CLINICAL PROTOCOL: 105LC101

Title:	A PHASE 1B DOSE-ESCALATION STUDY OF TRC105 IN COMBINATION WITH PACLITAXEL/CARBOPLATIN AND BEVACIZUMAB IN PATIENTS WITH STAGE 4 NON-SQUAMOUS CELL LUNG CANCER
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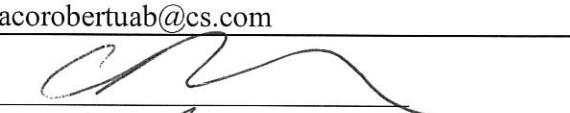
Signature & Date:	Signed:  Print: C Theuer Dated: 2 SEP 2015
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PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

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1. SYNOPSIS

Name of Sponsor/Company: TRACON Pharmaceuticals, Inc./UAB Cancer Center	
Name of Investigational Product: TRC105	
Name of Active Ingredient: TRC105	
Title of Study: A PHASE 1B DOSE-ESCALATION STUDY OF TRC105 IN COMBINATION WITH PACLITAXEL/CARBOPLATIN AND BEVACIZUMAB IN PATIENTS WITH STAGE 4 NON-SQUAMOUS CELL LUNG CANCER	
Study center(s): This study will be performed at University of Alabama at Birmingham	
Principal Investigator: Dr. Francisco Robert	
Studied period (years): Estimated date first patient enrolled: September 2015 Estimated date endpoint obtained: April 2016 Estimated date last patient completed: December 2016 Total Numbers of Patients: 18 Estimated duration of treatment per patient: 6 months	**Phase of development:** 1b
Rationale: Bevacizumab is a monoclonal antibody to vascular endothelial growth factor (VEGF) that inhibits angiogenesis and extends survival in non-squamous non-small cell lung cancer (NSCLC) patients when given with carboplatin and paclitaxel. TRC105 is an antibody to endoglin, an essential angiogenic target expressed on proliferating endothelial cells that is distinct from the VEGFR and overexpressed in response to VEGF inhibition. TRC105 inhibits angiogenesis, tumor growth and metastases in preclinical models and complements the activity of antibodies and small molecules that target the VEGFR. In a phase 1b study, the combination of TRC105 and bevacizumab produced radiographic reductions in tumor volume in bevacizumab-refractory patients, and was well tolerated. TRC105 was also well tolerated with chemotherapy in a trial with capecitabine in breast cancer patients. The use of TRC105 with bevacizumab and paclitaxel/carboplatin may result in more effective angiogenesis inhibition and improved clinical efficacy over that seen with bevacizumab and paclitaxel/carboplatin alone.	

Objectives:

Primary:

- To evaluate safety and tolerability and determine a recommended phase 2 dose for TRC105 when added to standard dose bevacizumab and paclitaxel/carboplatin in treatment-naive patients with stage IV non-squamous NSCLC

Secondary:

- To assess preliminary evidence of antitumor activity when TRC105 is added to bevacizumab and paclitaxel/carboplatin, by assessing objective response rate, median progression-free survival, the proportion (%) of patients progression-free at 6 months, and the overall survival
- To characterize the pharmacokinetic profile of TRC105 when given with bevacizumab and paclitaxel/carboplatin
- To evaluate TRC105 Anti-Product Antibodies
- To explore pharmacodynamic effects on circulating angiogenic biomarkers

Methodology:

This is a single center, open-label, nonrandomized, phase 1b, dose-finding study of TRC105 in combination with standard dose bevacizumab and paclitaxel/carboplatin in treatment-naive patients with stage IV non-squamous NSCLC. Escalating doses of i.v. TRC105 will be administered weekly beginning with Dose Level 1 in combination with bevacizumab 15 mg/kg given intravenously every 3 weeks and paclitaxel 200 mg/m^2 and Carboplatin 6 AUC administered intravenously on day 1 of each 21 day cycle. Intermediate TRC105 doses (below the MTD established during the trial) may be explored based upon clinical, PK, and/or biomarker data.

Level	Number of Evaluable Subjects	Bevacizumab mg/kg IV every 3 weeks	Paclitaxel mg/m^2 IV every 3 weeks	Carboplatin AUC IV every 3 weeks	TRC105 mg/kg IV, weekly (beginning cycle 1 day 8)[a]
-1	3-6	15	200	6	6
1 (starting dose)	3-6	15	200	6	8
2	3-6	15	200	6	10
Expanded Cohort	9-12 (up to 15 total at the MTD)	15	200	6	MTD

[a]The first weekly TRC105 dose will be split into two doses whereby 3 mg/kg is administered on cycle 1 day 8 and the balance is administered on cycle 1 day 11.

Patients will receive 15 mg/kg of bevacizumab, 200 mg/m^2 of paclitaxel and 6 AUC of carboplatin every 3 weeks beginning with cycle 1 day 1. TRC105 dosing will begin at 8 mg/kg (Dose Level 1) on cycle 1 day 8. A -1 Dose Level has also been included (6 mg/kg) and will be enrolled if 8 mg/kg TRC105 dosed with bevacizumab, paclitaxel and carboplatin exceeds the MTD. The DLT evaluation period, for purposes of dose expansion, will be the first 6 weeks (42 days) of dosing bevacizumab, paclitaxel, carboplatin and TRC105 (e.g., from cycle 1 day 1 through cycle 2 day 21). Each cycle will be 3 weeks (21 days) in duration.

Three patients will be initially enrolled and treated at each dose level. If none of these 3 patients experiences a dose-limiting toxicity (DLT) during the initial 42-day evaluation period when all drugs are dosed together (extending from cycle 1 day 1 through cycle 2 day 21), dose escalation will proceed following review of safety data with site staff including the principal investigators at all sites.

If 1 of 3 patients experiences DLT, the dose level will be expanded to 6 patients. The maximum tolerated dose (MTD) will have been exceeded if ≥ 33% of patients experience DLT at a given dose level. DLT will have occurred when a patient has 1 or more toxicity listed in the table below that is at least possibly related to the combination of bevacizumab, paclitaxel, carboplatin and TRC105 during the first 42 days of concomitant dosing. Patients who exit the study for reasons other than DLT prior to completion of the 42-day DLT evaluation period will be replaced to ensure an adequate safety assessment in each cohort. Patients who experience DLT who receive less than the prescribed dose of TRC105 or bevacizumab or paclitaxel or carboplatin due to documented toxicity during the DLT evaluation period will be considered evaluable for dose escalation purposes. A given TRC105 dose level may be reenrolled at an intermediate dose level upon agreement of study investigators.

Toxicity Category	Drug-Related Toxicity/Grade
Hematologic	Any Grade 4 toxicity
	Neutropenic infection: grade ≥ 3 neutropenia with grade ≥ 3 infection
	Grade ≥ 3 thrombocytopenia and grade ≥ 3 hemorrhage
Nonhematologic	Grade 3 toxicity with the following exceptions: • Nausea, vomiting or diarrhea for < 48 hours[a] • Asymptomatic electrolyte abnormalities that are corrected to grade 1 or better in < 72 hours[b]
	Any Grade 4 toxicity

[a]Patients with related grade 3 or 4 diarrhea, nausea or vomiting for ≥ 48 hours despite optimal medical therapy will require a one-level dose-reduction of TRC105.
[b]Patients with related grade 3 or 4 electrolyte abnormalities that persist for ≥ 72 hours will require a one-level dose reduction of TRC105.

Up to 15 treatment-naive patients with stage IV non-squamous NSCLC will be treated at the MTD (or top dose level if a MTD is not determined) to further characterize safety and tolerability.

Number of patients (planned):

Approximately 18 treatment-naive patients with stage IV non-squamous NSCLC will be enrolled.

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

1. Stage 4 Non-Squamous Cell Lung Cancer that has not been treated previously with systemic chemotherapy or bevacizumab, but may have received prior targeted treatment (e.g., alk1 inhibitor)
2. Measurable disease by RECIST
3. Age of 18 years or older
4. ECOG performance status ≤ 1
5. Resolution of all acute adverse events resulting from prior cancer therapies to NCI CTCAE grade ≤ 1 or baseline (except alopecia or neuropathy)
6. 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 28 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
- ≤ 1+ proteinuria
- INR from 0.8 to 1.2

7. Willingness and ability to consent for self to participate in study
8. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures
9. Men who are sterile (including vasectomy confirmed by post vasectomy semen analysis) OR agree to use at least two forms of a reliable and highly effective method of birth control (refer to Section 2.5.1) and to not donate sperm and for at least 180 days following last dose of TRC105, bevacizumab, paclitaxel, and/or carboplatin
10. 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, OR woman of child bearing potential who test negative for pregnancy at time of enrollment based on serum pregnancy test and agree to use at least 2 forms of a reliable and highly effective method of birth control (refer to section Section 2.5.1) during the study and for at least 180 days after stopping TRC105, bevacizumab, paclitaxel, and/or carboplatin

Exclusion Criteria:

1. Non-small cell lung cancer of squamous histology
2. Prior treatment with TRC105
3. Current treatment on another therapeutic clinical trial
4. Receipt of a small molecule anticancer agent, including an investigational anticancer small molecule, within 14 days of starting study treatment
5. Receipt of a large molecule anticancer agent (e.g., antibody), including an investigational anticancer antibody, within 28 days of starting study treatment
6. No major surgical procedure or significant traumatic injury within 6 weeks prior to study registration, and must have 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

7. 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 study registration or those patients who have not recovered adequately from side effects of such therapy
8. 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 < 140/90 mm Hg)
9. 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 at least 28 days
10. 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 anticoagulated without the use of warfarin for at least 2 weeks. In this situation, low molecular weight heparin is preferred.
11. Active bleeding or pathologic condition that carries a high risk of bleeding (e.g. hereditary hemorrhagic telangiectasia). Patients who have been uneventfully anti-coagulated with low molecular weight heparin are eligible.
12. Thrombolytic use (except to maintain i.v. catheters) or anticoagulant use within 10 days prior to first day of study therapy
13. Cardiac dysrhythmias of NCI CTCAE grade ≥ 2 within the last 28 days
14. Known active viral or nonviral hepatitis or cirrhosis
15. History of hemorrhage or hemoptysis (> ½ teaspoon bright red blood) within 3 months of starting study treatment
16. History of peptic ulcer disease or erosive gastritis within the past 3 months, unless treated for the condition and complete resolution has been documented by esophagogastroduodenoscopy (EGD) within 28 days of starting study treatment
17. 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)
18. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness
19. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for this study

TRC105 investigational product dose and mode of administration:

Dosing will begin at 8 mg/kg (Dose Level 1); however a -1 Dose Level has also been included (6 mg/kg) and will be enrolled if 8 mg/kg is found to exceed the MTD. Following the appropriate premedication regimen, the first weekly TRC105 dose (cycle 1 day 8) will be split into two doses whereby 3 mg/kg is administered on cycle 1 day 8 and the balance (e.g., 5 mg/kg for Dose Level 1) is administered on cycle 1 day 11. Beginning with cycle 1 day 15 and thereafter, the full (e.g., 8 mg/kg for Dose Level 1) TRC105 dose will be administered i.v. weekly during each 21-day cycle. Intra-patient dose reductions are allowed beginning in cycle 2.

Bevacizumab dose and administration:

Bevacizumab will be administered intravenously at a dose of 15 mg/kg on day 1 of each 21-day cycle until disease progression. The initial bevacizumab dose should be delivered over 90 minutes.

Dose reduction of bevacizumab for adverse reactions is not recommended.

Paclitaxel dose and administration:

Paclitaxel will be administered intravenously following appropriate premedication at 200 mg/m^2 beginning on cycle 1 day 1 and on day 1 of each 21 day cycle for 6 cycles, in the absence of toxicity. Paclitaxel will be delivered over 3 hours. Dose reductions are allowed beginning in cycle 3 according to the package insert.

Carboplatin dose and administration:

Carboplatin will be administered intravenously following appropriate premedication at 6 AUC beginning on cycle 1 day 1 and on day 1 of each 21 day cycle for 6 cycles, in the absence of toxicity. Carboplatin will be delivered over 30 to 60 minutes. Dose reductions are allowed beginning in cycle 3 according to the package insert.

Combination dosing order:

Dosing will occur in the following order on day 1 of each cycle (Note: TRC105 will not be dosed on cycle 1 day 1):

- Pre-medication
- Paclitaxel 200 mg/kg (3 hour IV infusion)
- Carboplatin AUC of 6 (30 to 60 minutes IV infusion)
- Bevacizumab 15 mg/kg (30 minute IV infusion)
- TRC105 8 or 10 mg/kg (1 to 4 hour IV infusion)

TRC105 will be dosed alone on days 8 and 15 of each cycle, following appropriate pre-medication.

Duration of treatment:

Patients will be treated with induction therapy with carboplatin, paclitaxel, bevacizumab, and TRC105 for a maximum of 6 cycles of therapy. Patients who demonstrate a response of CR, PR or SD, after the

end of the induction therapy are eligible for maintenance therapy with bevacizumab and TRC105 until disease progression, unacceptable toxicity or withdrawal of consent, or other reasons. Patients who are not able to receive more than 4 cycles of induction therapy because significant and persistent > grade 2 neurotoxicity related to paclitaxel may be eligible for maintenance therapy (i.e., TRC105 + bevacizumab alone) if there is no evidence of progressive disease after 4 cycles of induction therapy. Patients may be scanned early at the end of cycle 4 to determine disease status.

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

1. RECIST 1.1-defined disease progression. In cases where RECIST cannot be applied, progression should be based on unequivocal evidence of progressive disease sufficient to require a change in therapy.
2. A need for surgery, radiation, or for other anticancer therapy not specified in the protocol.
3. Lost to follow-up or noncompliant.
4. Any TRC105 dose delay > 14 days, other than a dose delay for planned surgery or hematologic toxicity, in which case up to 6 weeks is allowed.
5. Pregnancy. Pregnant patients should be followed for the duration of the pregnancy and the outcome of the pregnancy should be documented.

Parameters to be assessed:

Safety:
Safety assessments will include physical exams, performance status, laboratory results (complete blood counts and serum chemistry) and 12-lead ECG's, and additional studies as clinically indicated. A formally chartered Safety Review Team will review safety data. In addition, recurring teleconferences will be held with the Investigator at the clinical site.

Pharmacokinetics:
Serum TRC105 concentrations will be measured using validated methods at the time points specified in the Schedule of Events.

Immunogenicity:
Anti-product antibody titers will be measured using validated methods at time points specified in the Schedule of Events.

Exploratory Biomarkers:
Concentrations of a panel of angiogenic protein biomarkers in plasma will be measured at baseline and during treatment to explore TRC105 pharmacodynamics.

Efficacy:
RECIST 1.1 will be applied to measurable disease to assess response and progression. Tumor markers will also be evaluated where available.

Statistical methods:

Evaluable Study Population:

The study population for safety and efficacy includes all patients receiving at least a portion of 1 dose of TRC105.

The number of patients to be enrolled in this study will depend upon the observed safety profile, which will determine the number of patients per dose level and the number of dose escalations. It is anticipated that a total of approximately 18 patients will be enrolled in this study.

The probability of escalation to the next higher dose for each underlying true DLT rate is shown in the table below. For example, for a toxicity that occurs in 5% of patients, there is a > 95% probability of escalating. Conversely, for a common toxicity that occurs with a rate of 70%, the probability of escalating is < 5%.

Probability of Escalation to the Next Dose for Each True Underlying DLT Rate at a Dose Level

True Underlying DLT Rate	5%	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of Escalating Dose	0.97	0.91	0.71	0.49	0.31	0.17	0.08	0.03	0.01	0.001

The probability of failing to observe toxicity in a sample size of 3 or 6 patients given various true underlying toxicity rates in shown in the table below. For example, with 6 patients, the probability of failing to observe toxicity occurring at least 40% of the time is < 5%.

Probability of Failing to Observe True Underlying DLT Rate at a Dose Level

True Underlying DLT Rate	5%	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of Failing to Observe Toxicity, N = 3	0.86	0.73	0.51	0.34	0.22	0.13	0.006	0.027	0.008	0.001
Probability of Failing to Observe Toxicity, N = 6	0.74	0.53	0.26	0.12	0.05	0.016	0.004	<0.001	<0.001	<0.001

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Table 2: Abbreviations and Specialist Terms

Abbreviation or specialist term	Explanation
ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
AE	Adverse Event
AFP	Alpha Fetoprotein
AIDS	Acquired Immunodeficiency Syndrome
ALKs	Activin receptor-Like Kinases
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
APA	Anti-Product Antibody
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AUC_{last}	Time of Last Measurable Concentration of Area Under the Curve
BALB/c mice	Mouse Strain
BMP	Bone Morphogenic Protein
BUN	Blood Urea Nitrogen
CABG	Coronary Artery Bypass Graft
CBC	Complete Blood Count
CEA	Carcinoembryonic Antigen
CHOP	Cyclophosphamide Hydroxydaunomycin Oncovin® Prednisone
CL	Clearance
C_{max}	Maximum Serum Concentration
CPA	Cyclophosphamide
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CTC	Common Terminology Criteria
dL	Deciliter
DLT	Dose Limiting Toxicity
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECM	Extracellular Matrix
EGFR	Epidermal Growth Factor Receptor
ELISA	Enzyme-Linked ImmunoSorbent Assay
EOS	End of Study
FDA	Food and Drug Administration
FGF	Fibroblast Growth Factor
FU	Fluorouracil
g	Gram
GOG	Gynecologic Oncology Group
GCP	Good Clinical Practice
GIST	Gastrointestinal Stromal Tumor
HACA	Human Anti-Chimeric Antibodies
HAMA	Human Anti-Murine Antibodies
Her-2	Human epidermal growth factor receptor 2

HHT-1	Hereditary Hemorrhagic Telangiectasia Type 1
HIF-1-α	Hypoxia-Inducible Factor-1-α
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HRA	Health Regulatory Authority
HUVECs	Human Umbilical Vein Endothelial Cells
ICH	International Conference on Harmonization
ID	Identification
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
INR	International Normalized Ratio
IP	Intraperitoneal
IRB	Institutional Review Board
i.v.	Intravenous
K_d	Avidity Binding Constant
kg	Kilogram
L	Liter
LDH	Lactate Dehydrogenase
LOQ	Limit of Quantification
µL	Microliter
Mg	Milligram
mL	Milliliter
MACA	Monkey Anti-Chimeric Antibody
MAMA	Monkey Anti-Murine Antibody
MI	Myocardial Infarction
mm	Millimeter
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCIC	National Cancer Institute of Canada
ng	Nanogram
NHP	Nonhuman Primate
NOAEL	No Adverse Effect Level
PBS	Phosphate-Buffered Saline
PD	Progressive Disease
PDGF	Platelet Derived Growth Factor
PDGFR	Platelet Derived Growth Factor Receptor
PlGF	Placental Growth Factor
pM	Picomolar
PR	Partial Response
PSA	Prostate Specific Antigen
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTT	Partial Thromboplastin Time
QA	Quality assurance
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors

SAE	Serious Adverse Event
sCD105	Soluble CD105/endoglin
SCID	Severe Combined Immunodeficient
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SN6j	Murine parent antibody of TRC105
sVEGFR2	Soluble VEGF Receptor 2
TGF-β	Transforming Growth Factor
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
US	United States of America
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
VEGFR TKI	Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitor

2. BACKGROUND

2.1. Angiogenesis and Cancer

The critical role of angiogenesis in the development, growth, and distant metastasis of solid tumors is well described [1,2] In addition to the delivery of oxygen and nutrients to, and the exportation of cellular waste products from tumor cells, the vascular supply provides a mechanism by which malignant cells disseminate into distant tissues [3]. As a tumor grows beyond 3-4mm, it becomes vitally dependent on angiogenesis to sustain vascular supply. Tumor angiogenesis results from the disequilibrium between pro- and anti-angiogenic signaling pathways and several targetable regulatory pathways have been identified. In 1971, vascular endothelial growth factor (VEGF) was described as a potent factor in inducing tumor angiogenesis and was explored as the first target for anti-angiogenic therapy [4]. Further characterization of the VEGF/VEGFR signaling pathway led to the identification of VEGF-A as the central angiogenesis promoter and subsequently bevacizumab (monoclonal antibody against VEGF-A165) was developed [5, 6]. Elevated VEGF levels are thought to cause endothelial leaks in tumor vascular supply thereby decreasing the delivery of chemotherapy to tumor [7]. In addition arresting the development of new vascular supply to the tumor, bevacizumab is felt to increase chemotherapy delivery to tumors through the inhibition of VEGF and stabilization of vascular endothelium [8].

Targeting angiogenesis via VEGF-A antagonists provides clinical benefit in several solid tumor types. 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 [9,10]. Bevacizumab is also effective therapy for renal cell cancer and malignant glioma [11-13]. Orally available small molecule VEGF inhibitors include sunitinib, sorafenib, pazopanib, and axitinib which have been shown to prolong survival in patients with metastatic renal cell cancer, hepatocellular cancer, colorectal cancer, and sarcoma [14-17].

2.1.1. Angiogenesis and Non-Small Cell Lung Cancer

Advanced non-small cell lung cancer has been historically difficult to treat, and novel agents are in dire need. Prognosis is poor, with 1 year survival rates of 30% to 40%. Two drug platinum-based chemotherapy regimens have long been the traditional treatment of choice, but a plateau effect is inevitably reached and survival is approximately 8 months, regardless of regimen chosen [18,19]. Since VEGF over-expression is typical in non-small cell lung cancer, bevacizumab was investigated in combination with platinum doublet chemotherapy. A randomized phase II study of treatment naïve patients with advanced NSCLC compared paclitaxel and carboplatin alone with paclitaxel, carboplatin, and bevacizumab at a dose of 7.5mg or 15 mg per kilogram body weight intravenously every three weeks [20]. Improved median time to progression was seen in the 15mg bevacizumab group, albeit at an increased risk of pulmonary hemorrhage. Based on this study, a landmark phase III study(ECOG 4599) of nearly 900 patients with advanced NSCLC was undertaken. Patients in this study were randomized to paclitaxel and carboplatin chemotherapy alone or paclitaxel, carboplatin, plus bevacizumab 15mg/kg every 3 weeks [10]. This study demonstrated an overall survival advantage of 2 months in the bevacizumab arm (12.3 months vs 10.3 months). The rates of clinically significant bleeding were slightly increased in the bevacizumab group (4.4% vs 0.7%). This trial led to the standardization

of paclitaxel, carboplatin, and bevacizumab as preferred first line therapy for patients with advanced NSCLC.

Subsequently, the AVAiL (Avastin in Lung) study confirmed the PFS benefit of adding bevacizumab to first-line cisplatin/gemcitabine, though an OS advantage was not demonstrated [21]. In an effort to evaluate two agents shown to have activity in the maintenance setting in advanced NSCLC patients, the investigators of the AVAPERL trial compared bevacizumab monotherapy to bevacizumab plus pemetrexed after induction with bevacizumab, cisplatin, and pemetrexed. In an unselected patient population with non-squamous advanced NSCLC who had responded to induction chemotherapy, bevacizumab plus pemetrexed maintenance was associated with significant PFS benefit (7.4mo vs 3.7 mo) compared to bevacizumab alone [22]. Given the benefit seen with the combination of bevacizumab and pemetrexed in the maintenance setting, there was interest in comparing pemetrexed in combination with bevacizumab and platinum with the standard platinum, paclitaxel, and bevacizumab as initial therapy. POINTBREAK was randomized phase III trial which compared the efficacy of pemetrexed, carboplatin, and bevacizumab followed by pemetrexed plus bevacizumab with paclitaxel, carboplatin, and bevacizumab followed by bevacizumab in patients with advanced NSCLC. This was a negative study as the primary end point of improved OS in the pemetrexed arm was not met. The median OS for both arms in the POINTBREAK trial was similar to the medial OS seen in ECOG 4599, at approximately 12.5 months [23]. As such, the regimen of carboplatin, paclitaxel, and bevacizumab followed by maintenance bevacizumab remains the standard front line therapy for patients with advanced NSCLC. It is the anti-angiogenic agent bevacizumab, rather than the addition of more chemotherapy, which seems to confer the greatest benefit against disease progression in advance NSCLC. This benefit is conceptually understandable in a tumor such as NSCLC in which the majority of cells over express VEGF [24]. Targeting angiogenesis, in addition to delivering cytotoxic chemotherapy, has led to the best outcomes for patients with advanced NSCLC.

2.1.2. CD105 and Angiogenesis

However despite the initial enthusiasm for anti-VEGF agents, their clinical effects have proven to be generally modest and transient, resulting in limited survival advantage [25, 26]. The underlying cause for clinical progression in patients treated with anti-VEGF therapy is the acquisition of resistance to therapy via up regulation of alternative pro-angiogenic pathways [27]. Surrogate pro-angiogenic signal cascades, including platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and placental growth factor (PlGF) are activated when VEGF-mediated angiogenesis is blocked [28]. In addition to these, the transforming growth factor β (TGF-β) plays a prominent role in tumor angiogenesis. TGF-β promotes tumor development by stimulating cancer cell invasion, immune suppression, and inducing angiogenesis [29]. The direct pro-angiogenic effects of TGF-β on endothelial cells are mediated by the expression of TGF-β co-receptor endoglin [30]. *Also known as CD105, endoglin is highly expressed on proliferating endothelial cells and high endoglin expression is associated with sites of active angiogenesis* [31, 32]. Therefore, endoglin has emerged as an attractive target for both anti-angiogenic therapy and response monitoring in patients with disease progression despite anti-VEGF therapy.

CD105 (endoglin) is a homodimeric cell membrane glycoprotein that was initially identified as a human leukemia-associated antigen [33] and later also found on endothelial cells [34,35].

CD105 is a TGF-β coreceptor that is essential for angiogenesis [36, 37] and CD105 is strongly expressed on the proliferating vascular endothelium of solid tumors [35, 38]. All of these properties make CD105 an attractive target for the antiangiogenic therapy of cancer [39]. Vascular targeted therapy may more effectively address large established tumors than conventional antiangiogenic therapy such as anti-VEGF therapy [40]. 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 [35,41-44]. Therefore, CD105 offers a novel alternative target relative to the VEGF inhibitors currently available for antiangiogenesis therapy.

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 [45]. 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 endothelium. Not surprisingly, prevention of CD105 activation by anti-CD105 antibody acts synergistically with TGF-β to inhibit endothelial cell growth [46]. Similarly, CD105 acts in concert with the bone morphogenic protein (BMP) receptor to phosphorylate SMAD 1 and 5 in response to binding BMP 9 and 10, to activate endothelium [47].

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) [48, 49]. CD105 has also been shown to protect hypoxic cells from apoptosis [50]. 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 [37].

CD105 is critical for normal human blood vessel development [51]. 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 [52]. 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 [53].

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 is limited to vascular endothelial cells and proerythroblasts, a red blood cell precursor [54].

CD105 expression is a prognostic factor in solid tumor patients. High microvessel density of CD105-positive vessels has been correlated with poor prognosis in clinical studies of breast cancer [55,56], lung cancer [57], prostate cancer [58,59], colorectal cancer [60,61], ovarian cancer [62,63], gastric cancer [64], endometrial cancer [65], astrocytic brain tumors [66], hepatocellular carcinoma [67], esophageal adenocarcinoma [68], and head and neck cancer [69,70].

Plasma CD105 levels 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 [60]. In the study, a positive correlation was observed between plasma CD105 concentration and stage of disease.

Importantly, CD105 expression is upregulated in tumor endothelial cells following inhibition of the VEGF pathway. CD105 expression increased more than 2-fold in human pancreatic cancers grown in mice treated with an antibody that binds VEGF [71]. 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 [72].

TRC105 is a novel IgG1 that binds CD105 with high avidity. Recent studies at Duke University explored the in vitro effects of dual angiogenesis inhibition using bevacizumab and TRC105 in human umbilical vein endothelial cells (HUVEC). Combination therapy was found to be more potent in decreasing HUVEC proliferation, migration, and tubular network formation than bevacizumab or TRC105 treatment alone [73]. Furthermore, TRC105 induced apoptosis in HUVEC, and promotes SMAD2/3 phosphorylation while inhibiting SMAD1/5/8 signaling, thereby inhibiting angiogenesis in response to VEGF and basic FGF [47]. Finally, antibody to mouse CD105 potentiates the activity of multitargeted kinase inhibition that targets the VEGFR-2, in mouse bearing cancer grafts [74].

2.2. TRC105 Background

TRC105 is a genetically engineered human/murine chimeric monoclonal antibody directed against human CD105 [66], a growth proliferation receptor found on the surface of normal and proliferating endothelial cells [35,41,49].

The antibody is an IgG1 kappa immunoglobulin containing murine variable region sequences and human constant region sequences [75]. TRC105 has an approximate molecular weight of 148 kDa. TRC105 has a binding avidity for human CD105 of approximately 5 pM. TRC105 is formulated as 20 mM L-Histidine/L-Histidine Monohydrochloride, 240 mM Trehalose, 0.01% Polysorbate 20 Formulation at a concentration of 25 mg/mL.

SN6j, the murine parent antibody of TRC105, binds to human umbilical vein endothelial cells (HUVECs) with nearly identical avidity as TRC105. SN6j has been shown to bind the tumor vasculature of malignant tissues including breast, colon, rectum, kidney and lung cancers and to inhibit the growth of tumor xenografts [42]. Reactivity with tumor tissues is restricted to the tumor endothelium, as CD105 is not generally expressed on epithelial tumor cells [41]. TRC105 induces ADCC on proliferating HUVECs at low conentrations and induces apoptosis and growth inhibition at higher concentrations.

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 [76]. Studies of TRC105 in prostate, bladder, and ovarian cancer and a phase 1b study of TRC105 in combination with bevacizumab have also been completed. Ongoing studies include a phase 1b study of TRC105 in combination with sorafenib in liver cancer, a phase 1b study of TRC105 in

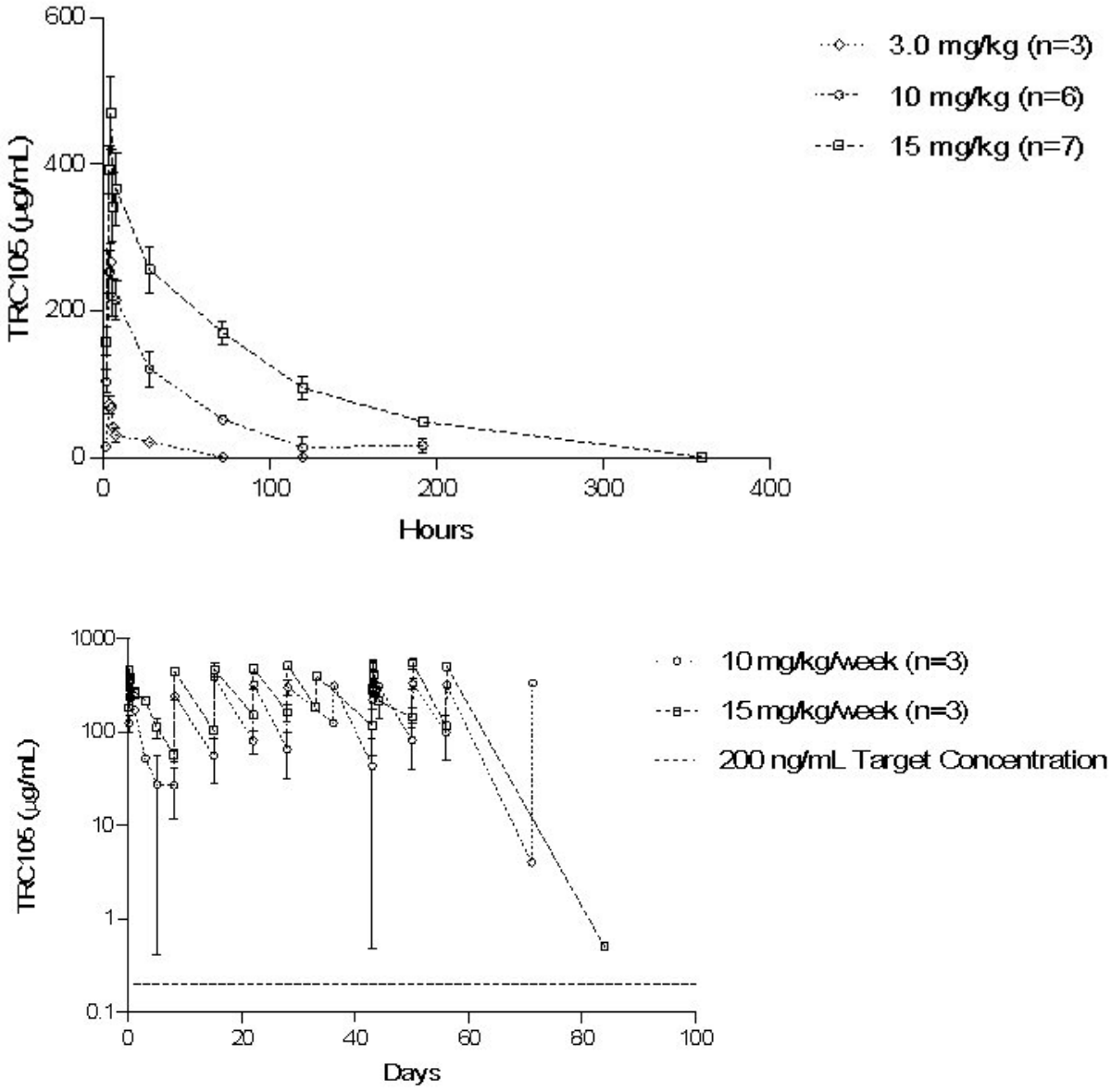
combination with axitinib in renal cell carcinoma, a phase 1b study of TRC105 in combination with pazopanib and a phase 1b study of TRC105 in combination with bevacizumab in glioblastoma multiforme.

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 1).

Figure 1: 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. Three of 4 patients at 15 mg/kg weekly developed grade 3 hypoproliferative anemia (without leucopenia or thrombocytopenia) in cycle 2, and one of the three progressed to grade 4 in cycle 3. Anemia was associated with accumulation of TRC105 and characterized by a low reticulocyte production index. Additional laboratory and clinical evaluations excluded common causes of anemia including blood loss, hemolysis, plasma volume expansion, inadequate erythropoietin, iron deficiency, and vitamin B-12 or folate deficiency. The anemia is believed to result from TRC105-mediated suppression of proerythroblasts, the only cells in the bone marrow known to express substantial levels of CD105 [47]. 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

TRC105 was studied in combination with bevacizumab in a Phase 1/2 trial that enrolled 38 patients [77].

2.2.1.2.1. 105ST102 Summary of Safety

Administration of TRC105 at a dose of 3 mg/kg weekly in combination with bevacizumab was well tolerated by three patients without the development of dose limiting toxicity (DLT) and

dose escalation occurred per the protocol to cohort 2 (6 mg/kg TR105 weekly). However, the concurrent administration of 6 mg/kg TRC105 and bevacizumab on day 1 resulted in the development of moderate or severe headaches (including two grade 3 headaches) in four of five treated patients. The 6 mg/kg dose of TRC105 was tolerated when the initial TRC105 dose was delayed one week following bevacizumab dosing at 10 mg/kg every two weeks. Tolerability was further improved when the initial dose of TRC105 was given over two days during the first week of TRC105 dosing, and dose escalation proceeded to the recommended phase 2 dose of 10 mg/kg TRC105 weekly. At the recommended phase 2 dose of both drugs (10 mg/kg), TRC105 serum concentration were present above target concentration continuously and immunogenicity was rarely observed.

A total of 38 patients were dosed on study across six cohorts and four dose levels. Other than headaches that were mitigated by adjusting the dosing schedule of TRC105, the combination of TRC105 and bevacizumab was well tolerated. Two patients experienced grade 3 serious adverse suspected events as described below. Most adverse events were graded as 1 or 2 and Grade 4 and 5 suspected adverse events were not observed. Grade 3 suspected adverse reactions included anemia (the dose limiting toxicity of TRC105 established as a single agent; 9 patients), headache (4 patients; three of which occurred prior to adjusting the schedule of TRC105), fatigue (2 patients), brain abscess (1 patient), infusion reaction (in a patient dosed at 6 mg/kg), and decreased appetite (1 patient). Headache was the most common suspected adverse event and occurred in 31 patients (86.1%); three patients (7.9%) experienced migraine headaches (two of grade 1 and one of grade 2 severity). Headaches were treated with triptans and NSAIDs.

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

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

Infusion reactions were, as expected, more notable at lower doses, and were rare at the MTD of TRC105 of 10 mg/kg, when TRC105 serum concentrations were maintained continuously. Two of nineteen patients (10%) dosed with 10 mg/kg of TRC105 each experienced a single infusion

reaction of grade 2 severity, both with the initial dose of TRC105, that required a brief interruption of the infusion prior to completion of the scheduled dose.

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

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

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

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

2.2.1.2.2. 105ST102 Summary of Efficacy

The combination of TRC105 and bevacizumab was active in patients with advanced refractory cancer who had progressed on prior bevacizumab or other VEGF inhibitor treatment. Thirty-three patients had measurable disease (31 patients) or evaluable disease (2 patients) at baseline and received at least one follow up scan and were evaluable for the primary efficacy outcome of ORR by RECIST 1.1. Eighteen patients with measureable disease (58%) had a best response of stable disease or partial response. Two patients (6%), both of whom had been treated with bevacizumab and chemotherapy prior to study entry and were then treated at the top dose level of TRC105 and bevacizumab, had RECIST 1.1- defined partial responses, including one patient with colorectal cancer who continues on treatment for more than 24 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 (19% 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 437+ days. Reductions in tumor markers ranging from 5% to 85% were observed in 15 of 28 (54%) patients with relevant tumor markers. Three patients demonstrated clinical benefit throughout the study (patient 10038102 at cycle 12 day 22, patient 10018106 at cycle 7 day 22 and patient 10028101 at cycle 17 day 1); two of them continue to receive treatment under a continuation protocol (105CON101).

2.3. Study Rationale

Given the critical role of anti-angiogenic therapy in the treatment of advanced NSCLC and the tendency of the tumor to develop escape pathways of angiogenesis when challenged with an anti-VEGF agent, investigation of dual anti-angiogenic therapy in advanced NSCLC is indicated.

Pre-clinical studies of CD105 targeted therapy have demonstrated both vascular targeting effects and anti-angiogenic effects by inducing regression of established tumors in addition to preventing new tumor growth [78-80]. TRC 105 is a genetically engineered human/murine chimeric monoclonal antibody directed against human CD-105 (endoglin) [75]. TRC-105 has been shown to enhance the anti-angiogenic effect of bevacizumab in pre-clinical models of human angiogenesis [73]. A phase I trial of TRC 105 in the advanced solid tumors demonstrated tolerability and efficacy of TRC-105 as monotherapy in the salvage setting (NCT00582985). Subsequently, several other early phase trials in patients with prostate, bladder, hepatocellular, glioblastoma, and ovarian cancer are either underway or have completed.

Most recently, a phase 1b study, the combination of TRC105 and bevacizumab produced radiographic reductions in tumor volume in bevacizumab-refractory patients, and was well tolerated. TRC105 was also well tolerated with chemotherapy in a trial with capecitabine in breast cancer patients [81]. By targeting an essential non-VEGF pathway that is upregulated following VEGF inhibition, the combination of TRC105 and bevacizumab has the potential to provide clinical benefit through the inhibition of two major driving pathways of tumor angiogenesis.

This trial is a phase 1b dose escalation study of TRC105 in combination with standard dose bevacizumab, paclitaxel and carboplatin for treatment-naive patients with stage IV non-squamous NSCLC in order to assess the safety and efficacy of CD105 blockade combined with bevacizumab, paclitaxel and carboplatin. A standard "3+3" dose- escalation design of patients with advanced solid tumors will be employed, followed by an expanded cohort to further assess the safety and tolerability of the recommended phase 2 dose (RPTD) of TRC105. The purpose of the dose escalation portion is to determine the maximum tolerated dose (MTD) of TRC105 when given in combination with bevacizumab, paclitaxel and carboplatin and to determine the dose limiting toxicities.

Patients will be treated with induction therapy with carboplatin, paclitaxel, bevacizumab, and TRC105 for a maximum of 6 cycles of therapy. Patients who demonstrate a response of CR, PR or SD, after the end of the induction therapy are eligible for maintenance therapy with bevacizumab and TRC105 until disease progression, unacceptable toxicity or withdrawal of consent, or other reasons. Patients who are not able to receive more than 4 cycles of induction therapy because significant and persistent > grade 2 neurotoxicity related to paclitaxel may be eligible for maintenance therapy (i.e., TRC105 + bevacizumab alone) if there is no evidence of progressive disease after 4 cycles of induction therapy. Patients may be scanned early at the end of cycle 4 to determine disease status.

2.4. Population to be Studied

Patients with stage 4 Non-Squamous Cell Lung Cancer who have not been treated previously with systemic chemotherapy or bevacizumab but may have received prior targeted treatment (e.g., alk1 inhibitor).

2.5. Potential Risks and Benefits to Human Patients

2.5.1. Potential Risks

TRC105

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

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

Grade 1 and 2 cutaneous telangiectasia related to TRC105 occur early in the course of therapy and have been the source of gingival bleeding and epistaxis. Telangiectasia are also seen in patients with hereditary hemorrhagic telangiectasia (HHT), a disease of CD105 haplotype insufficiency. Patients with HHT are at risk of hemorrhage from abnormal blood vessels and this could be exacerbated by treatment with TRC105. Other contraindications to TRC105 therapy include a history of significant hemorrhage or tumors located in the central chest or another location where bleeding is associated with high morbidity. All patients treated with TRC105 should be monitored for signs of hemorrhage and the risks and benefits of drug treatment reevaluated in any patient with hemorrhage.

Premedication including the use of glucocorticoids is required prior to infusion of TRC105 to reduce the frequency and severity of infusion reactions. Infusion reactions following TRC105 dosing generally occur with the first TRC105 dose and include a grade 4 vasovagal reaction that resolved without 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. Patients must have a platelet count of > 100,000/uL to enter this study (see inclusion criteria). A grade 2 transient ischemic attack was reported in a study of TRC105 and pazopanib. Transient Grade 3 hepatic encephalopathy occurred in one patient with cirrhosis and hepatocellular carcinoma who received TRC105 in

combination with sorafenib. 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.

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

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

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

Infections have been observed rarely. Grade 3 infected lipoma/cyst was observed in a Phase 2 study of TRC105 as a single agent in patients with metastatic bladder cancer. Grade 3 orbital cellulitis and grade 3 brain abscess were observed in patients treated with TRC105 and bevacizumab and considered possibly related to TRC105. Grade 1 and 2 gingivitis including infection and ulceration has also been observed. Overall, infections have been observed in fewer than 5% of patients and have largely been considered unrelated to treatment with TRC105.

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

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

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

<u>Paclitaxel</u>

Side effects associated with the use of paclitaxel are bone marrow suppression, hypersensitivity reactions, hypotension, ECG abnormalities, peripheral neuropathy, arthralgia/myalgia, liver function abnormalities, nausea, vomiting, diarrhea, mucositis, alopecia and edema.

Further details are available in the package insert [82].

Carboplatin

Side effects associated with the use of carboplatin are bone marrow suppression (leukopenia, neutropenia, and thrombocytopenia) which is dose-dependent and a dose limiting toxicity. Carboplatin can induce emesis, which can be more severe in patients previously receiving emetogenic therapy. Allergic reactions to carboplatin have been reported. These may occur within minutes of administration and should be managed with appropriate supportive therapy. There is increased risk of allergic reactions including anaphylaxis in patients previously exposed to platinum therapy. Carboplatin may cause fetal harm when administered to a pregnant woman. Carboplatin has been shown to be embryotoxic and teratogenic in rats. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Further details are available in the package insert [83].

Bevacizumab

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

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

Further details are available in the package insert [84].

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-induce nephrogenic systemic fibrosis in patients with poor renal function.

Venipuncture

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

Other Risks

This study treatment may involve risks to unborn children therefore patients should not become pregnant or father a baby while participating in this study. Patients should not nurse while on this study. Women of childbearing potential must have a negative pregnancy test before taking part in this study. 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 methods of effective and highly reliable methods of contraception at the same time [i.e., tubal sterilization (tubes tied), partner's vasectomy, intra-uterine device (IUD), male latex condom with or without spermicide, diaphragm with spermicide, cervical cap with spermicide, vaginal sponge (contains spermicide)] during study treatment (including during temporary breaks from treatment), and for at least 180 days after stopping TRC105, bevacizumab, paclitaxel, and/or carboplatin treatment. Men must agree to use two effective and highly reliable methods of contraception at the same time [i.e., vasectomy, male latex condom with or without spermicide, partner's tubal sterilization (tubes tied), partner's use of intra-uterine device (IUD), partner's use of diaphragm with spermicide, cervical cap with spermicide, vaginal sponge (contains spermicide)] during study treatment (including temporary breaks from treatment), and for at least 180 days after stopping TRC105, bevacizumab, paclitaxel, and/or carboplatin. The long term risk of infertility is unknown. Ovarian failure has been observed with other antiangiogenic agents.

2.5.2. Potential Benefits

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

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

2.6.1. Justification

The dose and schedule of TRC105 (8 mg/kg weekly up to 10 mg/kg weekly) were selected based on safety, pharmacokinetics and early evidence of activity in the phase 1 study of TRC105 for patients with solid tumors (Study 105ST101) and in the phase 1b study of TRC105 with bevacizumab. In phase 1, a weekly dose of 10 mg/kg was well tolerated and associated with clinical activity. Dose reduction was possible for treatment of anemia. Doses of 8 and 10 mg/kg were tolerated in combination with bevacizumab without the development of severe toxicity.

Notably, while the initial schedule of TRC105 was adjusted to decrease the frequency of headaches, there was no potentiation of life threatening toxicities associated with bevacizumab, nor potentiation of common VEGF inhibitor toxicities (e.g., hypertension and proteinuria).

Additionally, doses of 8 and 10 mg/kg of TRC105 were tolerated in combination with standard axitinib and pazopanib, without the development of severe toxicity in their respective studies.

Given the limited experience dosing TRC105 with VEGF inhibitors and chemotherapy, it is possible that TRC105 toxicities will potentiate bevacizumab, paclitaxel, and carboplatin toxicities, and vice versa. Therefore a TRC105 starting dose of 8 mg/kg weekly, which is 20% lower than the single-agent TRC105 MTD identified in the phase 1 single agent study and phase 1b studies with bevacizumab, pazopanib and axitinib was selected. In addition a 6 mg/kg (-1) dose level has also been included and will be enrolled should 8 mg/kg of TRC105 in combination with bevacizumab and paclitaxel and carboplatin exceed the MTD. As an added precaution, the first dose of TRC105 will be delayed by one (1) week following bevacizumab, paclitaxel, and carboplatin dosing and administered over 2 days. This administration schedule will limit immediate C_{max} effects of the combination of three drugs that could result in toxicity.

2.7. Conduct

The 105LC101 clinical trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirements.

3. TRIAL OBJECTIVES AND PURPOSE

3.1. Objectives

3.1.1. Purpose

The purpose of this study is to evaluate the safety and effectiveness of TRC105 in combination with bevacizumab, paclitaxel and carboplatin.

3.1.2. Primary objectives

- To evaluate safety and tolerability and determine a recommended phase 2 dose for TRC105 when added to standard dose bevacizumab and paclitaxel/carboplatin in treatment-naive patients with stage IV non-squamous NSCLC

3.1.3. Secondary objectives

- To assess preliminary evidence of antitumor activity when TRC105 is added to bevacizumab and paclitaxel/carboplatin, by assessing objective response rate, median progression-free survival, the proportion (%) of patients progression-free at 6 months, and the overall survival
- To characterize the pharmacokinetic profile of TRC105 when given with bevacizumab and paclitaxel/carboplatin
- To evaluate TRC105 Anti-Product Antibodies
- To explore pharmacodynamic effects on circulating angiogenic biomarkers

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

4.1.1. Overview

All patients must sign a consent form prior to undertaking any study-related procedures. Prospective patients will be screened to determine if they qualify for the study within 28 days of enrollment. Toxicities will be graded according to the NCI CTCAE Version 4.0.

4.1.1.1. Overview

This is a single center, open-label, nonrandomized, phase 1b, and dose-finding study of TRC105 in combination with standard dose bevacizumab, paclitaxel and carboplatin in treatment-naive patients with stage IV non-squamous NSCLC. Patients will be treated with induction therapy with carboplatin, paclitaxel, bevacizumab, and TRC105 for a maximum of 6 cycles of therapy. Patients who demonstrate a response of CR, PR or SD, after the end of the induction therapy are eligible for maintenance therapy with bevacizumab and TRC105 until disease progression, unacceptable toxicity or withdrawal of consent, or other reasons.

Escalating doses of i.v. TRC105 will be administered weekly beginning with Dose Level 1 in combination with bevacizumab 15 mg/kg intravenously every 3 weeks and paclitaxel 200 mg/m^2 and Carboplatin 6 AUC administered intravenously on day 1 of each 21 day cycle (see TRC105 Administration Section 6.1.6, Bevacizumab Dosing see Section 6.2.6 and Paclitaxel Dosing see Section 6.3.6 and Carboplatin Dosing see Section 6.4.6). Intermediate TRC105 doses (below the MTD established during the trial) may be explored based upon clinical, PK, and/or biomarker data.

Level	Number of Evaluable Subjects	Bevacizumab mg/kg IV every 3 weeks	Paclitaxel mg/m^2 IV every 3 weeks	Carboplatin AUC IV every 3 weeks	TRC105 mg/kg IV, weekly (beginning cycle 1 day 8)[a]
-1	3-6	15	200	6	6
1 (starting dose)	3-6	15	200	6	8
2	3-6	15	200	6	10
Expanded Cohort	9-12 (up to 15 total at the MTD)	15	200	6	MTD

[a]The first weekly TRC105 dose will be split into two doses whereby 3 mg/kg is administered on cycle 1 day 8 and the balance is administered on cycle 1 day 11.

Patients will receive 200 mg/m^2 of paclitaxel every 3 weeks beginning with cycle 1 day 1 for 6 cycles, AUC of 6 of carboplatin every 3 weeks beginning with cycle 1 day 1 for 6 cycles and 15 mg/kg of bevacizumab every 3 weeks beginning with cycle 1 day 1 until progression. TRC105

dosing will begin at 8 mg/kg (Dose Level 1) on cycle 1 day 8 and weekly thereafter until progression. A -1 Dose Level has also been included (6 mg/kg) and will be enrolled if 8 mg/kg TRC105 dosed with bevacizumab, paclitaxel and carboplatin exceeds the MTD. The DLT evaluation period, for purposes of dose expansion, will be the first 6 weeks (42 days) of dosing bevacizumab, paclitaxel, carboplatin and TRC105 (e.g., from cycle 1 day 1 through cycle 2 day 21). Each cycle will be 3 weeks (21 days) in duration.

Three patients will be initially enrolled and treated at each dose level. If none of these 3 patients experiences a dose-limiting toxicity (DLT) during the initial 42-day evaluation period when all drugs are dosed together (extending from cycle 1 day 1 through cycle 2 day 21), dose escalation will proceed following review of safety data with site staff including the principal investigator at the clinical site.

If 1 of 3 patients experiences DLT, the dose level will be expanded to 6 patients. The maximum tolerated dose (MTD) will have been exceeded if ≥ 33% of patients experience DLT at a given dose level. DLT will have occurred when a patient has 1 or more toxicity listed in the table below that is at least possibly related to the combination of bevacizumab, paclitaxel, carboplatin and TRC105 during the first 42 days of concomitant dosing. Patients who exit the study for reasons other than DLT prior to completion of the 42-day DLT evaluation period will be replaced to ensure an adequate safety assessment in each cohort. Patients who experience DLT who receive less than the prescribed dose of TRC105 or bevacizumab, paclitaxel or carboplatin due to documented toxicity during the DLT evaluation period will be considered evaluable for dose escalation purposes. A given TRC105 dose level may be reenrolled at an intermediate dose level upon agreement of study investigators.

Up to 15 treatment-naive patients with stage IV non-squamous NSCLC will be treated at the MTD (or top dose level if a MTD is not determined) to further characterize safety and tolerability.

Table 3: Dose Limiting Toxicity Definition and Criteria

Toxicity Category	**Drug-Related Toxicity/Grade**
Hematologic	**Any Grade 4 toxicity**
	Neutropenic infection: grade ≥ 3 neutropenia with grade ≥ 3 infection
	Grade ≥ 3 thrombocytopenia and grade ≥ 3 hemorrhage
Nonhematologic	**Grade 3 toxicity with the following exceptions:** • **Nausea, vomiting or diarrhea for < 48 hours[a]** • **Asymptomatic electrolyte abnormalities that are corrected to grade 1 or better in < 72 hours[b]**
	Any Grade 4 toxicity

[a]Patients with related grade 3 or 4 diarrhea, nausea or vomiting for ≥ 48 hours despite optimal medical therapy will require a one-level dose-reduction of TRC105.

Toxicity Category	Drug-Related Toxicity/Grade
Hematologic	**Any Grade 4 toxicity**
	Neutropenic infection: grade ≥ 3 neutropenia with grade ≥ 3 infection
	Grade ≥ 3 thrombocytopenia and grade ≥ 3 hemorrhage
Nonhematologic	**Grade 3 toxicity with the following exceptions:** • **Nausea, vomiting or diarrhea for < 48 hours[a]** • **Asymptomatic electrolyte abnormalities that are corrected to grade 1 or better in < 72 hours[b]**
	Any Grade 4 toxicity

[b]Patients with related grade 3 or 4 electrolyte abnormalities that persist for ≥ 72 hours will require a one-level dose-reduction of TRC105

4.1.2. Trial Procedures

All on-study procedures are permitted within the time window indicated in the Schedule of Assessments (Table 4).

4.1.2.1. Screening

The following screening procedures must be performed within 28 days prior to the first day of study therapy. Qualifying hematology (including Fe studies), serum chemistry (including TSH testing), coagulation, physical examination, ECG, pregnancy 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).

- Patient signature on current Institutional Review Board (IRB) approved informed consent form. Prior to undergoing any study-specific procedure, patients must read and sign the current Institutional Review Board (IRB) approved informed consent form. Patients may sign consent prior to the 28 day screening period.
- Medical history, baseline signs and symptoms, prior cancer therapy, prior cancer surgery, prior radiation therapy, drug allergies, 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 (INR) and serum chemistry (including thyroid stimulating hormone (TSH)) to be performed locally.
- Serum or urine pregnancy test for all females of childbearing potential to be performed locally.

- Urinalysis to be performed locally. Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated.
- CT or MRI scans of chest, abdomen and pelvis in addition to any other applicable sites of disease. Brain and bone scans to be performed if metastasis is suspected prior to starting the study.
- Single tracing 12-Lead ECG (QT, PR and QRS intervals and heart rate will be captured).
- Assessment of concomitant medications and treatments from 28 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. It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 20 unstained slides are requested for immunohistochemical analysis (sections of ~ 5 microns are preferred). See separate laboratory guide for further collection and shipment information

4.1.2.2. Trial Period

Qualifying hematology (including Fe studies), blood chemistry (including TSH testing), coagulation, urinalysis, physical examination, ECG, and pregnancy test do not need to be repeated on cycle 1 day 1 if acceptable screening assessments are performed within 7 days prior to the start of study therapy. On days of dosing, all assessments should be performed prior to dosing with TRC105 unless otherwise indicated in the Schedule of Assessments. Patients will receive 3 cycles (approximately 9 weeks) of treatment. Patients will be treated with induction therapy with carboplatin, paclitaxel, bevacizumab, and TRC105 for a maximum of 6 cycles of therapy. Patients who demonstrate a response of CR, PR or SD, after the end of the induction therapy are eligible for maintenance therapy with bevacizumab and TRC105 until disease progression, unacceptable toxicity or withdrawal of consent, or other reasons. Each cycle is 3 weeks in duration. The following will be performed according to the Schedule of Assessments (Table 4).

- Physical examination including examination of all major body systems, ECOG performance status, weight and vital signs (heart rate, temperature, blood pressure, respiratory rate).
    - Assessment of vital signs during TRC105 infusion: Vital signs are to be assessed pre-infusion (i.e., within 30 minutes of starting the infusion), every 30 minutes during the infusion (+/- 15 minutes), and at the end of the infusion (i.e., within 30 minutes after completing the infusion). Vital signs should be monitored more frequently and/or beyond the completion of the infusion if medically indicated (e.g. if the patient experiences an infusion reaction that has not yet resolved).
- Hematology, coagulation (INR) and serum chemistry (including TSH) to be performed locally.
- Single tracing 12-Lead ECG (QT, PR and QRS intervals and heart rate will be captured).

- Urinalysis to be performed locally. Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated.
- Blood sampling for TRC105 pharmacokinetics will include a pre-infusion trough sample to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection times, procedures, processing, storage and shipment).
- Blood sampling for immunogenicity to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).
- Blood sampling for protein biomarker analysis by a third party laboratory (see laboratory manual for specific instructions regarding collection processing, storage and shipment)
- CT or MRI scans of chest, abdomen and/or pelvis in addition to any other applicable sites of disease. Scan of the chest, abdomen, and pelvis to be performed on-study as outlined in the assessment table. Known areas of disease should be consistently followed throughout the study. Assessments should be performed whenever disease progression is suspected. Allowable window for tumor imaging studies is +/- 7 days. Brain and bone scans to be performed if metastasis is suspected prior to starting the study and during study conduct.
- Administration of TRC105. TRC105 diluted in normal saline will be administered as a 1 to 4 hour infusion (+/- 15 minutes) on day 1, day 8, day 15 of each 21 day cycle following premedication (see Section 6.1.6) for all cycles except cycle 1. The first TRC105 dose will be split into two doses such that 3 mg/kg is administered on cycle 1 day 8, and the balance is administered on cycle 1 day 11. The entire weekly dose of TRC105 (6, 8 or 10 mg/kg) is then given on cycle 1 day 15 and weekly thereafter (e.g., if TRC105 is given at 3 mg/kg on cycle 1 day 8 and at 5 mg/kg on cycle 1 day 11, then 8 mg/kg is given on cycle 1 day 15). 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. Duration of infusion administration may be increased as medically necessary.
- Bevacizumab dosing. Administer 15 mg/kg as an intravenous infusion on day 1 of every 3 week cycle until disease progression, as described in the package insert.
- Paclitaxel dosing. Administer 200 mg/m² as an intravenous infusion, on day 1 of every 3 week cycle for 6 cycles, as described in the package insert.
- Carboplatin dosing: Administer AUC of 6 as intravenous infusion, on day 1 of every 3 week cycle for 6 cycles, as described in the package insert.
- Assessment of adverse events.
- Assessment of concomitant medications and concomitant treatments.

4.1.3. End of Study Assessments

Assessments other than TRC105 pharmacokinetics, immunogenicity and protein biomarkers only need to be completed if they were not completed during the previous 2 weeks on study (during

the last 8 weeks on study for radiologic tumor assessments). The following will be performed according to the Schedule of Assessments (Table 4).

- Physical examination including examination of all major body systems, ECOG performance status, and vital signs.
- Single tracing 12-Lead ECG (QT, PR and QRS intervals and heart rate will be captured).
- Hematology, and serum chemistry (including 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 TRC105 pharmacokinetics to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection times, procedures, processing, storage and shipment).
- Blood sampling for immunogenicity to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).
- Blood sampling for protein biomarker analysis by a third party laboratory (see laboratory manual for specific instructions regarding collection processing, storage and shipment)
- CT or MRI scans of chest, abdomen and pelvis in addition to any other applicable sites of disease.
- Assessment of adverse events.
- Assessment of concomitant medications and concomitant treatments.

4.1.4. Post Treatment Follow-up

The following will be performed according to the Schedule of Assessments (Table 4). Samples should be collected and assessments performed even if new anti-cancer therapy commences during the follow-up period.

- Assessment of adverse events. The Investigator should continue to report any related or possibly related adverse events that occur beyond the adverse event reporting period.
- Blood sampling for TRC105 pharmacokinetics to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).
- Blood sampling for immunogenicity to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).
- Assessment of concomitant medications and concomitant treatments.
- Serum or urine pregnancy test for all females of childbearing potential to be performed locally.

Table 4: Schedule of Assessments

Protocol Activities	Screening	Cycle 1 [25]				Cycles 2 & 3 [26]			Cycle 4+ Responding Patients[23] [25]			End of Study [3]	28 Day Follow-up [24]
	Day -28	Day 1 [1]	Day 8 [1]	Day 11 [1]	Day 15 [1]	Day 1 [1]	Day 8 [1]	Day 15 [1]	Day 1 [1]	Day 8 [1]	Day 15 [1]		
Baseline Documentation													
Informed Consent [4]	X												
Medical/Oncology History [5]	X												
Baseline Signs and Symptoms [5]	X												
Physical Examination [6]	X	X				X			X			X	
Vital Signs [7]	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Studies													
Hematology [8]	X+Fe	X+Fe			X	X			X			X	
Coagulation [8]	X	X											
Blood Chemistry [8]	X+TSH	X + TSH			X	X + TSH			X + TSH			X + TSH	
Pregnancy Test [9]	X	X											X
Urinalysis [10]	X	X				X			X			X	
Treatment w/ Study Drug													
TRC105 Dosing [11]			X Split	X Split	X	X	X	X	X	X	X		
Bevacizumab [12]		X				X			X				
Paclitaxel [13]		X				X			X				
Carboplatin [14]		X				X			X				
Tumor Assessments													
CT or MRI Scans [15]	X							Cycle 3			Cycles 6. 9. 12. Etc.	X	
Other Clinical Assessments													
12-Lead ECG [16]	X	X			X							X	
Concomitant Medications/Treatments [17]	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events [18]		X	X	X	X	X	X	X	X	X	X	X	X
Special Laboratory Assessments													
APA [19]		X				Cycle 3			Cycles 6. 9. 12. Etc.			X	X
Protein Biomarkers [20]		X				Cycle 3			Cycles 6. 9. 12. Etc.			X	
TRC105 PK Pre-Dose [21]			X			Cycle 3			Cycles 6. 9. 12. Etc.				
Archival Tumor Tissue [22]	X												

Schedule of Assessments Footnotes

1. **Days of Treatment with TRC105:** All assessments should be performed prior to the TRC105 infusion unless otherwise indicated. Each cycle is 21 days in duration.
2. **Cycle 1 day 1:** Hematology (including iron studies), blood chemistry (including TSH testing), urinalysis, physical examination, ECG and pregnancy test not required if acceptable screening assessment is performed within 7 days prior to the start of treatment on cycle 1 day 1.
3. **End of Study:** The end of study visit should generally occur within 7 days (+/- 1 day) of the last dose of TRC105. Assessments other than PK, immunogenicity and protein biomarkers do not need to be repeated if performed within the previous 2 weeks (previous 8 weeks for radiologic tumor assessments). Follow-up visits should occur 28 days following the last dose of TRC105 study drug as outlined in the Schedule of Assessments.
4. **Informed Consent:** Must be obtained prior to undergoing any study specific procedure and may occur prior to the 28-day screening period.
5. **Medical and Oncologic History, Demographics and Baseline Signs and Symptoms:** 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.
6. **Physical Examination:** Examination of major body systems and ECOG performance status.
7. **Vital Signs:** Heart rate, temperature, blood pressure, respiratory rate, weight. Assessment during TRC105 Infusions: Vital signs are to be assessed pre-infusion (i.e., within 30 minutes of starting the infusion) every 30 minutes during the infusion (+/- 15 minutes) and at the end of the infusion (i.e. within 30 minutes after completing the infusion). Vital signs should be monitored more frequently and/or beyond the completion of the infusion if medically indicated (e.g. if the patient experiences an infusion reaction that has not yet resolved).
8. **Hematology, Chemistry & Coagulation:** Testing to be performed locally. Thyroid stimulating hormone to be tested at screening, day 1 of each cycle and at the end of study visit. Cycle 1 day 1 assessments only need to be performed if screening assessments were performed more than 7 days prior to cycle 1 day 1. Iron studies (FE) to be performed according to the schedule of assessments and as clinically indicated during the study. Lab assessments can be may be performed within 3 days prior to TRC105 dosing. In addition to the assessments scheduled for the clinical trial, patients should undergo assessment as appropriate to ensure safe treatment. See Section 8.1.1.1 for specific panel collection requirements.
9. **Pregnancy Test:** Testing to be performed locally. All female patients of childbearing potential must have a negative serum or urine pregnancy test within 7 days of cycle 1 day 1 and 28 days following the last dose of TRC105
10. **Urinalysis:** To be performed locally. Cycle 1 day 1 urinalysis only needs to be performed if screening urinalysis was performed more than 7 days prior to cycle 1 day 1. Microscopic analysis and/or urine protein creatinine ratio or 24-hour urine protein collection should be performed as clinically indicated.
11. **TRC105 Administration:** Intravenous TRC105 diluted in normal saline will be administered every 7 days. The first weekly TRC105 dose will be given on cycle 1 day 8 and split into two doses whereby 3 mg/kg is administered on cycle 1 day 8 and the balance is administered on cycle 1 day 11. The entire weekly dose of TRC105 (6, 8 or 10 mg/kg) is then given on cycle 1 day 15 and weekly thereafter. See Section 6.1.6 for specific TRC105 administration guidelines.
12. **Bevacizumab Dosing:** Intravenous bevacizumab at a dose of 15 mg/kg diluted in normal saline will be administered on day 1 of every 3 week cycle, starting on cycle 1 day 1 as described in the package insert. See Section 6.2 for specific dosing guidelines.
13. **Paclitaxel Dosing:** Intravenous paclitaxel at a dose of 200 mg/m² diluted in 0.9% Sodium Chloride Injection, USP, to a final concentration of 0.3 to 1.2 mg/mL, will be administered on day 1 of each 3 week cycle for 6 cycles, starting on cycle 1 day 1. See Section 6.3.6 for specific dosing guidelines.
14. **Carboplatin Dosing:** Intravenous carboplatin a dose of 6 AUC will be administered on day 1 of each 3 week cycle for 6 cycles, starting on cycle 1 day 1. See Section 6.4.6 for specific dosing guidelines.

15. **CT or MRI Tumor Imaging:** Images of the chest, abdomen, and pelvis to be performed at screening, and on-study as outlined in the assessment table. Known areas of disease should be consistently followed throughout the study. Assessments should be performed whenever disease progression is suspected. Allowable window for tumor imaging studies is +/- 7 days. Brain and bone scans are to be performed if metastases are suspected at screening or during study therapy. Patients who are not able to receive more than 4 cycles of induction therapy because significant and persistent > grade 2 neurotoxicity related to paclitaxel may be scanned early (i.e., at the end of cycle 4) to rule out disease progression and allow for study continuation on maintenance therapy (i.e., TRC105 + bevacizumab alone).
16. **12-Lead ECG:** Single tracing 12-lead ECG will be performed at screening and at the time-points indicated in the Schedule of Assessments (pre-dose). If the patient develops an arrhythmia, the ECG should be repeated on day 1 of each subsequent cycle. For a QTc >500 ms, the ECG should be evaluated by a cardiologist at the site for confirmation. Additional ECGs may be performed on study as clinically indicated.
17. **Concomitant Medications and Treatments:** Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 28 days following the last dose of study treatment. Required TRC105 premedications should be recorded on TRC105 premedications CRF.
18. **Adverse Events:** Patients must be followed for adverse events from the first day of treatment with paclitaxel or carboplatin or bevacizumab or TRC105 study drug until at least 28 days after the last dose of TRC105 or bevacizumab or paclitaxel or carboplatin study drug treatment, or until all serious or TRC105 related toxicities have resolved or are determined to be “chronic” or “stable”, whichever is later. "Baseline-signs and symptoms” will be recorded from the date of informed consent on corresponding case report forms. Any serious AE that is possibly related to TRC105 occurring from the time of first TRC105 dose or at any point after the reporting period must be promptly reported to TRACON.
19. **Anti-product antibody:** 5 mL blood sample will be collected to assess anti-product antibody at the time-points indicated in the schedule of assessments and stored at approximately -70°C to be analysed by a central laboratory. Samples will be batch shipped as indicated in the laboratory manual to a third-party laboratory. See separate laboratory guide for further collection and shipment information. Additional samples may also be collected at the time of unexpected clinical events.
20. **Protein Biomarkers:** One 10 mL purple top (K_3EDTA) tube will be collected at the time-points indicated in the schedule of assessments and stored at approximately -70°C to be analysed by a central laboratory. See separate laboratory guide for further collection and shipment information.
21. **TRC105 Pharmacokinetics Trough Concentration**: A 5 mL 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. Samples will be batch shipped as indicated in the laboratory manual to a third-party laboratory. See separate laboratory guide for further collection and shipment information. Additional PK samples may also be collected at the time of unexpected clinical events.
22. **Archival Tumor Tissue:** Archival specimens (formalin-fixed, paraffin-embedded) are required of the primary cancer and/or metastatic cancer specimen for each study participant. It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 20 unstained slides are requested for immunohistochemical analysis (sections of 5 microns are preferred). See separate laboratory guide for further collection and shipment information.
23. **Cycle 4+ Treatment:** Patients who demonstrate a response of CR, PR or SD will be eligible for additional treatment until progression.
24. **Follow-up:** The follow-up visit should occur 28 days following the last dose of TRC105. The allowable visit window is +/- 7 days.
25. **Visit Windows:** Allowable window for each visit within the cycle is +/- 2 days unless otherwise stated.

5. SELECTION AND WITHDRAWAL OF PATIENTS

5.1. Patient Inclusion Criteria

1. Stage 4 Non-Squamous Cell Lung Cancer that has not been treated previously with systemic chemotherapy or bevacizumab, but may have received prior targeted treatment (e.g., alk1 inhibitor)
2. Measurable disease by RECIST
3. Age of 18 years or older
4. ECOG performance status ≤ 1
5. Resolution of all acute adverse events resulting from prior cancer therapies to NCI CTCAE grade ≤ 1 or baseline (except alopecia or neuropathy)
6. 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 28 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
   - ≤ 1+ proteinuria
   - INR from 0.8 to 1.2
7. Willingness and ability to consent for self to participate in study
8. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures
9. Men who are sterile (including vasectomy confirmed by post vasectomy semen analysis) OR agree to use at least two forms of a reliable and highly effective method of birth control (refer to section 2.5.1) and to not donate sperm and for at least 180 days following last dose of TRC105, bevacizumab, paclitaxel, and/or carboplatin
10. 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, OR woman of child bearing potential who test negative for pregnancy at time of enrollment based on serum pregnancy test and agree to use at least 2 forms

of a reliable and highly effective method of birth control (refer to Section 2.5.1) during the study and for at least 180 days after stopping TRC105, bevacizumab, paclitaxel, and/or carboplatin

5.2. Exclusion Criteria

1. Non-small cell lung cancer of squamous histology
2. Prior treatment with TRC105
3. Current treatment on another therapeutic clinical trial
4. Receipt of a small molecule anticancer agent, including an investigational anticancer small molecule, within 14 days of starting study treatment
5. Receipt of a large molecule anticancer agent (e.g., antibody), including an investigational anticancer antibody, within 28 days of starting study treatment
6. No major surgical procedure or significant traumatic injury within 6 weeks prior to study registration, and must have 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
7. 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 study registration or those patients who have not recovered adequately from side effects of such therapy
8. 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 < 140/90 mm Hg)
9. 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 at least 28 days
10. 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 anticoagulated without the use of warfarin for at least 2 weeks. In this situation, low molecular weight heparin is preferred.
11. Active bleeding or pathologic condition that carries a high risk of bleeding (e.g. hereditary hemorrhagic telangiectasia). Patients who have been uneventfully anti-coagulated with low molecular weight heparin are eligible.

12. Thrombolytic use (except to maintain i.v. catheters) or anticoagulant use within 10 days prior to first day of study therapy
13. Cardiac dysrhythmias of NCI CTCAE grade ≥ 2 within the last 28 days
14. Known active viral or nonviral hepatitis or cirrhosis
15. History of hemorrhage or hemoptysis (> ½ teaspoon bright red blood) within 3 months of starting study treatment
16. History of peptic ulcer disease or erosive gastritis within the past 3 months, unless treated for the condition and complete resolution has been documented by esophagogastroduodenoscopy (EGD) within 28 days of starting study treatment
17. 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)
18. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness
19. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for this study

5.3. Patient Withdrawal Criteria

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

1. RECIST 1.1-defined disease progression. In cases where RECIST cannot be applied, progression should be based on unequivocal evidence of progressive disease sufficient to require a change in therapy.
2. A need for surgery, radiation, or for other anticancer therapy not specified in the protocol.
3. Lost to follow-up or noncompliant.
4. Any TRC105 dose delay > 14 days, other than a dose delay for planned surgery or hematologic toxicity, in which case up to 6 weeks is allowed.
5. Pregnancy. Pregnant patients should be followed for the duration of the pregnancy and the outcome of the pregnancy should be documented.

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.

6.1.1. 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.

6.1.2. TRC105 Dose Level

Each patient will be dosed with 6, 8 or 10 mg/kg up to a **maximum dose of 850 mg of TRC105 for women and 1,000 mg of TRC105 for men (i.e., 85 kg for women and 100 kg for men is the maximum weight that should be used for purposes of dose calculation on this study).** TRC105 is distributed according to lean body mass rather than overall body weight. Patients who are overweight would be at risk for high serum levels of TRC105 if the doses were not capped. Eighty-five kg for women and 100 kg for men represent accepted maximum lean body masses for the two genders. The first weekly dose will be split into two doses whereby 3 mg/kg will be administered on cycle 1 day 8 and the balance will be administered on cycle 1 day 11. The entire weekly dose of TRC105 (6, 8 or 10 mg/kg) is then given on cycle 1 day 15 and weekly thereafter (until progression) in combination with intravenous 15 mg/kg bevacizumab every three weeks starting on cycle 1 day 1 (until progression) and intravenous 200 mg/m^2 paclitaxel every three weeks starting on cycle 1 day 1 (for 6 cycles) and intravenous carboplatin 6 AUC every three weeks starting on cycle 1 day 1 (for 6 cycles). The DLT evaluation period, for purposes of dose escalation, will be the first 42 days of dosing with all drugs (i.e., cycle 1 day 1 through cycle 2 day 21).

Each cycle will be 21 days in duration.

6.1.3. 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 TRC105/4mL single-use vial

400 mg TRC105/16mL single-use vial

6.1.4. TRC105 Storage and Shipping

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

6.1.5. 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 for women and 100 kg for men (note: there is not a weight restriction for enrollment purposes).** If the patient's weight changes by > 10% during the study, the dose of TRC105 will be recalculated. At that time a new baseline weight will be established such that subsequent weight changes by >10% from the new baseline weight would require further recalculation of the TRC105 dose. The calculated volume of TRC105 will be diluted with normal saline. Appropriate judgment should be exercised in withdrawing an adequate amount of saline necessary to permit injection of the appropriate volume of antibody into a normal saline bag in accordance with the dose needed. The final TRC105 concentration must be between 0.3 mg/mL and 10 mg/mL. The prepared TRC105 must be gently inverted several times in order to ensure a homogeneous solution. The diluted infusion solution of TRC105 should be used within 8 hours of preparation if stored at room temperature, or within 24 hours of dilution if stored at 2 ° to 8 °C (36 to 46 ºF). 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.

6.1.6. TRC105 Administration

Dosing will occur in the following order on day 1 of each cycle (Note: TRC105 is NOT dosed on cycle 1 day 1):

- Pre-medications
- Paclitaxel 200 mg/kg (3 hour IV infusion) (for 6 cycles)
- Carboplatin AUC of 6 (30 to 60 minutes IV infusion) (for 6 cycles)
- Bevacizumab 15 mg/kg (30 minute IV infusion) (until progression)
- TRC105 10 mg/kg – (1 to 4 hour IV infusion) (until progression)

TRC105 infusions will be given weekly until progression. TRC105 will be dosed alone on days 8 and 15 of each cycle following appropriate pre-medication (note: TRC105 will be held on cycle 1 day 1, the first dose will be given on cycle 1 day 8 and split over two days whereby 3 mg/kg is given on cycle 1 day 8 and the remainder is give on cycle 1 day 11).

Patients should be encouraged to drink abundant fluid (e.g., two eight ounce glasses of water or juice) prior to the first treatment. Intravenous hydration prior to and during therapy is left to the discretion of the Investigator, but should be considered for patients that may be volume depleted.

The following TRC105 premedications, including the dexamethasone infusion, should be completed 2 hours to 30 minutes prior to initiating Paclitaxel infusions (on days of Paclitaxel dosing) or TRC105 infusions (all other dosing days where TRC105 is given):

Table 5: Cycle 1 Premedication Regimen

	Day 1	**Day 8**	**Day 11**	**Day 15**
Acetaminophen 650 mg p.o. x 1	Yes	Yes	Yes	Yes
Dexamethasone 20 mg i.v. x 1	Yes	Yes	Yes	Given if the patient develops an infusion reaction ≥ grade 2 during the immediate prior TRC105 infusion
Famotidine 20 mg i.v. or p.o. (or similar H2 blocker) x 1	Yes	Yes	Yes	Yes
Cetirizine 10 mg i.v. or p.o. x 1 (or similar oral or intravenous antihistamine)	Yes	Yes	Yes	Yes

Table 6: Cycle 2 through Cycle 6 Premedication Regimen

	Day 1	**Day 8**	**Day 15**
Acetaminophen 650 mg p.o. x 1	Yes	Yes	Yes
Dexamethasone 20 mg i.v. x 1	Yes	Given in the case of a delay of > 10 days between any two TRC105 doses or if the patient develops an infusion reaction ≥ grade 2 during the immediate prior TRC105 infusion	Given in the case of a delay of > 10 days between any two TRC105 doses or if the patient develops an infusion reaction ≥ grade 2 during the immediate prior TRC105 infusion
Famotidine 20 mg i.v. or p.o. (or similar H2 blocker) x 1	Yes	Does not need to be given prior to TRC105 infusions starting with Cycle 2 in the absence of TRC105 infusion reactions with the prior dose.	Does not need to be given prior to TRC105 infusions starting with Cycle 2 in the absence of TRC105 infusion reactions with the prior dose.
Cetirizine 10 mg i.v. or p.o. x 1 (or similar oral or intravenous antihistamine)	Yes	Does not need to be given prior to TRC105 infusions starting with Cycle 2 in the absence of TRC105 infusion reactions with the prior dose.	Does not need to be given prior to TRC105 infusions starting with Cycle 2 in the absence of TRC105 infusion reactions with the prior dose.

Table 7: Cycle 7+ Premedication Regimen (TRC105 + Bevacizumab Maintenance Phase of the Protocol)

	Day 1	**Day 8**	**Day 15**
Acetaminophen 650 mg p.o. x 1	Yes	Yes	Yes
Dexamethasone 20 mg i.v. x 1	Given in the case of a delay of > 10 days between any two TRC105 doses or if the patient develops an infusion reaction ≥ grade 2 during the immediate prior TRC105 infusion	Given in the case of a delay of > 10 days between any two TRC105 doses or if the patient develops an infusion reaction ≥ grade 2 during the immediate prior TRC105 infusion	Given in the case of a delay of > 10 days between any two TRC105 doses or if the patient develops an infusion reaction ≥ grade 2 during the immediate prior TRC105 infusion
Famotidine 20 mg i.v. or p.o. (or similar H2 blocker) x 1	Does not need to be given prior to TRC105 infusions starting with Cycle 2 in the absence of TRC105 infusion reactions with the prior dose.	Does not need to be given prior to TRC105 infusions starting with Cycle 2 in the absence of TRC105 infusion reactions with the prior dose.	Does not need to be given prior to TRC105 infusions starting with Cycle 2 in the absence of TRC105 infusion reactions with the prior dose.
Cetirizine 10 mg i.v. or p.o. x 1 (or similar oral or intravenous antihistamine)	Does not need to be given prior to TRC105 infusions starting with Cycle 2 in the absence of TRC105 infusion reactions with the prior dose.	Does not need to be given prior to TRC105 infusions starting with Cycle 2 in the absence of TRC105 infusion reactions with the prior dose.	Does not need to be given prior to TRC105 infusions starting with Cycle 2 in the absence of TRC105 infusion reactions with the prior dose.

TRC105 premedication, including the dexamethasone infusion, should be completed 2 hours to 30 minutes prior to initiating Paclitaxel infusions (on days of Paclitaxel dosing) or TRC105 infusions (all other dosing days where TRC105 is given). TRC105 will be administered intravenously utilizing an infusion pump. TRC105 has been demonstrated to be compatible with polyethylene lined, non-DEHP infusion sets and polyvinyl chloride, non-DEHP infusion sets. TRC105 is required to be administered with a 0.2 micron downstream filter. The attachment of the infusion pump administration set to the i.v. bag and transport of the TRC105 study drug to the patient will be performed as per standard study site procedures.

The first weekly TRC105 dose will be split into two doses whereby 3 mg/kg is administered on cycle 1 day 8 over 4 hours (+/- 15 minutes). Do not increase the infusion rate above 25 mg/min during the Cycle 1 Day 8 dose. The remainder of the Cycle 1 Day 8 dose will be administered on Cycle 1 Day 11 (e.g., 7 mg/kg) over 2 hours (+/- 15 minutes). The full TRC105 dose (e.g., 8 mg/kg for Dose Level 1) will be administered on Cycle 1 Day 15, and weekly thereafter, over 1 hour (+/- 15 minutes). Patients must complete at least one 4 hour infusion 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 without the development of any infusion

reactions in order to reduce subsequent TRC105 infusions to 1 hour (+/- 15 minutes). Patients with infusion reactions of any kind should be managed appropriately (see Section 6.1.8) and are not permitted to reduce the duration of the next planned infusion.

The rate of TRC105 infusion must not exceed 25 mg/min. When the i.v. bag containing TRC105 is empty, flush the i.v. line with 20 mL normal saline. The dose level, time of transfer to i.v. bag, and the infusion start and stop times must be recorded in the source documents.

If a patient misses a weekly TRC105 dose (i.e., ≥ 10 days between doses), the dexamethasone dose should be reinstituted as per the initial infusion and first TRC105 dose should be administered over two days as was done for the initial dose.

6.1.7. TRC105 Dose Modification/Dose Interruptions

TRC105 dose reductions and interruptions should be avoided in cycle 1. In cycle 2 and beyond, TRC105 dose reductions are allowed for grade 3 or 4 related adverse events that resolve to grade 1 or baseline (including anemia). Any TRC105 dose delay > 14 days will require discontinuation of TRC105 treatment, other than a dose delay for planned surgery or recovery from hematologic toxicity, in which case up to 6 weeks is allowed. Treatment dose delays cannot exceed 6 consecutive weeks (i.e., dosing with all drugs held).

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

Table 8: Allowable TRC105 Dose Modifications

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

Patients with arterial thrombosis or grade 3 or 4 venous thrombosis should discontinue TRC105 and bevacizumab therapy but may remain on study on carboplatin and paclitaxel. Patients with grade 1 or 2 venous thrombosis who require anticoagulation will have their TRC105 therapy interrupted. TRC105 therapy may resume once the following criteria are met:

- The patient is on a stable dose of heparin or low molecular weight heparin.
- The patient has a platelet count > 100,000.
- The patient has not had a hemorrhagic event of grade 2 or higher while on study.
- The patient does not have a pathological condition that carries a high risk of bleeding (e.g., tumor involving major vessels).
- The patient is benefiting from TRC105 therapy (no evidence of disease progression).

6.1.8. Management of TRC105 Infusion Reactions

If a patient experiences a grade 2 or higher adverse reaction during infusion, the infusion should be interrupted and the patient treated accordingly. Antipyretic, antihistamine, antiemetic, anti-inflammatory, or other symptomatic medications including epinephrine may be administered as indicated. For grade 2 and certain grade 3 infusion reactions, the infusion may be restarted at half of the previous rate if and when the infusion reaction has resolved and then increased per patient tolerance to a maximum of 25 mg/min. For grade 4 infusion reactions, the infusion should not be restarted and the patient should be discontinued from study treatment. Infusion reactions will be recorded as AEs in the case report form. Interventions should be documented as concomitant medications or concomitant treatments as appropriate.

Table 9: 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).

6.1.9. 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.

6.1.10. TRC105 Study Drug Handling and Disposal

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

6.2. Description of Bevacizumab

See bevacizumab package insert [84].

6.2.1. Composition of Bevacizumab

See bevacizumab package insert [84].

6.2.2. Bevacizumab Dose Level

Fifteen mg/kg will be dosed every 3 weeks, starting on cycle 1 day 1, until disease progression or unacceptable toxicity [84].

6.2.3. Bevacizumab Packaging and Labeling

See bevacizumab package insert [84].

6.2.4. Bevacizumab Storage

See bevacizumab package insert [84].

6.2.5. Bevacizumab Preparation

Commercially available bevacizumab will be utilized in this study. Patients will receive 15 mg/kg on day 1 of each 3 week cycle until progression. Bevacizumab should be prepared according to the package insert [84].

6.2.6. Bevacizumab Dosing

Dosing will occur in the following order on day 1 of each cycle (Note: TRC105 is NOT dosed on cycle 1 day 1):

- Pre-medications
- Paclitaxel 200 mg/kg (3 hour IV infusion) (for 6 cycles)
- Carboplatin AUC of 6 (30 to 60 minutes IV infusion) (for 6 cycles)
- Bevacizumab 15 mg/kg (30 minute IV infusion) (until progression)
- TRC105 10 mg/kg (1 to 4 hour IV infusion) (until progression)

Do not administer as an intravenous push or bolus. Administer only as an intravenous (IV) infusion.

- Administered over 30 minutes per institutional guidelines

Do not initiate bevacizumab until at least 28 days following major surgery. Administer bevacizumab after the surgical incision has fully healed.

6.2.7. Bevacizumab Dose Modification

Dose reduction of bevacizumab for adverse reactions is not recommended. Patients with arterial thrombosis or grade 3 or 4 venous thrombosis should discontinue TRC105 and bevacizumab therapy but may remain on study on carboplatin and paclitaxel alone. If indicated, bevacizumab should either be discontinued or temporarily suspended, see bevacizumab package insert for specific information related to different adverse events [84].

6.2.8. Bevacizumab Drug Accountability

The investigator must maintain an accurate accounting of bevacizumab product that is used. During the study, the following information must be maintained:

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

6.2.9. Bevacizumab Drug Handling and Disposal

The Site Pharmacist will be responsible for documenting the destruction (according to institutional requirements) of used or expired vials.

6.3. Description of Paclitaxel

Commercially available paclitaxel will be used in this study. See paclitaxel package insert for additional information [82].

6.3.1. Composition of Paclitaxel

See paclitaxel package insert [82].

6.3.2. Paclitaxel Dose Level

Each patient will be dosed with 200 mg/m^2 paclitaxel on day 1 of each 3 week cycle, starting on cycle 1 day1 for 6 cycles.

6.3.3. Paclitaxel Packaging and Labeling

See paclitaxel package insert [82].

6.3.4. Paclitaxel Storage

See paclitaxel package insert [82].

6.3.5. Paclitaxel Preparation

Commercially available paclitaxel will be used in this study. See paclitaxel package insert for specific preparation instructions [82].

6.3.6. Paclitaxel Dosing

Dosing will occur in the following order on day 1 of each cycle (Note: TRC105 is NOT dosed on cycle 1 day 1):

- Pre-medications
- Paclitaxel 200 mg/kg (3 hour IV infusion) (for 6 cycles)
- Carboplatin AUC of 6 (30 to 60 minutes IV infusion) (for 6 cycles)
- Bevacizumab 15 mg/kg (30 minute IV infusion) (until progression)
- TRC105 10 mg/kg (1 to 4 hour IV infusion) (until progression)

Patients will be dosed with 200 mg/m^2 paclitaxel on day 1 of each 3 week cycle, starting on cycle 1 day1 for 6 cycles. Paclitaxel is to be administered as an intravenous infusion over 3 hours.

All patients should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions – see Table 5, Table 6, and Table 7 for details.

See paclitaxel package insert for additional dosing information [82].

6.3.7. Paclitaxel Dose Modification

See paclitaxel package insert [82]. Patients with arterial thrombosis or grade 3 or 4 venous thrombosis should discontinue TRC105 and bevacizumab therapy but may remain on study on carboplatin and paclitaxel alone.

6.3.8. Paclitaxel Drug Accountability

The investigator must maintain an accurate accounting of paclitaxel product that is used. During the study, the following information must be maintained:

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

6.3.9. Paclitaxel Handling and Disposal

See paclitaxel package insert [82].

The Site Pharmacist will be responsible for the destruction, according to institutional requirements, of used or partially used vials.

6.4. Description of Carboplatin

Commercially available carboplatin will be used in this study. See carboplatin package insert [83].

6.4.1. Composition of Carboplatin

See carboplatin package insert [83].

6.4.2. Carboplatin Dose Level

Each patient will be dosed with an AUC of 6 carboplatin on day 1 of each 3 week cycle, starting on cycle 1 day1 for 6 cycles.

6.4.3. Carboplatin Packaging and Labeling

See carboplatin package insert [83].

6.4.4. Carboplatin Storage

See carboplatin package insert [83].

6.4.5. Carboplatin Preparation

See carboplatin package insert [83].

6.4.6. Carboplatin Dosing

Dosing will occur in the following order on day 1 of each cycle (Note: TRC105 is NOT dosed on cycle 1 day 1):

- Pre-medications
- Paclitaxel 200 mg/kg (3 hour IV infusion) (for 6 cycles)
- Carboplatin AUC of 6 (30 to 60 minutes IV infusion) (for 6 cycles)
- Bevacizumab 15 mg/kg (30 minute IV infusion) (until progression)
- TRC105 10 mg/kg (1 to 4 hour IV infusion) (until progression)

Patients will be dosed with an AUC of 6 carboplatin on day 1 of each 3 week cycle, starting on cycle 1 day1 for 6 cycles. Carboplatin is to be administered as an intravenous infusion over 30 to 60 minutes.

6.4.7. Carboplatin Dose Modification

See carboplatin package insert [83]. Patients with arterial thrombosis or grade 3 or 4 venous thrombosis should discontinue TRC105 and bevacizumab therapy but may remain on study on carboplatin and paclitaxel alone.

6.4.8. Carboplatin Drug Accountability

The investigator must maintain an accurate accounting of carboplatin product that is used. During the study, the following information must be maintained:

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

6.4.9. Carboplatin Handling and Disposal

The site pharmacist will be responsible for the destruction, according to institutional requirements, of used or partially used vials.

6.5. Concomitant Medications

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

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

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

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

The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when paclitaxel is concomitantly administered with known substrates (e.g., midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (e.g., rifampin and carbamazepine) of CYP3A4.

Caution should also be exercised when paclitaxel is concomitantly administered with known substrates (e.g., repaglinide and rosiglitazone), inhibitors (e.g., gemfibrozil), and inducers (e.g., rifampin) of CYP2C8.

Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

The renal effects of nephrotoxic compounds may be potentiated by carboplatin.

6.6. Treatment Compliance

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

6.7. Patient Enrollment

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

7. ASSESSMENT OF EFFICACY

7.1. Radiological Tumor Assessment

The primary efficacy assessment will be best overall response as defined in Section 7.1.2. The determination of antitumor efficacy will be based on objective tumor assessments made by the Investigator according to RECIST version 1.1 [85]. Investigators will make treatment decisions based on these assessments. 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), and whenever disease progression is suspected. Another tumor assessment will be performed at the End of Study Visit if an assessment has not been performed within the prior 8 weeks. All patient files and radiological images must be available for CRF source verification.

7.1.1. Measurability of Tumor Lesions

At Screening, individual tumor lesions will be categorized by the Investigator as either target or non-target according to RECIST 1.1 as 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. Lytic bone lesions, with an identifiable soft tissue component, evaluated by CT or MRI, can be considered measurable lesions if the soft tissue component otherwise meets the definition of measurability previously described. Blastic bone lesions are non-measurable. Lesions in previously irradiated areas (or areas treated with local therapy) should not be selected as target lesions, unless there has been demonstrated progression in the lesion. 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 other than lytic 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 (unless there has been demonstrated progression in the lesion), and disease documented by indirect evidence only (e.g. by laboratory tests such as alkaline phosphatase).

7.1.1.1. Recording Tumor Measurements

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

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

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

7.1.2. Definitions of Tumor Response

7.1.2.1. Target Lesions

- **Complete response (CR)** is defined as the disappearance of all target lesions.
- **Partial response (PR)** is defined as a $\geq$ 30% decrease in the sum of the dimensions of the target lesions taking as a reference the baseline sum dimensions.
- **Progressive disease (PD)** is defined as a $\geq$ 20% relative increase and $\geq$ 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 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.

7.1.2.2. Non-Target Lesions

- **Complete response (CR)** is defined as the disappearance of all non-target lesions.
- **non-CR/non-PD** is defined as a persistence of $\geq$ 1 non-target lesions.
- **Progressive disease (PD)** is defined as unequivocal progression of existing non-target lesions, or the appearance of $\geq$ 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.

7.1.2.3. Determination of Overall Response

7.1.2.3.1. By RECIST

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 10. Per RECIST 1.1, in non-randomized trials with response as a primary endpoint, confirmation of PR or CR is required. 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 10: Response Evaluation Criteria in Solid Tumors

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

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

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

NOTE: 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 "Need for additional anti-cancer therapy/surgery". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated by fine needle aspirate or biopsy before confirming the complete response status.

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, serum or urine pregnancy testing, and coagulation profile. Serum will also be assessed for immunogenicity to TRC105 (including anti-product antibody titers). In addition, single tracing 12-lead ECGs will be performed at the time-points indicated in the Schedule of Assessments (Table 4). QT, PR and QRS intervals and heart rate will be captured. ECGs will also be collected as clinically indicated throughout the study.

8.1.1. Laboratory Safety Assessments

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

8.1.1.1. Hematology, Serum Chemistry, Coagulation, Pregnancy Test

Assessments will be performed at the time points indicated in the Schedule of Assessments (Table 4) 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: International Normalized Ratio (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, magnesium, thyroid stimulating hormone and glucose
- Pregnancy Test: Serum or urine pregnancy tests will be performed locally on all female patients of childbearing potential. Patients must be surgically sterile (i.e.: hysterectomy) or be postmenopausal, or must agree to use effective contraception during the study and for 90 days following last dose of TRC105. The definition of effective contraception will be based on the judgment of the Principal Investigator or a designated associate.

8.1.1.2. Urinalysis

Urinalysis (without microscopic analysis, unless indicated) will be performed at time points indicated in the Schedule of Assessments (Table 4) and analyzed by local laboratories.

Microscopic analysis, urine protein-creatinine ratio (UPCR), and 24 urine collection for protein should be performed as clinically indicated.

8.1.1.3. Physical Examination

A physical examination including, but not limited to, general appearance, head, eyes, ears, nose, throat, neck, heart, chest, abdomen, musculoskeletal, extremities, skin, lymph nodes, neurological genitourinary (as appropriate), and rectal (as appropriate) will be assessed at time points indicated within the Schedule of Assessments (Table 4). The physical examination will include examination of known and suspected sites of disease.

8.1.1.4. Vital Signs

Heart rate, temperature, blood pressure, respiratory rate and weight will be assessed at time points indicated within the Schedule of Assessments (Table 4). Heart rate, temperature, blood pressure, and respiratory rate will also be assessed during TRC105 infusions as described in Section 4.1.2.2 and the footnotes of the Schedule of Assessments (Table 4).

8.1.1.5. Performance Status

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

8.1.1.6. ECG

A single 12-lead (with a 10–second rhythm strip) tracing will be used for all ECGs. It is preferable that the machine used has a capacity to calculate standard intervals automatically. ECG will be performed at the time-points indicated in the Schedule of Assessments (Table 4) 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 will be reported as described below.

8.2.1. Definition of Adverse Event

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

- Clinically significant symptoms and signs including:
    - Worsening of signs and symptoms of the malignancy under trial (disease progression without worsening of signs and symptoms assessed by measurement of malignant lesions on radiographs or other methods should not be reported as adverse events).
    - Signs and symptoms resulting from drug overdose, abuse, misuse, withdrawal, sensitivity, dependency, interaction or toxicity.
    - All possibly related and unrelated illnesses, including the worsening of a preexisting illness.

  - Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (hip fracture from a fall secondary to dizziness), the medical condition (dizziness) and the outcome of the accident (hip fracture from a fall) should be reported as 2 separate adverse events.
  - Symptoms or signs resulting from exposure *in utero*.

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

8.2.2. Serious Adverse Events

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

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

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

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as SAEs unless the outcome is fatal during the trial or within the safety

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

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

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
- Outpatient same day surgery/procedure
- 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 that are not related to an SAE
    - Hospitalization for observation without an AE
- 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 with bevacizumab and/or paclitaxel and/or carboplatin and/or TRC105 study drug will be considered "baseline-signs and symptoms", will be recorded on corresponding case report forms and will not be retained for patients who fail screening. The adverse event reporting period for this trial begins when the patient has received even a portion of the first dose of bevacizumab and/or paclitaxel and/or carboplatin and/or TRC105 study drug and ends 28 days after the last dose of the latest study treatment (i.e. bevacizumab and/or paclitaxel and/or carboplatin and/or TRC105 study drug) is administered.

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

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 an SAE occurs, reporting will follow local and international regulations, as appropriate.

The Investigator must notify the Sponsor of any event that meets one of the criteria for an SAE immediately upon learning of the event. Any subsequent revisions that are made to information pertaining to serious suspected TRC105 adverse drug reactions (e.g.,: change in grade etc.), including a change in attribution to TRC105 study drug from "not related" to "suspected adverse drug reaction" should also be communicated to TRACON immediately. This notification should be made to:

Charles Theuer, MD PhD
TRACON Pharmaceuticals Inc.
8910 University Center Lane, Suite 700
San Diego, California 92122
Email: ctheuer@traconpharma.com
Cell Phone: (858) 344-9400
Office Phone: (858) 550-0780 x233

Following notification, the Investigator will report the SAE via the AE CRF via the data management system. The initial AE CRF is to be updated with more detailed adverse event information within **5 calendar days** of the event.

In the rare event that the Investigator is not immediately aware of an SAE (for example, if the study subject seeks urgent medical attention elsewhere), the Investigator is to notify the Sponsor immediately upon learning of it and document his/her first awareness.

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

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

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

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 on the CRFs.

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 (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 11: Adverse Event Grading

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

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

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for serious events.

8.3.6. Relationship to TRC105 Study Drug, Bevacizumab, Paclitaxel and Carboplatin

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

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

AE's related to TRC105 study drug or bevacizumab or paclitaxel or carboplatin are considered Adverse Drug Reactions (ADR).

8.3.7. Expectedness

All TRC105 adverse events and adverse drug reactions are considered "unexpected" if it's 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.

All bevacizumab or paclitaxel or carboplatin adverse events and adverse drug reactions are considered "unexpected" if it's not listed in the package insert or not listed at the specificity or severity that has been observed. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the package insert 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 bevacizumab or paclitaxel or carboplatin.

8.3.8. Exposure *in Utero*

If any trial patient (or partner of a trial patient) becomes or is found to be pregnant during the study or within 90 days of discontinuing the investigational medication/product, the Investigator

must report the information to TRACON, or designee via the Pregnancy Notification Report Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery.

The Investigator will follow the patient (or partner of a trial patient) until completion of the pregnancy or until pregnancy termination (i.e., induced abortion) and then notify TRACON, or its designee, of the outcome within 5 days or as specified below. The Investigator will provide this information as a follow-up to the initial report. The reason(s) for an induced abortion must be specified.

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

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

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

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

8.3.9. Follow-up of Unresolved Adverse Events

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

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

8.4. Safety Monitoring

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

- Surveillance for SAEs according to regulatory guidelines
- Routine monitoring of non-serious adverse experiences as they are recorded in the case report forms and the source documents at study sites

- A formally chartered TRACON in-house Safety Review Team that includes, among other staff, two physicians
- Periodic teleconferences with the Principal Investigators to share experiences and ensure communication
- Toxicity information that may affect the treatment of patients on this study will be promptly communicated in writing to all participating clinical sites and institutions participating in this clinical trial.

9. OTHER ASSESSMENTS

9.1. Other Laboratory Assessments

9.1.1. Pharmacokinetics

Samples will be sent to Fisher BioServices for storage See separate laboratory manual for specific collection, storage and shipping information.

9.1.1.1. TRC105 Trough Concentration

A 5 mL blood sample will be collected prior to dosing with TRC105 on the days indicated within the Schedule of Assessments (Table 4). Samples will be separated and stored at approximately -70 °C for shipment to third party laboratory. See separate laboratory guide for further collection and shipment information.

9.1.2. TRC105 Immunogenicity

Samples will be sent to Fisher BioServices for storage. See separate laboratory manual for specific collection, storage and shipping information.

Anti-product antibody concentrations will be measured using validated ELISA methods at the time points specified in the Schedule of Assessments (Table 4) in all patients. Anti-product antibody concentrations will be evaluated in the context of pharmacokinetic parameters and AE profiles. Samples will be separated and stored at approximately -70 °C for shipment to Fisher BioServices. See separate laboratory guide for further collection and shipment information.

9.1.3. Protein Biomarkers

One 10mL purple top (K_2EDTA) tube of blood will be collected on the days indicated within the Schedule of Assessments (Table 4). Samples will be stored at approximately -70 °C and shipped to Fisher BioServices Inc for storage until the time of analysis. Duke University Medical Center will analyze plasma for several biomarkers including but not limited to VEGF, VEGF-R2, PIGF and sCD105. Please see the separate laboratory guide for further collection and shipment information.

9.1.4. 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. It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 20 unstained slides are requested for immunohistochemical analysis (sections of ~ 5 microns are preferred). Samples will be stored at room temperature and shipped to Fisher BioServices Inc for storage until the time of analysis. See separate laboratory guide for further collection and shipment information.

10. STATISTICS

10.1. Statistical Design/Sample Size

10.1.1. Statistical Design/Sample Size

The number of patients to be enrolled in this study will depend upon the observed safety profile, which will determine the number of patients per dose level and the number of dose escalations. It is anticipated that up to 18 patients will be enrolled in the study.

The probability of escalation to the next higher dose for each underlying true DLT rate is shown in Table 12. For example, at a dose level with a true DLT rate of 5%, there is a greater than 95% probability of escalating. Conversely, for a dose level with a true DLT rate of 70%, the probability of escalating is < 5%.

Table 12: Probability of Escalation to the Next Dose for Each True Underlying DLT Rate at a Dose Level

True Underlying DLT Rate	5%	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of Escalating Dose	0.97	0.91	0.71	0.49	0.31	0.17	0.08	0.03	0.01	0.001

The probability of failing to observe DLT in a sample size of 3 or 6 patients given various true underlying DLT rates in shown in Table 13. For example, with 6 patients, the probability of failing to observe DLT occurring at least 40% of the time is less than 5%. The enrollment of 15 patients at a given dose level will reduce the probability of failing to observe toxicity occurring at least 30% of the time to < 5%.

Table 13: Probability of Failing to Observe True Underlying DLT Rate at a Dose Level

True Underlying DLT Rate	5%	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of Failing to Observe Toxicity if N = 3	0.86	0.73	0.51	0.34	0.22	0.13	.0064	0.027	0.008	0.001
Probability of Failing to Observe Toxicity if N = 6	0.74	0.53	0.26	0.12	0.047	0.016	0.0041	<0.001	<0.001	<0.001

10.1.1.1. Definition of Analyzed Study Populations

The following study populations will be considered when reporting study results:

- The study population for safety includes all patients receiving at least a portion of 1 dose of TRC105.
- The study population for PK includes also subjects with adequate data for PK modeling of TRC105.
- The study population for efficacy will include all safety population patients who have baseline and follow-up tumor measurements as required for assessment by RECIST 1.1.

Patients who experience DLT who receive less than the prescribed dose of TRC105 or bevacizumab, carboplatin or paclitaxel due to documented toxicity in cycle 1 will be considered evaluable for dose escalation purposes.

Only those patients who are deemed "ineligible" or who receive no therapy (i.e., no TRC105 or bevacizumab, carboplatin or paclitaxel) will be eliminated from the analysis. Ineligible patients who receive therapy will not be included in the assessment of efficacy endpoints, but their data will be included in the assessment of all adverse event reporting.

10.2. Data Analysis

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

10.2.1. Analysis of Primary Objective

10.2.1.1. Analysis of Primary Objective

For each cohort, DLTs will be summarized by category (hematologic and non-hematologic) and by MedDRA preferred term.

All AEs with an onset after initiation of treatment will be considered as treatment-emergent AEs. A preexisting condition that worsens during the treatment period will also be considered as a treatment emergent AE. All AEs will be coded by system organ class (SOC) and preferred term using NCI CTCAE (MedDRA) version 4.0.

The number and percentage of patients with the following types of treatment-emergent AEs will be summarized: common and serious AEs, AEs related to study medication, AEs resulting in study discontinuation, and clinically significant laboratory abnormalities. Non-treatment-emergent serious AEs will be described separately. Deaths will be reported with demographic information.

10.2.2. Analysis of Pharmacokinetics

Trough serum TRC105 concentrations will be measured using validated ELISA methods. The TRC105 pharmacokinetic data will be assessed for potential correlations with response, PFS, survival, adverse events, and baseline characteristics using descriptive statistics and models as appropriate.

10.2.3. Objective Response

The best response (CR, PR, SD or PD according to RECIST 1.1) for each patient with measurable disease who received at least one dose of TRC105 study drug will be listed by cohort. Stable disease will be defined as lack of tumor progression lasting for 3 cycles or longer.

10.2.4. Analysis of Protein Biomarkers

Angiogenic protein biomarker data for each patient who received at least one dose of TRC105 study drug will be listed.

10.2.5. Analysis of Immunogenicity

Anti-product antibody concentrations will be measured using validated ELISA methods at the time points specified in the Schedule of Assessments (Table 4). Anti-product antibody concentrations will be evaluated in the context of pharmacokinetic parameters and AE profiles.

10.2.6. Analysis of Archival Tumor Tissue

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

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 audits performed by TRACON or its representatives.

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

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

13. ETHICS

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

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

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

13.2. Ethical Conduct of the Study

The trial will be performed in accordance with the protocol, applicable local regulatory requirements and laws, and the International Conference on Harmonization Guideline on Good Clinical Practice, which supports the application of ethical principles that have their origin in the Declaration of Helsinki (see ICH E6, § 2.1).

13.3. Written Informed Consent

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

It is the responsibility of the Investigator to give each patient full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. This information must be provided to the patient prior to undertaking any trial-related procedure. Patients must be informed about their right to withdraw from the trial at any time. Furthermore, it is the responsibility of the Investigator to ensure all patients are appropriately informed before obtaining their 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, ICH E6 requirements for impartial witnesses will apply.

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

13.4. Patient Compensation

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

14. DATA HANDLING AND RECORDKEEPING

14.1. Inspection of Records

CRF's are required and should be completed for each patient who receives treatment with pazopanib or 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.

14.2. Retention of Records

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

If the Investigator relocates, retires, or for any reason withdraws from the study, then TRACON should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution. The Investigator must inform TRACON of any such transfer of responsibilities and properly identify the person or institution assuming the responsibility. The responsible investigator/institution must obtain TRACON's written permission before disposing of any records.

15. DEFINITION OF END OF TRIAL

15.1. End of Trial in all Participating Countries

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

15.2. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient patients have been recruited and completed the trial as stated in the regulatory application (e.g. the Clinical Trials Agreement (CTA)) and ethics application in the Member State. Poor recruitment is not a reason for premature termination but is considered a normal conclusion to the trial in that Member State.

15.3. 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 all participating patients within a 28 day time period. As directed by TRACON, all trial materials must be collected and all CRF data must be completed to the greatest extent possible.

16. PUBLICATION OF TRIAL RESULTS

Publication of trial results is discussed in the Clinical Trial Agreement.

17. FINANCING AND INSURANCE

Financing and Insurance are discussed in the Clinical Trial Agreement.

18. INVESTIGATOR PROTOCOL AGREEMENT: 105LC101

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 all applicable regulations, 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

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

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

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

20.2. Appendix 2: ECOG Performance Status

Grade	Performance
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.