessments may be performed within 3 days prior to study drug dosing. In addition to the assessments scheduled for the clinical trial, patients should undergo assessment as appropriate to ensure safe treatment. Hematology to include serum ion, ferritin, and total iron binding capacity. Thyroid stimulating hormone (TSH) is to be collected as clinically indicated. See Section 8.1.1.1 for specific assessments to be performed.
7. **Urinalysis:** To be performed locally. Microscopic analysis should be performed as clinically indicated.
8. **Bevacizumab Administration:** Commercially available bevacizumab will be administered per the package insert in this study according to Section 6.10, over at least 30 minutes. Bevacizumab will be dosed at 5 mg/kg every 2 weeks.
9. **CT or MRI Tumor Imaging:** Images of chest, abdomen, and pelvis to be performed as outlined in the assessment table. In addition, a brain MRI or CT with contrast and bone scans to be performed on study as needed if metastases are suspected. Known areas of disease should be consistently followed throughout the study with the same modality used at screening. Assessments should also be performed whenever disease progression is suspected. Allowable window for tumor imaging studies is +/- 7 days. Scans will be performed every 56

days from cycle 1 day 1. **Bone scans:** to be performed at screening only if bone metastasis is suspected; while on study, if bone metastasis is detected at baseline, then bone scans should be repeated to confirm complete response or when progression in bone is suspected but not observed on CT/MRI. If metastasis was not detected at baseline, then bone scans should be performed only when progression in bone is suspected but not observed on CT/MRI.

10. **Serum hCG (Other Tumor markers if Indicated):** Will be collected and analysed by central lab as indicated in the schedule of events and will include other markers in addition to hCG if applicable. See laboratory manual for additional details.
11. **Urine hCG:** Will be collected and analysed by local lab per PI discretion.
12. **Pelvic Ultrasound:** Women of child bearing potential **only**: ultrasound of pelvis to exclude pregnancy at screening and throughout the study, except women that enter the study with serum hCG > 100 IU/L and had maintained that level continuously after exclusion of pregnancy by a previous pelvic ultrasound. Women of childbearing potential must follow birth control guidance while on study therapy and for 180 days after discontinuing TRC105 or bevacizumab. Women of childbearing potential that restart study treatment due to rising hCG must have a pelvic ultrasound to exclude pregnancy. Pregnant patients are excluded from the study.
13. **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.
14. **Adverse Events (and Baseline Signs and Symptoms):** 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 a 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.
15. **Bevacizumab Pre-Dose PK (Trough):** A blood sample to be collected at the time-points indicated in the Schedule of Assessments, prior to starting the bevacizumab infusion. Samples will be stored at approximately -70°C. See separate laboratory guide for further collection and shipment information. Additional PK samples may also be collected at the time of unexpected clinical events.
16. **Bevacizumab Post-Dose PK (Peak):** A blood sample to be collected at the time-points indicated in the Schedule of Assessments, within 10 minutes of completion of the bevacizumab infusion. Samples will be stored at approximately -70°C. See separate laboratory guide for further collection and shipment information. Additional PK samples may also be collected at the time of unexpected clinical events.
17. **Protein Biomarkers:** A plasma sample (K_2EDTA tube) will be collected as indicated in the schedule of assessments and stored at approximately -70°C. See separate laboratory guide for further collection and shipment information.
18. **Anti-Product Antibody Testing:** A blood sample will be collected to assess APA at the time-points indicated in the Schedule of Assessments and stored at approximately -70°C. See separate laboratory guide for further collection and shipment information. Additional APA samples may also be collected at the time of unexpected clinical events.

19. **Long Term Follow-up:** 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. Patients with a CR who come off study treatment following consolidation therapy will have hCG levels measured every 2 weeks for 6 months or until resumption of study therapy; after 6 months, patients are no longer eligible for study therapy and will have hCG levels measured every month until disease progression, start of new therapy, or for a maximum of 2 years. Patients with measurable hCG who come off study therapy for reasons other than CR should have hCG levels measured at least every 2 weeks from last measurement until start of new therapy. All patients will also be contacted by phone every month for long term follow-up for two years. The allowable visit window is +/- 7 days for follow-up assessments.

Table 6: Combination Therapy Schedule of Assessments (TRC105 + Bevacizumab)

Protocol Activities	*Cycle Y					*Cycle Y+1				*Cycle Y+2+ Responding Patients				CR Discontinuation of Therapy Visit [2]	End of Study [3]	**Post Treatment Follow-up [22] (Up to 2 years total)		
	Day 1 [1,2]	Day 4 [1]	Day 8 [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]			Every 2 Weeks up to 6 Mo	28 Days after EOS Visit	Every Month up to 2 Yrs
Baseline Documentation																		
Physical Examination [4]	X					X				X				X	X			
Vital Signs [5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Laboratory Studies																		
Hematology [6]	X			X		X		X		X		X		X	X			
Coagulation [6]	X					X				X				X	X			
Blood Chemistry [6]	X					X				X				X	X			
Urinalysis [7]	X					X				X				X	X			
Treatment w/ Study Drug																		
TRC105 Dosing [8]	X	X	X	X	X	X	X	X	X	X	X	X	X					
Bevacizumab Dosing [9]	X			X		X		X		X		X						
Tumor Assessments																		
CT or MRI Scans [10]	**Every 56 days from Cycle 1 Day 1**													X	X			
Serum hCG Tumor Biomarker [11]	X		X	X	X	X	X	X	X	X	X	X	X	X	X			
Urine hCG Tumor Biomarker [12]	**Per PI discretion to rule out suspected false positive values from serum hCG assessment**																	
Other Clinical Assessments																		
Pelvic Ultrasound [13]					(X) Even Cycles													
Concomitant Medications/Treatments [14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Adverse Events [15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Special Laboratory Assessments																		
TRC105 Pre-Dose PK [16]	X		X	X	X	X	X	X	X	X				X	X			
TRC105 Post-Dose PK [17]	X					X												
Bevacizumab Pre-Dose PK [18]	X			X		X		X		X				X	X			
Bevacizumab Post-Dose PK [19]	X					X												
Anti-Product Antibody Testing [20]	X		X	X	X	X	X	X	X	X				X	X			
Protein Biomarkers [21]	X					X				X				X	X			
Long Term Follow-Up																		
Serum hCG Tumor Biomarker [11]																X		X
Phone Call [22]																		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

Combination Therapy Schedule of Assessments Footnotes:

1. **Days of Treatment with TRC105 and/or Bevacizumab:** All assessments should be performed prior to dosing with TRC105 and/or bevacizumab unless otherwise indicated. Each cycle is 28 days in duration.
2. **CR TRC105 + Bevacizumab Therapy Discontinuation Visit:** Assessments need to be completed if they were not completed during the previous 2 weeks on combination TRC105 + bevacizumab therapy (previous 7 days for radiologic tumor assessments) if the patient discontinues TRC105 + bevacizumab therapy due to CR following at least 3 cycles of consolidation therapy. Note: patients are eligible for treatment on this trial until they progress on the combination portion of the study (i.e., treatment with TRC105 combined with bevacizumab).
3. **End of Study Visit:** Assessments need to be completed if they were not completed during the previous 2 weeks on a given study therapy (previous 7 days 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 then 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.
4. **Physical Examination:** Examination of major body systems and ECOG performance status.
5. **Vital Signs:** Heart rate, temperature, blood pressure, respiratory rate, weight. Assessment of Vital Signs during TRC105 Infusions: Vital signs (except weight) are to be assessed pre-infusion (within 30 min of starting TRC105 infusions), every 30 minutes during the infusion (+/- 15 minutes), and at the end of infusion (within 30 minutes after completing infusion). Vital signs should be monitored more frequently and/or beyond the completion of the infusion if medically indicated (e.g. if a patient experiences an infusion reaction that has not yet resolved). For patients on bevacizumab alone, Vital Signs are only required on days of infusion.
6. **Hematology, Chemistry, Coagulation and TSH:** Testing to be performed locally. Lab assessments may be performed within 3 days prior to study drug dosing. In addition to the assessments scheduled for the clinical trial, patients should undergo assessment as appropriate to ensure safe treatment. Hematology to include serum ion, ferritin, and total iron binding capacity. Thyroid stimulating hormone (TSH) is to be collected as clinically indicated. See Section 8.1.1.1 for specific assessments to be performed.
7. **Urinalysis:** To be performed locally. Microscopic analysis should be performed as clinically indicated.
8. **TRC105 Administration:** 10 mg/kg IV TRC105 diluted in normal saline will be administered according to Section 6.7. The initial dose of TRC105 for the combination will be split only if there was ≥ 10 days between doses of TRC105: the first dose on resumption of TRC105 should be administered over two days as was done for the initial TRC105 dose such that 3 mg/kg is given on day 1 and 7 mg/kg is given on day 4.
9. **Bevacizumab Administration:** Commercially available bevacizumab will be administered per the package insert in this study according to Section 6.10, over at least 30 minutes.

10. **CT or MRI Tumor Imaging:** Images of chest, abdomen, and pelvis to be performed as outlined in the assessment table. In addition, a brain MRI or CT with contrast and bone scans to be performed on study as needed if metastases are suspected. Known areas of disease should be consistently followed throughout the study with the same modality used at screening. Assessments should also be performed whenever disease progression is suspected. Allowable window for tumor imaging studies is +/- 7 days. Scans will be performed every 56 days from cycle 1 day 1. **Bone scans:** to be performed at screening only if bone metastasis is suspected; while on study, if bone metastasis is detected at baseline, then bone scans should be repeated to confirm complete response or when progression in bone is suspected but not observed on CT/MRI. If metastasis was not detected at baseline, then bone scans should be performed only when progression in bone is suspected but not observed on CT/MRI.
11. **Serum hCG (Other Tumor markers if Indicated):** Will be collected and analysed by central lab as indicated in the schedule of events and will include other markers in addition to hCG if applicable. See laboratory manual for additional details.
12. **Urine hCG:** Will be collected and analysed by local lab per PI discretion to rule out suspected false positive values from the serum hCG assessment.
13. **Pelvic Ultrasound:** Women of child bearing potential **only**: ultrasound of pelvis to exclude pregnancy at screening and throughout the study, except women that enter the study with serum hCG > 100 IU/L and had maintained that level continuously after exclusion of pregnancy by a previous pelvic ultrasound. Women of childbearing potential must follow birth control guidance while on study therapy and for 180 days after discontinuing TRC105 or bevacizumab. Women of childbearing potential that restart study treatment due to rising hCG must have a pelvic ultrasound to exclude pregnancy. Pregnant patients are excluded from the study.
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. **Adverse Events (and Baseline Signs and Symptoms):** 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 a 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. **TRC105 Pre-Dose PK (Trough):** A blood sample to be collected at the time-points indicated in the Schedule of Assessments, prior to starting the TRC105 infusion. Samples will be stored at approximately -70°C. See separate laboratory guide for further collection and shipment information. Additional PK samples may also be collected at the time of unexpected clinical events.
17. **TRC105 Post-Dose PK (Peak):** A blood sample to be collected at the time-points indicated in the Schedule of Assessments, within 10 minutes of completion of the TRC105 infusion. Samples will be stored at approximately -70°C. See separate laboratory guide for further collection and shipment information. Additional PK samples may also be collected at the time of unexpected clinical events.

18. **Bevacizumab Pre-Dose PK (Trough):** A blood sample to be collected at the time-points indicated in the Schedule of Assessments, prior to starting the bevacizumab infusion. Samples will be stored at approximately -70°C. See separate laboratory guide for further collection and shipment information. Additional PK samples may also be collected at the time of unexpected clinical events.

19. **Bevacizumab Post-Dose PK (Peak):** A blood sample to be collected at the time-points indicated in the Schedule of Assessments, within 10 minutes of completion of the bevacizumab infusion. Samples will be stored at approximately -70°C. See separate laboratory guide for further collection and shipment information. Additional PK samples may also be collected at the time of unexpected clinical events.

20. **Anti-Product Antibody Testing:** A blood sample will be collected to assess APA at the time-points indicated in the Schedule of Assessments and stored at approximately -70 °C. See separate laboratory guide for further collection and shipment information. Additional APA samples may also be collected at the time of unexpected clinical events.

21. **Protein Biomarkers:** A plasma sample (K_2EDTA tube) will be collected as indicated in the schedule of assessments and stored at approximately -70°C. See separate laboratory guide for further collection and shipment information.

22. **Long Term Follow-up:** 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. Patients with a CR who come off study treatment following consolidation therapy will have hCG levels measured every 2 weeks for 6 months or until resumption of study therapy; after 6 months, patients are no longer eligible for study therapy and will have hCG levels measured every month until disease progression, start of new therapy, or for a maximum of 2 years. Patients with measurable hCG who come off study therapy for reasons other than CR should have hCG levels measured at least every 2 weeks from last measurement until start of new therapy. All patients will also be contacted by phone every month for long term follow-up for two years. The allowable visit window is +/- 7 days for follow-up assessments.

5. SELECTION AND WITHDRAWAL OF PATIENTS

Note: patients must initially qualify for the study according to the following criteria and if study therapy is resumed > 56 days after last dose of study drug for patients with a CR who come off study treatment following consolidation therapy, the investigator must confirm that the patient continues to be eligible to receive study therapy.

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. Elevated serum hCG (in cases of choriocarcinoma); elevated hCG or measurable disease (in cases of PSTT or ETT).
4. Histologically proven trophoblastic neoplasia, or clinically demonstrated trophoblastic neoplasia that has progressed following treatment with at least one chemotherapy regimen that included two or more chemotherapy agents.
5. Female age of 16 years or older
6. ECOG performance status ≤ 1
7. Resolution of all acute adverse events resulting from prior cancer therapies to NCI CTCAE grade ≤ 1 or baseline (except alopecia or neuropathy)
8. Adequate organ function as defined by the following criteria:
    - Serum aspartate transaminase (AST; serum glutamic oxaloacetic transaminase [SGOT]) and serum alanine transaminase (ALT; serum glutamic pyruvic transaminase [SGPT]) ≤ 2.5 x upper limit of normal (ULN) or ≤ 5 x ULN in cases of liver metastases
    - Total serum bilirubin ≤ 1.5 times the upper limit of normal
    - Absolute neutrophil count (ANC) ≥ 1500/μL
    - Platelets ≥ 100,000/μL without transfusion support within the past 28 days
    - Hemoglobin ≥ 9.0 g/dL without transfusion support within the past 14 days (erythropoietin or darbepoetin permitted)
    - Serum creatinine ≤ 1.5 times the upper limit of normal or creatinine clearance > 30 mL/min by Cockcroft-Gault formula
    - INR from 0.8 to 1.2
9. Woman of non-child bearing potential due to surgical sterilization (at least 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by medical history or menopause (i.e., no menstrual bleeding for more than 12 months in a woman aged 45 years or more), OR woman of child bearing potential who agrees to use at least two acceptable methods of birth control, one of which must be

highly effective during the study and for at least 180 days after stopping TRC105 or bevacizumab (refer to Section 2.3.1). Women that enter the study with a hCG > 100 IU/L and had maintained that level continuously after exclusion of pregnancy by a previous pelvic ultrasound are excluded from the birth control requirement unless their hCG decreases to ≤ 100 IU/L.

10. Women of child bearing potential **only**: ultrasound of pelvis to exclude pregnancy at screening except women that enter the study with a hCG > 100 IU/L and had maintained that level continuously after exclusion of pregnancy by a previous pelvic ultrasound.

5.2. Patient Exclusion Criteria

1. Males are excluded from the study
2. Prior treatment with TRC105
3. Current treatment on another therapeutic clinical trial
4. Uncontrolled chronic hypertension defined as systolic > 150 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 < 150/90 mm Hg)
5. Symptomatic pericardial effusion, pleural effusion, or ascites
6. Active bleeding or pathologic condition that carries a high risk of bleeding (i.e. hereditary hemorrhagic telangiectasia)
7. Tumors located in the central chest or other location where bleeding is associated with high morbidity
8. Thrombolytic use (except to maintain i.v. catheters) within 10 days prior to first day of study therapy
9. Angina, MI, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack, arterial embolism, pulmonary embolism, PTCA or CABG within the past 6 months. Deep venous thrombosis within 6 months, unless the patient is therapeutically anti-coagulated without the use of warfarin for at least 2 weeks. In this situation, low molecular weight heparin is preferred.
10. Known active viral or nonviral hepatitis
11. Pregnant or actively breastfeeding without intention to discontinue prior to initiation of study
12. Open wounds or unhealed fractures within 28 days of starting study treatment
13. 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
14. History of gastrointestinal perforation or fistula in the past 6 months, or while previously on antiangiogenic therapy, unless underlying risk has been resolved (e.g., through surgical resection or repair)

15. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness
16. Other severe acute or chronic medical (including bone marrow suppressive diseases) 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
17. History of brain involvement with cancer, spinal cord compression, or carcinomatous meningitis, or new evidence of brain or leptomeningeal disease. Patients with radiated or resected lesions are permitted, provided the lesions are fully treated and inactive, patients are asymptomatic, and no steroids have been administered for brain edema for at least 28 days.
18. Receipt of systemic anticancer therapy, or any investigational agents, within 28 days of starting study treatment. If anticancer therapy was given within 28 days of starting study treatment, patients may be included if 5 times the elimination half-life of the drug has passed
19. Patients who have received wide field radiotherapy ≤ 28 days (defined as > 50% of volume of pelvic bones or equivalent) or limited field radiation for palliation < 14 days prior to cycle 1 day 1 or those patients who have not recovered adequately from side effects of such therapy
20. Major surgical procedure or significant traumatic injury within 6 weeks prior to study registration, and or not fully recovered from any such procedure; date of surgery (if applicable) or the anticipated need for a major surgical procedure within the next six months. Note: the following are not considered to be major procedures and are permitted up to 7 days before therapy initiation: Thoracentesis, paracentesis, port placement, laparoscopy, thoracoscopy, tube thoracostomy, bronchoscopy, endoscopic ultrasonographic procedures, mediastinoscopy, skin biopsies, incisional biopsies, imaging-guided biopsy for diagnostic purposes, and routine dental procedures.
21. Patients with known hypersensitivity to the active substance or any of the excipients, or Chinese hamster ovary products or other recombinant human, chimeric, or humanized antibodies.
22. Patients with active infection that requires systemic therapy.

5.3. Patient Withdrawal Criteria

Patients 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 a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome. Data to be collected at the end of study visit are described in the Schedule of Assessments (Table 4, Table 5 and Table 6). Patients will be followed for at least 28 days after the last dose of TRC105 or bevacizumab study drug for adverse events. If a patient withdraws consent, no further evaluations should be performed, and no attempts should be made to collect additional data. In addition, patients will be withdrawn from treatment in the case of:

1. Disease Progression while receiving TRC105 and bevacizumab as combination therapy.
2. There is a need for anticancer therapy not specified in the protocol including cancer surgery or radiation therapy.
3. Lost to follow-up or noncompliant.
4. 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 TRC105 and/or bevacizumab treatment. If the planned duration of full dose anticoagulation is < 2 weeks, TRC105 and/or bevacizumab should be held until the full dose anticoagulation period is over. If the planned duration of full dose anticoagulation is > 2 weeks, TRC105 and/or 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 > grade 1 on study. 3. The subject has a stable dose of heparin or a Factor X inhibitor or has an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting TRC105 and/or bevacizumab. 4. If thromboembolism worsens/recurs upon resumption of TRC105 and/or bevacizumab, despite anticoagulation, study drugs (TRC105 and/or bevacizumab) should be discontinued.
5. Missed study drug treatment (i.e., single agent TRC105, single agent bevacizumab or BOTH TRC105 and bevacizumab if dosing with the combination regimen) for > 8 consecutive weeks without CR as defined in Section 7 OR discontinuation of study therapy (i.e., single agent TRC105, single agent bevacizumab or BOTH TRC105 and bevacizumab if dosing with the combination regimen) for > 6 months following CR.
6. Pregnancy. Pregnant patients should be followed for the duration of the pregnancy and the outcome of the pregnancy should be documented.
7. Discontinuation of bevacizumab treatment for other toxicities is at the discretion of the investigator, after considering the individual risk and benefit to the patient of continued treatment and per appropriate product labeling.

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 Level

Patients will receive 10 mg/kg TRC105 weekly as a single-agent, or in combination with 5 mg/kg bevacizumab every 2 weeks of each 28 day cycle. Patients who respond to TRC105 monotherapy may receive 15 mg/kg TRC105 every two weeks as a single-agent (see Section 6.7.1).

6.4. TRC105 Packaging and Labeling

TRC105 will be provided in the following presentations.

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).** Patient weight will be assessed at baseline and

used for calculation of each TRC105 dose, unless the patient's weight changes by more than 10% from baseline, in which case the patient's weight on the day of treatment will be 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 (237 mL) 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 a 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 at a dose of 500 mg to 1000 mg (e.g., 650 mg) x 1
- Methylprednisolone 100 mg i.v. (or dexamethasone 20 mg i.v.) will be given prior to the Cycle 1 Day 1 and Cycle 1 Day 4 infusions only. **In addition, methylprednisolone (or dexamethasone) will be given in the case of a delay of ≥ 10 days between any two scheduled weekly doses, a delay of ≥ 17 days between any two scheduled every other week doses, or if a 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 (or dexamethasone) infusion, should be administered 2 hours to 30 minutes prior to initiating TRC105 infusions.

On days of combination dosing with TRC105 and bevacizumab, there will be at least 60 minutes between the completion of the bevacizumab infusion and the initiation of the TRC105 infusion. TRC105 premedication will be administered after the completion of the bevacizumab infusion but at least 30 minutes prior to initiation of the TRC105 infusion. In addition, methylprednisolone or dexamethasone will be administered at least 30 minutes following the completion of the bevacizumab infusion.

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 a patient will be performed as per standard study site procedures.

Following the appropriate premedication regimen, patients will receive TRC105 on days 1, 4, 8, 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 1 and infused over 4 hours (+/- 15 minutes) and 7 mg/kg administered on cycle 1 day 4 and infused over 2 hours (+/- 15 minutes), and then the full dose of 10 mg/kg given on cycle 1 day 8 and weekly thereafter and will be administered over 1 hour (+/- 15 minutes). Patients 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 a patient develops infusion reactions of any kind they should be managed appropriately (see Section 6.7.3) and the patient is not permitted to reduce the duration of the next planned infusion.

Initially, TRC105 will be administered weekly: 10 mg/kg TRC105 on days 1, 8, 15, and 22 of each 28-day cycle, with split dosing on days 1 and 4 of cycle 1. Patients who achieve CR on **single-agent** TRC105 and have received at least 2 cycles of weekly TRC105 may transition to TRC105 15 mg/kg administered every two weeks (see Section 6.7.1). Note: patients receiving TRC105 in combination with bevacizumab will be dosed with TRC105 weekly. Refer to Section 4.1.1 for the sequential treatment algorithm and efficacy definitions.

If a patient misses a TRC105 dose and dosing is resumed ≥ 10 days after the previous infusion, the first weekly dose will be split over two days with full premedication, including methylprednisolone (or dexamethasone), with 3 mg/kg administered on the first day of dosing and 7 mg/kg administered 3 days later, and then the full dose of 10 mg/kg given weekly thereafter. Premedication will also be given if a patient develops an infusion reaction > grade 2 during the immediate prior infusion. If a patient achieves complete response they will be treated with at least 3 consolidation cycles of therapy that produced the response (single agent TRC105, single agent bevacizumab, or combination of TRC105 + bevacizumab).

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 at least 20 mL of 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.

Table 7: Ideal Cycle 1 TRC105 Dosing Schema

	C1D1	C1D4	C1D8	C1D15	C1D22	C2D1+
TRC105 Dose: 10 mg/kg weekly[a]	3 mg/kg	7 mg/kg	10 mg/kg	10 mg/kg	10 mg/kg	10 mg/kg
Infusion Duration	4 hrs	2 hrs	1 hr	1 hr	1 hr	1 hr
Premedication[b]						
Methylprednisolone[d]	100 mg i.v.	100 mg i.v.	None[c]	None	None	None
Famotidine (or similar H2 blocker)	20 mg i.v. or p.o.	20 mg i.v. or p.o.	20 mg i.v. or p.o.	20 mg i.v. or p.o.	20 mg i.v. or p.o.	None[c]
Cetirizine (or similar antihistamine)	10 mg i.v. or p.o.	10 mg i.v. or p.o.	10 mg i.v. or p.o.	10 mg i.v. or p.o.	10 mg i.v. or p.o.	None[c]
Acetaminophen	500 - 1000 mg	500 - 1000 mg	500 - 1000 mg	500 - 1000 mg	500 - 1000 mg	500 - 1000 mg

[a]If a patient misses a TRC105 dose and dosing is resumed ≥ 10 days after the last infusion, the first weekly TRC105 dose should be administered over two days as was done for the initial dose.
[b]Premedication will be given in the case of a delay of ≥ 10 days between any two doses or if a patient develops an infusion reaction > grade 2 during the immediate prior infusion.
[c]May be discontinued in the absence of infusion reaction with the prior dose (starting with Cycle 2 for famotidine and cetirizine).
[d]Dexamethasone (20 mg i.v.) may be substituted for methylprednisolone.

6.7.1. TRC105 15 mg/kg Every 2 Week Dosing

Patients who achieve CR on single-agent TRC105 and have received at least 2 cycles of weekly TRC105 may transition to TRC105 15 mg/kg administered every two weeks. The first administration of TRC105 at 15 mg/kg does not need to be split over two days unless there has been delay of ≥ 10 days since the **last weekly infusion**. In this case, TRC105 will be administered over two days with 3 mg/kg administered on day 1 and 12 mg/kg on day 4 and premedication will be given as outlined for C1D1 and C1D4 in the Ideal Cycle 1 TRC105 Dosing Schema table above.

The first non-split dose of TRC105 at 15 mg/kg will be infused over 90 minutes (+/- 15 minutes) and the second non-split dose will be infused over 60 minutes (+/- 15 minutes) with full premedication, including methylprednisolone (or dexamethasone), given 2 hours to 30 minutes prior to the start of infusion as described above. Premedication (except acetaminophen) may be discontinued in the absence of infusion reaction for subsequent doses of TRC105 at 15 mg/kg and infused over 60 minutes (+/- 15 minutes). If the administration of the first non-split dose of TRC105 at 15 mg/kg is after a split dose of TRC105 15 mg/kg was given, the infusion time can be decreased to 60 minutes (+/- 15 minutes) for this first dose as long as there was no infusion reaction with the prior dose.

If a patient misses a TRC105 dose and dosing is resumed ≥ 17 days after the last every two week infusion, the first TRC105 dose should be administered over two days with full premedication, including methylprednisolone (or dexamethasone). Premedication will also be given if a patient develops an infusion reaction > grade 2 during the immediate prior infusion.

Table 8: Ideal Monotherapy TRC105 15 mg/kg Dosing Schema

	C3D1	C3D15	C4D1	C4D15	C5D1+
TRC105 Dose: 15 mg/kg every 2 weeks[a]	15 mg/kg	15 mg/kg	15 mg/kg	15 mg/kg	15 mg/kg
Infusion Duration	1.5 hrs	1 hr	1 hr	1 hr	1 hr
Premedication[b]					
Methylprednisolone[d]	100 mg i.v.	100 mg i.v.	None[c]	None	None
Famotidine (or similar H2 blocker)	20 mg i.v. or p.o.	20 mg i.v. or p.o.	None[c]	None	None
Cetirizine (or similar antihistamine)	10 mg i.v. or p.o.	10 mg i.v. or p.o.	None[c]	None	None
Acetaminophen	500 mg - 1000 mg	500 mg - 1000 mg	500 mg - 1000 mg	500 mg - 1000 mg	500 mg - 1000 mg

[a]If a patient misses an every 2 week TRC105 dose and dosing is resumed ≥ 17 days after the last infusion, the dose should be administered over two days (3 mg/kg on the first day and the balance three days later).
[b]Premedication will be given in the case of a delay of ≥ 17 days between any two doses or if a patient develops an infusion reaction > grade 2 during the immediate prior infusion.
[c]May be discontinued in the absence of infusion reaction with the prior dose (starting with Cycle 4 for famotidine and cetirizine).
[d]Dexamethasone (20 mg i.v.) may be substituted for methylprednisolone.

6.7.2. 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., either TRC105 or bevacizumab as single agents or in combination). However, patients with a complete response may remain off therapy for a maximum of 6 months following consolidation therapy. Following treatment on the combination portion of the study, if a patient cannot tolerate bevacizumab or TRC105 therapy and 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 should be held for two weeks prior to and for two weeks following surgical procedures. However, resumption of study treatment can be shorter (but no less than 7 days) or longer than two weeks based on clinical judgement of adequate wound healing and recovery from the procedure.

Table 9: Allowable TRC105 Dose Modifications

Toxicity Attributed to TRC105	**Dose Adjustment for Next Dose of TRC105**	
Dose Schedule	10 mg/kg weekly	15 mg/kg every 2 weeks
Grade 1 or 2	Maintain Dose Level	Maintain Dose Level
Grade 3 or 4		
• 1st appearance	8 mg/kg weekly	12 mg/kg every 2 weeks[a]
• 2nd appearance	6 mg/kg weekly	10 mg/kg every 2 weeks[a]
• 3rd appearance	4 mg/kg weekly	8 mg/kg every 2 weeks[a]
• 4th appearance	Discontinue treatment permanently	Discontinue treatment permanently[a]

[a]After discussion with and agreement of the Sponsor, patients receiving TRC105 every two weeks have the option to return to weekly dosing if dosing every 2 weeks is not tolerable (i.e., 4th appearance of a Grade 3 or 4 toxicity attributable to TRC105 occurs) and the investigator believes that the patient is receiving benefit from the treatment.

Note: if a patient is dose reduced and subsequently misses a dose, 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.

TRC105 (and bevacizumab) will be discontinued for 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 TRC105 and bevacizumab treatment. If the planned duration of full dose anticoagulation is < 2 weeks, TRC105 and/or bevacizumab should be held until the full dose anticoagulation period is over. If the planned duration of full dose anticoagulation is > 2 weeks, TRC105 and/or 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 > grade 1 on study; 3. The subject has a stable dose of heparin or a Factor X inhibitor or has an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting TRC105 and/or bevacizumab. If thromboembolism worsens/recurs upon resumption of TRC105 and/or bevacizumab, despite anticoagulation, study drugs (TRC105 and/or bevacizumab) should be discontinued.

6.7.3. Management of TRC105 Infusion Reactions

If patients experience grade 2 or higher adverse reaction during infusion, the infusion should be interrupted and 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 patients 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 10: 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).

6.7.4. 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.

6.7.5. 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 country-specific/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

Patients will receive 5 mg/kg every 2 weeks for each 28-day cycle. Bevacizumab should be prepared according to the appropriate product labeling and 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 product labeling (Section 20).

6.10. Bevacizumab Administration

In the case of a sustained partial response (see Section 7) without continued improvement following treatment with single-agent TRC105, the patient will receive bevacizumab in addition to TRC105. In the absence of a partial or complete response to single agent TRC105, the patient will be receive single agent bevacizumab. Single agent bevacizumab should be initiated 2 weeks following discontinuation of single agent TRC105 (i.e., patients should wash out for 2 weeks prior to starting bevacizumab therapy). No washout is required for initiation of combination therapy. Bevacizumab will be administered at 5 mg/kg every 2 weeks for each 28-day cycle in all cases. **Bevacizumab will be administered according to the appropriate product labeling and on days of combination dosing, there will be at least 60 minutes between the completion of the bevacizumab infusion and the initiation of the TRC105 infusion.**

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 the current applicable product labeling for bevacizumab for specific information related to different adverse events. However, following treatment on the combination portion of the study, if a 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, patients may continue on study on TRC105 or bevacizumab alone.

Bevacizumab and TRC105 will be discontinued for 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 TRC105 and bevacizumab treatment. If the planned duration of full dose anticoagulation is < 2 weeks, TRC105 and/or bevacizumab should be held until the full dose anticoagulation period is over. If the planned duration of full dose anticoagulation is > 2 weeks, TRC105 and/or 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 > grade 1 on study;
3. The subject has a stable dose of heparin or a Factor X inhibitor or has an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting TRC105 and/or bevacizumab. If thromboembolism worsens/recurs upon resumption of TRC105 and/or bevacizumab, despite anticoagulation, study drugs (TRC105 and/or bevacizumab) should be discontinued.

6.11. Bevacizumab Drug Accountability

The Investigator must maintain an accurate accounting of bevacizumab. During the study, the following information must be recorded:

- ID number of the patient to whom the product is dispensed
- The date(s), quantity, and lot number(s) 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.

6.12. 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.

Low dose aspirin may be used if medically indicated. Patients who receive NSAIDs on study should also receive peptic ulcer disease (PUD) prophylaxis with an H2 or proton pump inhibitor.

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

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

7. ASSESSMENT OF EFFICACY

7.1. Assessment of Efficacy by Serum hCG

Treatment decisions will be made based on central lab serum hCG results. Tumor Response by serum hCG measurement results will be defined as follows:

- **Complete response (CR)** is defined as normalization of serum hCG on two consecutive measurements separated by at least two weeks
- **Partial response (PR)** is defined as > 50% decrease of serum hCG from starting value on consecutive measurements separated by at least two weeks. (A change in study treatment should be made for a sustained partial response without evidence of continued disease improvement over 4 consecutive weekly hCG measurements after partial response is confirmed for patients on single agent TRC105 or single agent bevacizumab.)
- **Progressive disease (PD)** is defined as a rise in hCG of >20% (the absolute increase must be ≥10 IU/L) above nadir on consecutive measurements separated by at least two weeks
- **Stable disease (SD)** is defined as absence of response or progression on three consecutive hCG measurements separated by at least two weeks

7.2. Radiologic Tumor Assessment

Radiologic assessment of Target and Non-target lesions will be done by RECIST version 1.1, based on objective tumor assessments made by the Investigator. All lesions will be classified as Target or Non-target 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 4, Table 5 and Table 6), and whenever disease progression is suspected in patients with measurable disease. Another tumor assessment will be performed at the End of Study Visit if an assessment has not been performed within the prior 7 days.

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).

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.

7.2.1. Definitions of Tumor Response by RECIST 1.1

7.2.1.1 Target Lesions

- **Complete response (CR)** is defined as the disappearance of all target lesions.
- **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. (A change in study treatment should be made for a sustained partial response without evidence of continued disease improvement at the subsequent imaging evaluation after partial response is confirmed for patients on single agent TRC105 or single agent bevacizumab.)
- **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.
- **Stable disease (SD)** is defined as neither sufficient radiographic 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.

7.2.2. Determination of Overall Response by RECIST 1.1

Assessment of efficacy by RECIST 1.1 is an exploratory endpoint in patients with choriocarcinoma and measurable disease. 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 11 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 11: 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	Non-PD	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.

7.3. Determination of Best Overall Response by Histology

7.3.1. Determination of Best Overall Response in Patients with Choriocarcinoma

In patients with choriocarcinoma, determination of antitumor efficacy will be based solely on serum hCG measurement (per Section 7.1) and investigators will make treatment decisions based on this assessment. Patients with choriocarcinoma and measurable disease will also undergo radiologic assessment by RECIST 1.1 as an exploratory endpoint (per Section 7.2).

7.3.2. Determination of Best Overall Response in Patients with PSTT and ETT

Best Overall Response in Patients with PSTT and ETT will be determined per Table 12 using radiologic assessments and hCG. In cases where hCG is within the normal range at baseline, efficacy will be determined using RECIST (Table 11). In cases where hCG is elevated and no lesion can be measured, patients will be assessed without employing target lesion criteria (i.e., radiographic lesions will be considered exclusively as non-target lesions). 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 12 below. As is the case in RECIST 1.1 guidelines, a modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

Table 12: Best overall response in PSTT and ETT patients with measurable disease and who are also evaluable by hCG

Target Lesion[a]	Nontarget[b]	New Lesion	hCG	Overall Best Response	
CR	CR	No	Normal	CR	Best RECIST 1.1 response for CR and PR also requires it to be confirmed and maintained for at least 28 days
CR	Non-CR Non-PD	No	Not PD	PR	
CR	CR	No	PR but not normal	PR	
CR	NE	No	PR	PR	
PR	Non-PD or NAE	No	Not PD	PR	
NAE	Non-PD	No	PR	PR	
PD or New >28 days from hCG PR[c]			PR	PR	
SD[d]	Non-PD	No	PR	PR	
SD[d]	Non-PD or NAE	No	Not PR and not PD	SD	
PD or New ≤28 days from hCG PR[c]			PR	PD	
PD	Any	Yes or No	Any	PD	
Any	PD	Yes or No	Any	PD	
Any	Any	Yes	Any	PD	
Any	Any	Yes or No	PD	PD	

[a]Target lesions include up to 5 measurable lesions (2 per organ) as defined by RECIST 1.1.
[b]Nontarget lesions include ascites and peritoneal thickening which are not measurable according to RECIST 1.1.
[c]Patients who have a hCG response that occurs more than 28 days from PD according to RECIST 1.1 are considered a PR, according to best response, but PD if the RECIST 1.1 PD is within 28 days of hCG response.
[d]The protocol should specify the minimum time interval between 2 measurements for classification as stable disease.
NE, Not evaluated; NAE, not all evaluated.

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). Each patient's radiographic best response assignment will depend on the achievement of both measurement and confirmation criteria.

NOTE: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time 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 4, Table 5 and Table 6) 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. Iron studies (serum iron, ferritin and total iron binding capacity).
- Coagulation: Prothrombin Time (PT) or Internalized Normalized Ration (INR) will be assessed
- Serum Chemistry: Total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, lipase, amylase, 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 4, Table 5 and Table 6) and analyzed by local laboratories. Microscopic analysis and/or urine protein-creatinine ratio (UPCR) 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 4, Table 5 and Table 6). 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 4, Table 5 and Table 6). 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 4, Table 5 and Table 6) 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 not stipulated in the protocol, 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 "Medical History and Baseline Signs and Symptoms" 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, and under no circumstances should this exceed 24 hours following knowledge of an SAE or of a change in an event that renders it reportable. This notification should be made to:

Primary Medical Monitor
Richard Yocum, MD
TRACON Pharmaceuticals, Inc.
8910 University Center Lane, Suite 700
San Diego, California 92122
Office Phone: 1.858.550.0780 x230
Cell Phone: 1.858.229.8585
Email: ryocum@traconpharma.com

Secondary Medical Monitor
Charles Theuer, MD, PhD
TRACON Pharmaceuticals, Inc.
8910 University Center Lane, Suite 700

San Diego, California 92122
Office Phone: 1.858.550.0780 x233
Cell Phone: 1.858.344.9400
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 (within 24 hours)** 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 +1 (858) 229-8585.

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 TRC105 will be reported to the US Food and Drug Administration (FDA), Competent Authorities and Ethics Committees in other countries taking part in the study, as well as all participating clinical sites in all countries. Investigators should report to their local IEC/IRB as dictated by their board's policies and procedures. 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 regulatory authorities within 7 calendar days of receipt of the SAE information. For all other events that are serious, unexpected, and associated with use of TRC105, 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.

Investigative sites are responsible for bevacizumab safety reporting to the manufacturer.

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 13: 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/Bevacizumab

In this study, TRC105 study drug is given in combination with bevacizumab. The relationship of an adverse event to TRC105 study drug and bevacizumab should be classified by the Investigator using the following guidelines:

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

AEs may be related to both drugs. 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

If patients are status post a hysterectomy then no exposure in utero is possible. If patients still have a uterus *in situ* then appropriate contraceptive measures will be undertaken to prevent both exposure *in utero* but also prevent pregnancy which would result in a rising serum hCG which could be confused for progression of disease. Appropriate contraception should be continued during follow up and for 180 days after the last dose of TRC105 or bevacizumab to prevent pregnancies which could be confused with recurrence or progression.

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; every effort should be made to make this determination by the 28 day follow-up visit. 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"; every effort should be made to make this determination by the 28 day follow-up visit. 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. TRC105 Trough Concentration

A blood sample will be collected immediately prior to dosing with TRC105 on the days indicated within the Schedule of Assessments (Table 4 and Table 6). Samples will be stored at approximately -70 °C. See separate laboratory guide for further collection and shipment information.

9.1.2. TRC105 Peak Concentration

A blood sample will be collected within 10 minutes after completion of the TRC105 infusion on the days indicated within the Schedule of Assessments (Table 4 and Table 6). Samples will be stored at approximately -70 °C. See separate laboratory guide for further collection and shipment information.

9.1.3. Bevacizumab Trough Concentration

A blood sample will be collected immediately prior to dosing with bevacizumab on the days indicated within the Schedule of Assessments (Table 5 and Table 6). Samples will be stored at approximately -70 °C. See separate laboratory guide for further collection and shipment information.

9.1.4. Bevacizumab Peak Concentration

A blood sample will be collected within 10 minutes after completion of the bevacizumab infusion on the days indicated within the Schedule of Assessments (Table 4 and Table 6). Samples will be stored at approximately -70 °C. See separate laboratory guide for further collection and shipment information.

9.1.5. TRC105 Immunogenicity

Anti-Product Antibody (APA) concentrations will be measured using validated ELISA methods at the time points specified within the Schedule of Assessments (Table 4, Table 5 and Table 6). APA concentrations will be evaluated in the context of pharmacokinetic profiles and AE profiles. Samples will be separated and stored at approximately -70 °C. See separate laboratory guide for further collection and shipment information.

9.1.6. Protein Biomarker

A K_2EDTA plasma blood sample will be collected on the days indicated within the Schedule of Assessments (Table 4, Table 5 and Table 6). Samples will be stored at approximately -70 °C. 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.

9.1.7. CD16 Genotype

A blood sample will be collected on Cycle 1 Day 1 according to the Schedule of Assessments (Table 4, Table 5 and Table 6). Samples will be stored at approximately -70 °C. See separate laboratory guide for further collection and shipment information.

9.1.8. Archival Tumor Specimens

Archival specimens (formalin-fixed, paraffin-embedded) of the primary cancer and/or metastatic cancer specimen for each study participant will be obtained, if they are available. It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 10 unstained slides are requested for immunohistochemical analysis (sections of ~5 microns are preferred). Samples will be stored at room temperature and shipped to a third party laboratory for storage until the time of analysis. See separate laboratory guide for further collection and shipment information.

10. STATISTICS

10.1. Data Analysis

10.1.1. Analysis of Co-Primary Objectives

ORR by hCG in cases of choriocarcinoma or by integrated radiologic and hCG assessments in cases of PSTT or ETT, will be calculated form the time of cycle 1 day 1 until the time of progression, and will include separate assessments while on TRC105, bevacizumab and while receiving both agents. hCG for purposes of calculating ORR (and overall treatment decisions) will be measured by the central laboratory. ORR to single agent TRC105 will include PR or CR. ORR to the combination of TRC105 and bevacizumab will include PR or CR. ORR for purposes of determining the co-primary endpoints will include the ORR to TRC105 given as a single agent and when combined with bevacizumab (in bevacizumab refractory patients) in each patient.

The point estimates and two-sided exact binomial 95% confidence intervals will be provided for ORR for each of the two co-primary populations.

10.1.2. Analysis of Secondary Objectives

Secondary endpoints include progression-free survival (PFS) and duration of response (DR). PFS is defined as the time from initial dosing until time of progression or death, with progression documented either hCG in cases of choriocarcinoma or by integrated radiologic and hCG assessments in cases of PSTT or ETT. DR is defined as the time from initial documentation of response until time of progression or death, whichever occurs first. PFS and DR will include separate assessments while on TRC105, bevacizumab and while receiving both agents.

The distribution of PFS will be analyzed using the Kaplan-Meier method. Secondary endpoints defined as proportions will be summarized using point estimates and two-sided exact binomial 95% confidence intervals.

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

10.1.2.1. Analysis for Pharmacokinetics

Serum TRC105 and bevacizumab concentrations will be measured using validated methods and assessed for potential correlations with response, PFS, survival, adverse events, baseline characteristics and immunogenicity using descriptive statistics and models as appropriate.

10.1.2.2. Analysis of Protein Biomarkers

Angiogenic protein biomarker data for each patient who received at least one dose of study drug will be compared based on treatment with TRC105, bevacizumab and while receiving both agents.

10.1.2.3. Analysis of CD16 Genotype

CD16 genotype will be quantified for each patient who received at least one dose of study drug and will be listed by cohort.

10.1.2.4. Analysis of Archival Tumor Tissue

CD105 expression within the tumor vasculature will be quantified for each patient who received at least one dose of study drug and will be listed by cohort. Expression will be determined by IHC and/or by PCR. Other markers that may relate to efficacy or toxicity of TRC105 will also be explored.

10.2. Sample Size Justification

The sample size of 30 patients is not based on statistical considerations. If five or more responses to TRC105 given as a single agent or when combined with bevacizumab (in a bevacizumab refractory patient) are detected among 30 patients, then the lower limit of the two-sided exact binomial 95% confidence interval will be greater than 5%. For example, with five responses, the 95% confidence interval would be (5.64%, 34.72%).

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.

Protocol deviations will be captured in TRACON's electronic data capture system.

13. ETHICS

13.1. Health Authorities and Independent Ethics Committees/Institutional Review Boards

Before this study starts, the trial protocol, protocol amendments, informed consent forms, and any other information for patients will be submitted to the FDA, EMA, or other national health authority and to eat IEC/IRB for review, as applicable. As required, the study will not start at a given investigational center before the IEC/IRB and health authority (where applicable) for the center gives written approval or a favorable opinion.

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 relevant 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/health authorities 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 each patient full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. This information must be provided to each patient prior to undertaking any trial-related procedure. Each 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 each patient is appropriately informed before obtaining 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 each patient's original signed consent form in the Investigator/site files.

13.4. Patient Compensation

Patients will not be compensated for participation in this trial; this will be outlined in the 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.

Essential documents will be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a

longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor.

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 TRIAL

15.1. End of Trial in all Participating Countries

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.

For clinical investigational centers located in the EU, a declaration of the end of the clinical study will be made according to the procedures outlined in Directive 2001/20/ED, Article 10(c); for other countries, local regulations will be followed.

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.

The sponsor is responsible for ensuring that the public has access to the appropriate information about the study by conforming to local and regional requirements for registration and posting of results.

The study will be listed in public databases on clinical studies www.clinicaltrials.gov and the European clinical trials database (EudraCT). The summary of the study results will also be available on www.clinicaltrials.gov and www.clinicaltrialsregister.eu websites.

17. FINANCING AND INSURANCE

Financing and Insurance are discussed in detail in the Clinical Trial Agreement.

18. INVESTIGATOR PROTOCOL AGREEMENT: 105GTN201

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.

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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://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.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

http://www.gene.com/download/pdf/avastin_prescribing.pdf