CLINICAL STUDY PROTOCOL

Title:	A RANDOMIZED PHASE 3 TRIAL OF TRC105 AND PAZOPANIB VERSUS PAZOPANIB ALONE IN PATIENTS WITH ADVANCED ANGIOSARCOMA (TAPPAS)
Protocol Number:	105SAR301
EudraCT Number:	2016-000485-34
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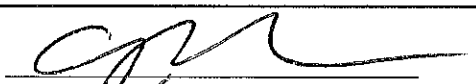
Signature & Date:	Signed:  Print: C Theuer MD Dated: 25 July 2018
Version Date:	Original Protocol: 14November2016 Amendment #1: 10January2017 Amendment #2: 14February2018 Amendment #3: 27April2018 Amendment #4: 23July2018

PROCEDURES IN CASE OF EMERGENCY

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1. SYNOPSIS

Name of Sponsor/Company: TRACON Pharmaceuticals, Inc.

Name of Investigational Product: TRC105

Name of Active Ingredient: TRC105 (carotuximab)

Title of Study:

A RANDOMIZED PHASE 3 TRIAL OF **T**RC105 **A**ND **P**AZOPANIB VERSUS **P**AZOPANIB ALONE IN PATIENTS WITH ADVANCED **A**NGIO**S**ARCOMA (TAPPAS)

Investigators and Study center(s): Approximately 40 centers in North America and Europe

Studied period (years):	**Phase of development:** 3
Date first patient enrolled: December 2016 Estimated date last patient enrolled: March 2020 Estimated date phase 3 endpoint obtained: September 2020	

Rationale:

Angiosarcoma, a subtype of soft tissue sarcoma, is a rare and aggressive vascular malignancy associated with poor prognosis. About half of these patients present with primary cutaneous lesions (tumor arising from the skin, often consisting of multiple lesions and located in critical areas like head and neck). Risk factors for this presentation include prior radiation exposure as well as inflammatory damage in chronically sun exposed skin. Non-cutaneous angiosarcoma may also occur in the setting of prior radiation exposure. Angiosarcoma has also been associated with prolonged lymphedema from any cause or prolonged immune-suppression. Although complete resection with curative intent, followed by adjuvant radiotherapy, is the treatment of choice for localized disease amenable to surgery, approximately 50% of these patients will develop metastases and die from the disease. Furthermore, metastases are frequently present at the time of diagnosis. Current treatment options are limited and of modest benefit. Median overall survival is approximately 8 to 11 months for patients with metastatic disease. Aside from pazopanib, standard regimens for advanced angiosarcoma include taxanes, anthracyclines, and gemcitabine. Tumor control with these therapies is short-lived with median progression-free survival (PFS) ranging from 3.9 to 6.6 months. The short time to progression following current treatment emphasizes that angiosarcoma is a disease in need of more effective and well tolerated treatment options.

Pazopanib is an oral inhibitor of multiple receptor tyrosine kinases, including vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, and VEGFR-3 at therapeutic plasma concentrations. These receptors are implicated in pathologic angiogenesis, tumor growth, and cancer progression. Pazopanib is approved based on improved PFS in the United States for the treatment of patients with advanced soft tissue sarcoma who have received prior chemotherapy and approved in Europe for adult patients with selective subtypes of advanced soft tissue sarcoma who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy. However, activity in angiosarcoma is limited; no complete responses were observed in the largest series of angiosarcoma patients treated with single agent pazopanib reported to date (n=30).

TRC105 (carotuximab) is a monoclonal antibody to endoglin (CD105), an essential angiogenic target highly expressed on tumor vessels that is distinct from VEGFR. Endoglin is also expressed directly on tumor cells in angiosarcoma and is upregulated following VEGF inhibition. TRC105 inhibits angiogenesis, tumor growth and metastases in preclinical models and complements the activity of

bevacizumab and multi-kinase inhibitors that target the VEGFR. In a phase 1 study of advanced solid tumors, single agent TRC105 therapy reduced tumor burden at doses that were well-tolerated.

By targeting a non-VEGF pathway that is upregulated following VEGF inhibition, TRC105 has the potential to complement VEGFR tyrosine kinase inhibitors (TKIs) and could represent a major advance in the treatment of angiosarcoma. Together, the use of TRC105 with pazopanib may result in more effective angiogenesis inhibition and improved clinical efficacy over that seen with pazopanib alone.

In a phase 1b/2 study of TRC105 and pazopanib in advanced soft tissue sarcoma, TRC105, at its recommended phase 2 dose of 10 mg/kg given by weekly intravenous infusion, was combined safely with pazopanib given at 800 mg p.o. once daily. Interim efficacy data from the Phase 1b/2 study indicated tumor reductions in all 5 of the first patients with angiosarcoma, of whom 2 had progressed following prior pazopanib treatment; notably, median PFS was greater than 12.9 months in these 5 patients and 2 of the 3 patients with cutaneous angiosarcoma achieved durable complete responses by Response Evaluation Criteria in Solid Tumor version 1.1 (RECIST 1.1). Data available from the patients in the expansion cohorts enrolling angiosarcoma patients continues to demonstrate activity and tolerability of TRC105 in combination with pazopanib.

Objectives:

Primary:

- To compare PFS of TRC105 and pazopanib vs single agent pazopanib in patients with unresectable angiosarcoma

Secondary:

- To compare the objective response rate (ORR) of TRC105 and pazopanib vs single agent pazopanib in patients with unresectable angiosarcoma
- To compare overall survival (OS) of TRC105 and pazopanib vs single agent pazopanib in patients with unresectable angiosarcoma
- To assess the overall safety and tolerability of TRC105 and pazopanib vs single agent pazopanib in patients with unresectable angiosarcoma
- To characterize patient reported outcomes between the two arms of the study
- To characterize the pharmacokinetic (PK) profile of TRC105 and pazopanib between the two arms of the study
- To assess PFS and ORR by Investigator assessment between the two arms of the study
- To characterize the immunogenicity of TRC105

Exploratory:

- To correlate efficacy endpoints (e.g., PFS, ORR and OS) with endoglin expression on angiosarcoma tumor samples
- To correlate efficacy endpoints (e.g., PFS, ORR and OS) with circulating angiogenic protein biomarkers
- To correlate efficacy endpoints (e.g., PFS, ORR and OS) with numbers of endoglin expressing circulating tumor cells (CTCs)

Endpoints:

Primary:

- PFS is defined as time from randomization to either first disease progression (per independent radiology review of images by RECIST 1.1) or death from any cause. For the purpose of analysis for patients who are alive at the time of analysis and have not had disease progression, the following rules will apply: (1) The patient will be censored on the date of the last tumor assessment documenting absence of progressive disease; (2) if the patient was given antitumor treatment other than study drug treatment, the patient will be censored as of the date of the last tumor assessment prior to initiating that antitumor therapy; (3) if the patient was removed from study for toxicity or other reason, the patient will be censored as of the date of the last tumor assessment on study. With regard to missed tumor assessments, in the event of one missed tumor assessment followed by a subsequent assessment of progressive disease (PD), the subsequent PD assessment qualifies as objective tumor progression. In the event of more than one consecutive missing tumor assessment followed by a subsequent assessment of PD, the patient will be censored at the last adequate tumor assessment.

Secondary:

- Objective response rate (ORR) is defined as the number of patients with a best response of complete response (CR) or partial response (PR) divided by the number of randomized patients. ORR is defined as the best response designation recorded between the date of randomization and the date of documented progression, as determined by Central Radiographic Review according to RECIST 1.1, or date of subsequent therapy, whichever occurs first. For patients without documented progression or subsequent therapy, all available response designations will contribute to the ORR determination. A designation of CR or PR in this study requires confirmation at a subsequent consecutive assessment at least 4 weeks following the initial designation of CR or PR, respectively. Duration of response (DR) will be reported in patients who achieve ORR, but without a formal statistical comparison between arms.
- Overall Survival (OS) is defined as the time between the date of randomization and the date of death from any cause. Overall survival will be calculated in days as: Date of Death – Date of Randomization +1. Subjects alive or lost to follow-up at the time of analysis will be censored at the date when they were last known to be alive.
- Type, incidence, severity (graded by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Version 4.03), timing, seriousness, and relatedness of AEs and laboratory abnormalities.
- Patient reported outcomes as measured by the EuroQol five dimensions questionnaire (EQ-5D-5L) and the EORTC QLQ-C30 questionnaire.
- TRC105 and pazopanib pharmacokinetic (PK) concentrations will be measured using validated methods from peak and trough samples.
- Anti-TRC105 antibodies will be measured using validated methods and anti-drug antibody (ADA) titers will be correlated with PK parameters and AEs.

Study Design:

This is a multinational, multicenter, randomized, open label, parallel group, phase 3 study of TRC105 in combination with standard dose pazopanib compared to single agent pazopanib in patients with angiosarcoma not amenable to curative intent surgery (e.g., metastatic or bulky disease, and disease for which surgical resection would carry an unacceptable risk to the patient) who have not received pazopanib or TRC105 previously.

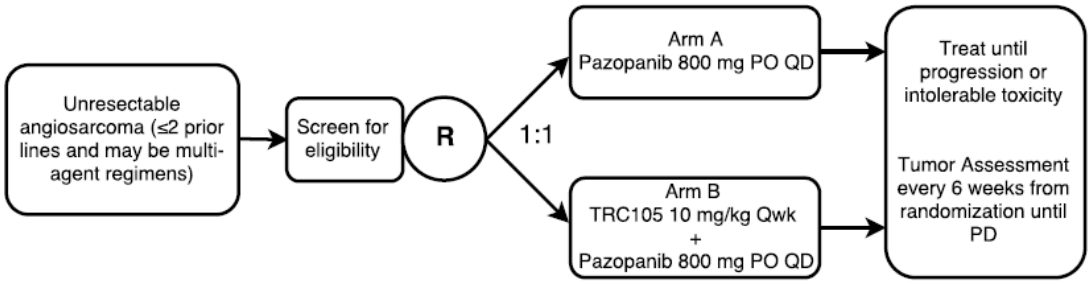
Adult patients will be randomized in a 1:1 ratio to TRC105 in combination with standard dose pazopanib (Arm B) vs standard dose single agent pazopanib (Arm A). Patients will be stratified by angiosarcoma subtype (cutaneous vs non-cutaneous) and the number of lines of prior systemic therapy for angiosarcoma (0 versus 1 or 2). For the purposes of this study, cutaneous angiosarcoma will include primary skin/scalp angiosarcoma; all other angiosarcoma including primary subcutaneous angiosarcoma will be categorized as non-cutaneous (e.g., visceral, bone, soft tissue).

Due to possible differences in treatment effect in the cutaneous and non-cutaneous angiosarcoma subgroups, an adaptive enrichment design will be employed. An interim analysis is planned after 40 events or 30 days after the enrollment of 120 patients from Cohort 1 and will result in one of the following decisions: (1) no change to the study design and sample size, (2) no change to the study design but an increase in the sample size, or (3) termination of enrollment of the non-cutaneous subtype and adjustment of the sample size of the cutaneous subtype. Cohort 1 is defined as the adult patients enrolled prior to the interim analysis.

Enrollment at a given site will be limited to a maximum of 15% of total patients. Additionally, enrollment of Cohort 1 will be monitored to ensure that no more than 50% of the total adult patients enrolled will have the non-cutaneous subtype.

Treatment in the assigned arm must start within 3 calendar days of randomization.

Trial Design Schema:



Number of patients (planned):

At least 190 patients will be enrolled. The number of patients enrolled may increase to a maximum of approximately 340 after the planned, prospectively specified interim analysis.

Patient Selection:

Inclusion Criteria:

1. Histologically-confirmed angiosarcoma that is not amenable to curative intent surgery (e.g., metastatic or bulky disease and disease for which surgical resection would carry an unacceptable risk to the patient). Pathology report will be reviewed by sponsor prior to randomization.
2. Documented progression on or following most recent systemic chemotherapy regimen (not required for chemotherapy-naïve patients), within 4 months prior to screening
3. Measurable disease by RECIST v1.1
4. Age of 18 years or older; in addition, patients age 12 to 17 years may enroll beginning in Cohort 2 if weight ≥ 40 kg
5. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
6. Resolution of all acute AEs resulting from prior cancer therapies to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03) grade ≤ 1 or to that patient's pre-study baseline (except alopecia or neuropathy)
7. 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 x ULN
   - Absolute neutrophil count (ANC) ≥ 1500/μL
   - Platelets ≥ 100,000/μL (without transfusion support within 28 days prior to randomization)
   - Hemoglobin ≥ 9.0 g/dL (without transfusion support within 14 days prior to randomization; erythropoietin or darbepoetin permitted)
   - Serum creatinine ≤ 1.5 times the upper limit of normal or creatinine clearance > 30 mL/min by Cockcroft-Gault formula
   - International normalized ratio (INR) ≤ 1.2 unless the patient is receiving a direct Factor Xa inhibitor
8. Willingness and ability to consent (and assent if under age 18) for self to participate in study
9. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures
10. Angiosarcoma tumor specimen, if available
11. Men who are sterile (including vasectomy confirmed by post vasectomy semen analysis) OR agree to use a condom with spermicide (refer to Section 2.6.1.3) and to not donate sperm during the study and for at least 180 days following last dose of TRC105 or pazopanib
12. Woman of non-child bearing potential due to surgical sterilization (at least 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by

medical history or menopause (i.e., no menstrual bleeding for more than 12 months in a women aged 45 years or more), 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 acceptable methods of birth control, one of which must be highly effective, during the study and for at least 180 days after stopping TRC105 or pazopanib (refer to Section 2.6.1.3).

Exclusion Criteria:

1. Prior treatment with TRC105
2. Prior treatment with any VEGF inhibitor
3. More than two prior lines (may be combination regimens) of chemotherapy for angiosarcoma (neoadjuvant/adjuvant treatment does not count as a line of treatment)
4. Current treatment or participation on another therapeutic clinical trial
5. Women who are pregnant or breastfeeding
6. Receipt of systemic anticancer therapy, including investigational agents, within 5 times the agent's elimination half-life or 14 days of starting study treatment, whichever is shorter
7. Major surgical procedure or significant traumatic injury within 4 weeks prior to randomization and must have fully recovered from any such procedure or injury; planned 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 randomization: Thoracentesis, paracentesis, laparoscopy, thoracoscopy, tube thoracostomy, bronchoscopy, endoscopic ultrasonographic procedures, mediastinoscopy, skin biopsies, and imaging-guided biopsy for diagnostic purposes
8. 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 randomization
9. Uncontrolled hypertension defined as systolic > 150 or diastolic > 100 mm Hg on the average of the 3 most recent BP readings. Anti-hypertensives may be started prior to randomization.
10. Ascites or pleural effusion requiring intervention or that required intervention or recurred within three months prior to randomization
11. Pericardial effusion (except trace effusion identified by echocardiogram) within three months prior to randomization
12. 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 prior to randomization
13. Angina, myocardial infarction, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack, arterial embolism , pulmonary embolism, percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) within 6 months prior to randomization. Deep venous thrombosis within 3 months prior to randomization unrelated to a central venous catheter, unless the patient is anti-coagulated without the use of warfarin for at least 2 weeks prior to randomization. In this situation, low molecular weight heparin or a direct Factor Xa inhibitor is preferred

14. Active bleeding or pathologic condition that carries a high risk of bleeding (e.g., hereditary hemorrhagic telangiectasia). Patients with bleeding cutaneous lesions not actively requiring transfusions are eligible. Patients who have been uneventfully anti-coagulated with a direct Factor Xa inhibitor or low molecular weight heparin are eligible
15. Hemoptysis (> ½ teaspoon [2.5 mL] of bright red blood) within 6 months prior to randomization
16. Thrombolytic use (except to maintain i.v. catheters) within 10 days prior to randomization
17. Known active viral or nonviral hepatitis or cirrhosis
18. Peptic ulcer within the past 3 months prior to randomization, unless treated for the condition and complete resolution has been documented by esophagogastroduodenoscopy (EGD)
19. Presence of tumor(s) invading into the heart or great vessels (including carotid artery) or another location where bleeding is associated with high morbidity including patients with primary cardiac or great vessel angiosarcoma
20. Gastrointestinal perforation or fistula in the 6 months prior to randomization unless underlying risk has been resolved (e.g., through surgical resection or repair)
21. Presence of a malabsorption syndrome, gastrointestinal disorder, or gastrointestinal surgery that could affect the absorption of pazopanib
22. History of prior malignancy except adequately treated basal cell or squamous cell skin cancer or adequately treated, with curative intent, cancer from which the patient is currently in complete remission per Investigator's judgment; patients with history of breast cancer and no evidence of disease on hormonal therapy to prevent recurrence and patients with prostate cancer on adjuvant hormonal therapy with undetectable PSA are eligible
23. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness
24. Active infection that requires systemic treatment
25. Concurrent use or receipt of a strong CYP3A4 inducer within 12 days prior to randomization or a strong CYP3A4 inhibitor within 7 days prior to randomization (see Table 10)
26. History of severe hypersensitivity reaction to any monoclonal antibody
27. Other severe acute or chronic medical (including bone marrow suppressive diseases) or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation, impede the ability of the patient to complete all protocol-specified activities, 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:

Patients randomized to the combination arm (Arm B) will receive intravenous TRC105 at 10 mg/kg weekly beginning on cycle 1 day 1 (C1D1) following appropriate premedication. Treatment must

start within 3 days of randomization. Each cycle is 21 days in duration. Dose modification of TRC105 is allowed per patient tolerance.

Pazopanib dose and administration:

Adult and adolescent patients with a BSA > 1.8 m^2 will receive 800 mg of pazopanib beginning on C1D1 and once daily thereafter, in the absence of toxicity. All other pediatric patients will receive 600 mg of pazopanib beginning on C1D1 and once thereafter, in the absence of toxicity. Treatment must start within 3 days of randomization. Dose modification of pazopanib is allowed per patient tolerance.

Duration of treatment:

Patients are eligible for treatment until disease progression, unacceptable toxicity or withdrawal of consent, or other reasons. 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 confirmed by central radiographic review.
2. A need for surgery, radiation, or other anticancer therapy not permitted under this protocol.
3. Lost to follow-up or substantial noncompliance with the protocol.
4. Pregnancy. Pregnant patients should be followed for the duration of the pregnancy and the outcome of the pregnancy should be documented.
5. Arterial thrombosis of any grade (including that causing cerebrovascular ischemia, cardiac ischemia/infarction, or peripheral or visceral arterial ischemia) or grade 4 venous thrombosis (including grade 4 pulmonary thromboembolism).
6. Missed study drug treatment for > 8 consecutive weeks (i.e., both TRC105 and pazopanib dosing if assigned to the combination arm or pazopanib if assigned to the pazopanib alone arm). Patients in the combination arm who cannot tolerate pazopanib or TRC105 therapy and who demonstrate a response of complete response (CR), partial response (PR) or stable disease (SD) with the combination and are thought to benefit from continued single agent therapy may continue on study on TRC105 or pazopanib alone.

Statistical Considerations:

Efficacy Analyses

The study population for efficacy (i.e., the intent-to-treat, ITT, population) will include all randomized adult patients. Patients age 12 to 17 will not be randomized and will receive treatment with TRC105 and pazopanib and therefore will not be included in the ITT population. The primary endpoint is PFS and the primary analysis will compare the TRC105 plus pazopanib and the single-agent pazopanib groups using a one-sided, stratified by angiosarcoma location (cutaneous versus non-cutaneous) and by number of lines of prior systemic chemotherapy for angiosarcoma (0 versus 1-2) log rank test at the two-tailed alpha = 0.05 level of significance. Estimates of median PFS will be provided along with 2-sided 95% confidence intervals. The PFS distributions in the two arms will be summarized using the Kaplan-Meier method. The primary analyses of efficacy endpoints dependent on disease assessments (PFS and ORR) will be performed in the ITT population based on results of the independent central application of modified RECIST 1.1. Imaging will be performed every 42 days from date of randomization.

Sample Size Justification

A hazard ratio of 0.55 is considered to be clinically relevant. Based on 1:1 randomization and the use of log-rank test at the 2-sided alpha of 0.05 level of significance, 95 events provides 83% power to detect a hazard ratio of 0.55.

The expected PFS of angiosarcoma patients treated with pazopanib who have progressed following first line treatment is 4 months. A hazard ratio of 0.55 corresponds to an improvement of median PFS from 4 months to 7.27 months. Due to the uncertainty of the treatment effect, and heterogeneity among the cutaneous and non-cutaneous subgroups, an adaptive enrichment design will be employed. The initial study design calls for enrolling two cohorts, with 120 adult patients in cohort 1 and 70 adult patients in cohort 2. The initially planned final analysis will be conducted when 60 events are observed from cohort 1 and 35 events are observed from cohort 2, whichever comes at a later time. A formal interim analysis based on unblinded data review by the Independent Data Monitoring Committee (IDMC) will be conducted and the trial might be expanded to enroll a total of 340 adult patients from the full population or enriched to enroll a total of 280 adult patients including 120 adult patients from cohort 1 from full population and 160 adult cutaneous disease patients for cohort 2 from the cutaneous subgroup only.

The operational and statistical details for implementing this adaptive enrichment are included in the statistical analysis plan (SAP).

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Table 2: Abbreviations and Specialist Terms

Abbreviation or specialist term	Explanation
2D	Two Dimensional
ADA	Anti-Drug Antibody
ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
ADR	Adverse Drug Reaction
AE	Adverse Event
ALKs	Activin receptor-Like Kinases
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AUC_{last}	Time of Last Measurable Concentration of Area Under the Curve
BMP	Bone Morphogenic Protein
BUN	Blood Urea Nitrogen
CABG	Coronary Artery Bypass Graft
CA-125	Cancer Antigen 125
CBC	Complete Blood Count
CEA	Carcinoembryonic Antigen
CFR	Code of Federal Regulations
CHO	Chinese Hamster Ovary
CL	Clearance
C_{max}	Maximum Serum Concentration
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CTC	Common Terminology Criteria
CTC	Circulating Tumor Cell
CTCAE	Common Terminology Criteria for Adverse Events
DEHP	Di(2-ethyl-hexyl)phthalate
DICOM	Digital Imaging and Communications in Medicine
dL	Deciliter
DLT	Dose-Limiting Toxicity
DR	Duration of Response
ECG	Electrocardiogram
ECL	Electrochemiluminescent
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDTA	Ethylenediamine Tetra-Acetic Acid
EGFR	Epidermal Growth Factor Receptor
ELISA	Enzyme-Linked ImmunoSorbent Assay
EMA	European Medicines Agency

EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of Study
EU	European Union
FDA	Food and Drug Administration
Fe	Iron
FGF	Fibroblast Growth Factor
g	Gram
GCP	Good Clinical Practice
GIST	Gastrointestinal Stromal Tumor
HACA	Human Anti-Chimeric Antibodies
HAMA	Human Anti-Murine Antibodies
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
HUVECs	Human Umbilical Vein Endothelial Cells
IB	Investigational Brochure
ICH	International Conference on Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
i.m.	Intramuscular
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine Device
i.v.	Intravenous
kg	Kilogram
L	Liter
µL	Microliter
mg	Milligram
MI	Myocardial Infarction
mL	Milliliter
mm	Millimeter
mM	Millimolar
mm HG	Millimeters of Mercury
MRI	Magnetic Resonance Imaging
MTD	Maximum-Tolerated Dose
NCI	National Cancer Institute
NICE	National Institute for Health and Care Excellence
NE	Non-evaluable
ng	Nanogram
NSO	Murine Myeloma Cell Line
OS	Overall Survival

PBS	Phosphate-Buffered Saline
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PIGF	Placental Growth Factor
pM	Picomolar
p.o.	Orally
PPM	Pixels Per Millimeter
PR	Partial Response
PSA	Prostate-Specific Antigen
PTCA	Percutaneous Transluminal Coronary Angioplasty
QA	Quality Assurance
QT	QT Wave Interval on ECG
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
STS	Soft tissue sarcoma
TGF-β	Transforming Growth Factor - Beta
TSH	Thyroid Stimulating Hormone
UK	United Kingdom
ULN	Upper Limit of Normal
UPCR	Urine Protein-Creatinine Ratio
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
WHO	World Health Organization

2. BACKGROUND

2.1. Angiosarcoma

Sarcomas are rare tumors that originate from mesenchymal tissues (e.g., bone, cartilage, fat and muscle). In the United States, the incidence of bone and soft tissue sarcomas is approximately 13,000 new cases per year, leading to more than 5,000 deaths annually [1]. According to the WHO classification of 2002, over 70 different types of sarcoma have been described [2]. Localized tumors are curable but patients with metastatic disease have a median survival of approximately 12 months[3]. Standard systemic chemotherapy regimens are poorly tolerated and of limited usefulness with response rates in the range of 10-40% [3].

Angiosarcomas are rare, aggressive, and heterogenous tumors of endothelial cell origin accounting for approximately 2% of soft tissue sarcoma (STS) [4]. Anigiosarcoma can arise in any soft-tissue structure or viscera. About half of patients present with a primary cutaneous lesion (skin, scalp). The pathogenesis of this presentation includes prior radiation exposure as well as inflammatory damage in chronically sun exposed skin. Non-cutaneous angiosarcoma (soft tissue, bone, viscera) can occur in the setting of prior radiation exposure or other unknown causes. Angiosarcoma has also been associated with prolonged lymphedema from any cause. Although complete resection with curative intent followed by adjuvant radiotherapy is the treatment of choice for localized disease amenable to surgery, approximately 50% of these patients will develop metastasis and die from the disease. Furthermore, metastases are frequently present at the time of diagnosis [5]. The surgical removal of metastatic lesion is rarely feasible [6]. Treatment options are limited for advanced disease and of modest benefit. The median overall survival is <12 months for patients with metastatic disease [5, 7, 8]. There are no approved therapies specifcially for angiosracoma. Aside from pazopanib, standard regimens for advanced angiosarcoma include taxanes, anthracyclines, and gemcitabine. Tumor control with these therapies have been short-lived with median PFS ranging from 3.9 to 6.6 months [5, 9].

Recently, the VEGFR TKI pazopanib was approved based on improved progression free survival (PFS) in the United States for the treatment of patients with advanced soft tissue sarcoma who have received prior chemotherapy and approved in Europe for adult patients with selective subtypes of advanced soft tissue sarcoma who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy. Pazopanib improved PFS in chemotherapy refractory patients compared to placebo (PFS of 4.6 months with pazopanib versus 1.6 months with placebo) and was generally well tolerated, with the most common AEs seen at higher levels than in patients treated with placebo being fatigue, diarrhea, nausea, weight decreased and hypertension. However, activity in angiosarcoma is limited; no complete responses and median PFS of 3.02 months were observed in the largest series of angiosarcoma patients (n=30) treated with pazopanib reported to date [10]. Studies of other VEGFR TKIs confirm a poor response rate and PFS of $\leq$ 4 months [5].

The short time to progression following current treatment emphasizes that angiosarcoma is a disease in need of more effective and well tolerated treatment options.

2.2. Angiogenesis and Cancer

Angiogenesis is required for the survival and growth of solid cancers [11, 12]. It is generally accepted that solid cancers have two phases, an avascular phase and a vascular phase [12].

During the initial avascular phase, tumors exist as small aggregates of malignant cells supported by simple diffusion of oxygen and nutrients. The progressive growth of solid cancers beyond clinically occult sizes requires the continuous formation of new blood vessels, a process known as tumor angiogenesis. Tumor growth and metastasis require angiogenesis. Therefore, inhibition of tumor angiogenesis and selective inhibition of the tumor vasculature represent potentially effective strategies for the prevention and treatment of solid cancers.

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

Indeed, agents that target pathways required for tumor angiogenesis have an important role in the therapy of cancer patients. The monoclonal antibody bevacizumab, which binds to the angiogenic cytokine VEGF, significantly prolongs overall survival for patients with advanced colorectal cancer or non-small cell lung cancer when added to standard chemotherapy regimens [13, 14]. Bevacizumab is also effective therapy for renal cell cancer and malignant glioma [15-17]. 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 [18-21].

2.2.1. Endoglin (CD105) and Angiogenesis

Endoglin (CD105) is a homodimeric cell membrane glycoprotein that was initially identified as a human leukemia-associated antigen [22] and later also found on endothelial cells [23, 24]. Endoglin is a transforming growth factor-β (TGF-β) coreceptor that is essential for angiogenesis [25, 26] and is strongly expressed on the proliferating vascular endothelium of solid tumors [24, 27]. Endoglin acts to modulate signaling of multiple kinase receptor complexes of the TGF-β superfamily, including TGF-β receptors, activin receptor-like kinases (ALKs), bone morphogenic protein (BMP) receptors, and activin receptors [28]. TGF-β binds to endoglin complexed with TGF-β receptors causing phosphorylation of SMAD 2 and 3 proteins, which inhibit endothelial cell growth. However, BMP activates endoglin complexed with BMP receptor 2, causing phosphorylation of SMAD 1 and 5, which activate endothelium by overriding the growth inhibitory effects of TGF-β receptor signaling on endothelium [29]. Not surprisingly, prevention of endoglin activation by endoglin antibody acts synergistically with TGF-β to inhibit endothelial cell growth [30].

Endoglin expression is required for endothelial cell proliferation and is upregulated in the setting of hypoxia through the induction of hypoxia-inducible factor-1-α (HIF-1-α) [31, 32]. Endoglin has also been shown to protect hypoxic cells from apoptosis [33]. In adults, endoglin expression is limited to vascular endothelial cells, activated monocytes, activated fibroblasts, and proerythroblasts, a red blood cell precursor [34]. All of these properties make endoglin an

attractive target for the antiangiogenic therapy of cancer [35]. In animal models, endoglin targeted therapy has demonstrated antiangiogenic effects by inducing regression of established tumors as well as by preventing new tumor formation and inhibiting expansion of existing tumors [24, 36-39]. Therefore, endoglin offers a novel alternative target relative to the VEGF inhibitors currently available for antiangiogenesis therapy.

Importantly, endoglin expression is upregulated in tumor endothelial cells following inhibition of the VEGF pathway. Endoglin expression increased more than 2-fold in human pancreatic cancers grown in mice treated with an antibody that binds VEGF [40]. As well, treatment of human bladder cancers grown in mice with an antibody that blocks activation of the VEGF receptor increased endoglin expression within the core tumor vasculature [41]. Preclinical data suggest that targeting the endoglin pathway and the VEGF pathway concurrently is a more effective means of inhibiting angiogenesis than targeting either pathway individually [42, 43].

Endoglin is critical for normal human blood vessel development [44]. Endoglin 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 telangiectasia involving the nasal, buccal, gastrointestinal mucosa and skin microvasculature. Telangiectasia also occur in vessels from internal organs including the lungs, liver and brain [45]. 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 characterized by vascular effects, indicating the specific role of endoglin in vascular development [46].

2.2.2. Endoglin and Angiosarcoma

Endoglin is also expressed on the tumor tissue of certain tumor types in addition to the tumor vasculature. Endoglin is a marker of mesenchymal stem cells, the normal cell type from which sarcomas originate [47, 48]. Endoglin-expressing sarcomas are relatively frequent and express endoglin at higher density than carcinoma cell lines. In one report, high surface expression of endoglin by whole cell flow cytometry was seen in 7 of 8 sarcoma cell lines compared to only 4 of 16 carcinoma cell lines [49]. Moreover, the level of endoglin expression correlated with proliferative capacity, and the addition of neutralizing endoglin antibodies reversed the increase in proliferation.

Endoglin expression in human sarcoma tumor tissue has been reported by several groups. Gromova *et al.* found endoglin on 26 of 49 human gastrointestinal stromal tumors (GIST), and higher expression correlated with more aggressive tumors and high risk disease [50]. Moreover, endoglin knockdown reversed the increased tumor cell plasticity, invasiveness, and anchorage independent growth associated with endoglin expression [51]. Other endoglin-expressing sarcomas identified in the literature include angiosarcoma, osteosarcoma, leiomyosarcoma, malignant fibrous histiocytoma (undifferentiated pleomorphic sarcoma), Kaposi's sarcoma, Wilms tumor, and chondrosarcoma [52-56].

Endoglin expression was evaluated by immunohistochemistry on archival tumor samples from almost 150 patients with various types of sarcoma [57]. Among the sarcoma tumor types evaluated, angiosarcoma expressed endoglin on tumor tissue most universally (19 of 20 samples) and densely. TRC105 is expected to be more active in tumor types, particularly angiosarcoma, that densely express endoglin on tumor tissue in addition to tumor vasculature.

2.3. TRC105 Background

TRC105 is a novel immunoglobulin G1 (IgG1) antibody that binds endoglin with high avidity. TRC105 is a genetically engineered human/murine chimeric monoclonal antibody directed against human endoglin [58], a growth proliferation receptor found on the surface of normal and proliferating endothelial cells [24, 32, 36].

The antibody is an IgG1 kappa immunoglobulin containing murine variable region sequences and human constant region sequences [58]. TRC105 has an approximate molecular weight of 148 kilodaltons (kDa). TRC105 has a binding avidity for human endoglin of approximately 5 pM. TRC105 binds to the endoglin orphan domain and competitively inhibits BMP binding, thereby inhibiting SMAD 1/5/8 phosphorylation necessary for endothelial cell activation [29].

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 [37]. Reactivity with carcinoma tissue is restricted to the tumor endothelium, as endoglin is not generally expressed on epithelial tumor cells [36]. TRC105 induces antibody-dependent cell-mediated cytotoxicity (ADCC) on proliferating HUVECs at low conentrations and induces apoptosis and growth inhibition at higher concentrations.

Studies at Duke University explored the *in vitro* effects of dual angiogenesis inhibition using bevacizumab and TRC105 in HUVECs. Combination therapy was found to be more potent in decreasing HUVEC proliferation, migration, and tubular network formation than bevacizumab or TRC105 treatment alone [39]. 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 fibroblast growth factor (FGF) [29]. Finally, antibody to mouse endoglin potentiated the activity of multitargeted kinase inhibition that targets the VEGFR-2, in mouse bearing cancer xenografts [59]. For these reasons, endoglin blockade using TRC105 in combination with VEGF inhibition by pazopanib may provide greater clinical benefit than would be seen with either drug alone.

2.3.1. Studies with TRC105

Several studies with TRC105 are underway or have been completed. As of the date of this report, there have been 10 completed clinical trials of CD105, and four trials are ongoing. A total of 438 patients had been exposed to TRC105 monotherapy or combination therapy, of whom 99 received the combination of TRC105 and pazopanib. For a complete review of clinical information, please refer to the current TRC105 Investigational Brochure (IB).

2.3.1.1. Study 105ST101 Phase 1 Monotherapy

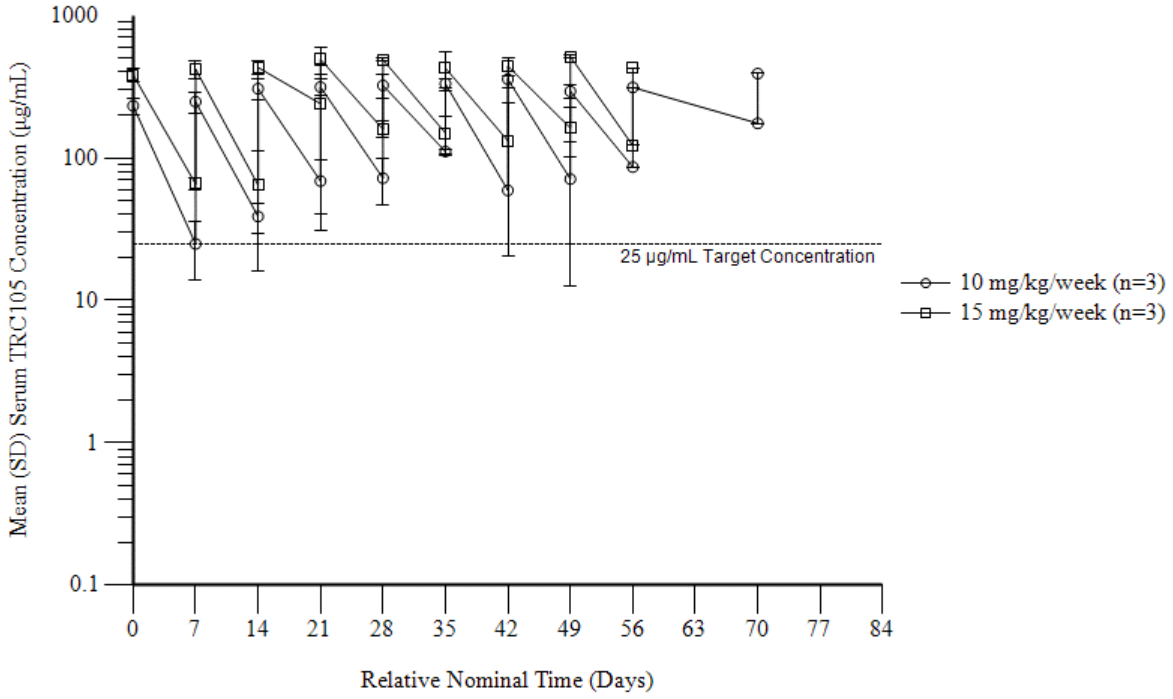
2.3.1.1.1. Study 105ST101 Phase 1 Monotherapy Pharmacokinetics

In the initial, safety Study 105ST101, TRC105 pharmacokinetics were assessed on patients with advanced or metastatic solid tumors (including renal cell, uterine, colorectal, synovial sarcoma, prostate, and GIST) enrolled at doses up to 15 mg/kg weekly. Detailed TRC105 pharmacokinetics are available from Study 105ST101, the first in human dose escalation study,

which explored a broad range of doses (0.01 to 15 mg/kg) and schedules (every 2 weeks and weekly).

Doses of 3 mg/kg, 10 mg/kg and 15 mg/kg dose levels produced measurable serum concentrations of TRC105 beyond the initial day of dosing. Volume of distribution at these doses was similar to plasma volume, which was consistent with preclinical toxicokinetics and would be expected for an antibody administered intravenously. Area under the curve (AUC) exposure increased supra-proportionally with dose whereas the maximum concentration (Cmax) appeared to be dose proportional. TRC105 clearance was consistent with target mediated disposition, and decreased clearance at higher doses was consistent with target saturation. Serum concentrations were achieved continuously in most but not all patients at a dose of 15 mg/kg every 2 weeks and were achieved continuously in all patients at a dose of 10 mg/kg weekly. TRC105 accumulated at a dose of 15 mg/kg weekly. Importantly, as shown in Figure 1, weekly dosing with 10 mg/kg produced continuous mean TRC105 serum concentrations above the target concentration of 25 µg/mL shown to saturate endoglin receptors and produce maximum inhibition of HUVEC activation *in vitro* (i.e., maximal inhibition of SMAD1 phosphorylation in response to BMP).

Figure 1: Single-Dose and Multiple-Dose Pharmacokinetic Data from Study 105ST101



2.3.1.1.2. Study 105ST101 Phase 1 Monotherapy Safety

A total of 50 patients with advanced or metastatic solid tumors (including renal cell, uterine, colorectal, synovial sarcoma, prostate, and GIST) 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 2 weeks and then 10 and 15 mg/kg weekly. Dose escalation proceeded stepwise until the top dose was reached. The maximum tolerated dose (MTD) was exceeded at 15 mg/kg weekly and the recommended phase 2 dose of TRC105 was therefore determined to be 10 mg/kg weekly or 15 mg/kg every 2

weeks. Three of 4 patients at 15 mg/kg weekly developed grade 3 hypoproliferative anemia (without leucopenia or thrombocytopenia) in cycle 2, and 1 of the 3 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 endoglin [34]. Anemia was reversible and manageable with dose reduction and standard supportive measures including erythropoietin and blood transfusion.

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

Infusion-related reactions were initially reported in the phase 1 study of TRC105 monotherapy (105ST101) in patients without premedication who received TRC105 produced in non-secreting murine myeloma (NS0) cells. Two of 21 patients treated up to 1.0 mg/kg with NS0 TRC105 drug supply experienced infusion-related reactions to TRC105. Both patients were among 6 treated at the 1.0 mg/kg NS0 TRC105 dose level. One patient experienced Grade 2 fever and Grade 1 chills after the initial infusion of TRC105, which resolved with oral acetaminophen and did not recur with acetaminophen premedication on subsequent infusion. A patient experienced Grade 3 hypersensitivity (allergic reaction) with the second infusion of TRC105. The hypersensitivity reaction consisted of symptomatic bronchospasm, urticaria, and hypotension that required parenteral medications and resulted in discontinuation of study treatment. TRC105 produced in Chinese hamster ovary (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 2 patients at 0.3 mg/kg treated with CHO-produced TRC105 experienced Grade 2 and Grade 3 infusion-related reactions with the first dose of TRC105 in the absence of premedication (the Grade 3 infusion-related reaction included diaphoresis, dyspnea, tachycardia and rigors). The Phase 1 105ST101 protocol was therefore amended to require a premedication regimen consisting of a glucocorticoid, acetaminophen, famotidine or a similar H2-histamine blocker, and an H1-histamine blocker such as diphenhydramine, and extend the initial infusion duration from 1 to 4 hours.

Mandating such premedication and extending the duration of the initial TRC105 infusion duration successfully reduced the frequency and severity of infusion-related reactions and allowed dose escalation to continue in the 105ST101 phase 1 study. One additional patient who received CHO-produced TRC105 at 1 mg/kg developed a Grade 3 infusion-related reaction with the third dose given over 2 hours despite premedication. This patient had experienced a Grade 2 infusion-related reaction when the dose was initially administered over 4 hours with premedication. In all 3 patients with Grade 3 infusion-related reactions, TRC105 was not detectable in serum at the time of dosing, which therefore allowed *de novo* binding of TRC105 to CD105 expressing endothelium within the vasculature. Grade 3 infusion-related reactions were not observed in patients dosed at 10 or 15 mg/kg in the Phase 1 105ST101 study who maintained TRC105 serum levels known to saturate CD105 binding sites for the full dosing interval. Only 7 patients have experienced a Grade 3 and only 1 patient experienced a Grade 4 infusion-related

reaction (of vasovagal reaction) out of 462 patients (1.7%) treated with TRC105 since the institution of the premedication regimen. For study 105SAR301 premedication will not include an H2-histamine blocker, as neutral stomach pH is known to decrease pazopanib exposure by up to 40% and H2-histamine blockade is not felt to significantly ameliorate typical signs and symptoms of TRC105 infusion-related reactions.

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 endoglin 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 (DLT) evaluation period. Fatigue was one of the more common AEs attributable to TRC105 and was more prevalent at doses above 3 mg/kg.

One patient developed DLT 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 with TRC105 0.1 mg/kg developed proteinuria considered a suspected adverse reaction to TRC105, but proteinuria was also noted prior to TRC105 dosing. Transient hypertension (156/112 mm Hg) without QT interval changes on electrocardiogram 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.

2.3.1.1.3. Study 105ST101 Phase 1 Monotherapy Efficacy

In study 105ST101 stable disease ≥ 2 months was observed in 21 of evaluable 45 patients (47%) and stable disease ≥ 4 months in 6 of 44 patients (14%) with advanced or metastatic solid tumors. Decreases in carcinoembryonic antigen (CEA), prostate-specific antigen (PSA), or cancer antigen 125 (CA-125) were noted in 7 of 21 patients (33%). One patient with castrate-refractory prostate cancer remains on TRC105 treatment after 8 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 3 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.

2.3.1.2. Study 105SAR101 Phase 1b/2a with Pazopanib

2.3.1.2.1. Study 105SAR101 Summary of Safety, Pharmacokinetics, and Immunogenicity

Study 105SAR101 was a Phase 1b/2 trial evaluating the combination of TRC105 and pazopanib in patients with advanced soft tissue sarcoma. In the Phase 1b dose escalation portion, the safety of TRC105 dosed weekly at 8 mg/kg and then 10 mg/kg given with pazopanib at 800 mg taken orally daily was evaluated. Because the single agent pazopanib dose is frequently de-escalated during the first month of dosing to ameliorate toxicity, the trial contained a 2- to 4-week run-in period of single agent pazopanib treatment, so that a tolerable dose would be determined in each patient prior to the introduction of TRC105. Using this schema, 3 patients were treated with TRC105 at 8 mg/kg weekly in and 15 patients were treated at 10 mg/kg weekly in the Phase 1b portion of the trial. There were no DLTs and the addition of TRC105 to pazopanib did not increase pazopanib toxicities [20].

Given the non-overlapping toxicity profile, Investigators recommended concurrent dosing of TRC105 with pazopanib starting on day 1 for the Phase 2 portion of the Phase 1b/2 study. Safety data from the Phase 2 portion of the trial that enrolled 63 soft tissue sarcoma patients indicate that toxicities remain non-overlapping and pazopanib dose adjustment can be made based on its product labeling, irrespective of concurrent dosing with TRC105. The toxicity profile of TRC105 was similar to that noted in single agent studies, recurrent infusion-related reactions were not observed, chronic steroid premedication was not required, and signs of the Osler-Weber-Rendu syndrome (e.g., low grade telangiectasia with associated epistaxis and gingival bleeding) were observed routinely. The safety profile for TRC105 in combination with pazopanib has been consistent with that observed in other studies of TRC105 where AEs characteristic of each individual drug did not increase in frequency or severity, with the possible exception of pneumothorax, when the two drugs were administered together.

AEs commonly (>10%) experienced by patients and believed by the sponsor to be reflective of the currently recognized toxicity profile of TRC105 include the following, which were predominantly grade 1-2: epistaxis (grade 1-3), headache (grade 1-3), fatigue (grade 1-3), gingival bleeding (grade 1), anemia (grade 1-3), infusion-related reaction (grade 1-3) and telangiectasia (grade 1). Patients also commonly (>10%) experienced the following AEs, judged by the investigator as being at least possibly related to TRC105: nausea (grade 1-2), vomiting (grade 1-3), flushing (grade 1-2), decreased appetite (grade 1-3), stomatitis (grade 1-2). One grade 4 suspected adverse drug reaction of acute respiratory distress syndrome (ARDS) was reported, from which the patient recovered. One suspected adverse drug reaction of grade 2 transient ischemic attack was reported. One patient experienced grade 3 colitis, 1 patient experienced grade 3 embolism and 1 patient experienced grade 1 bronchopulmonary hemorrhage.

Seven patients treated with the combination of TRC105 and pazopanib experienced a pneumothorax, a known adverse reaction associated with the use of pazopanib in soft tissue sarcoma. The frequency of pneumothorax was similar to the frequency reported with single agent

pazopanib [60, 61]. All 7 patients had lung metastases and grade 3 was the highest grade reported.

At 10 mg/kg weekly, continuous serum concentrations of TRC105 were achieved in 12 of 15 patients at exposures above the target concentration of 25 µg/mL by the time of the third weekly dose (N=15; mean: 97 µg/mL)) and were achieved in 27 of 28 patients at exposures above the target concentration of 25 µg/mL by the time of the fifth weekly dose (N=28; mean: 127 µg/mL). Notably, trough concentrations were similar following dosing with TRC105 at 10 mg/kg as a single agent or with pazopanib. Immunogenicity was rarely observed: 3 patients had samples with a moderate to high signal defined as greater than 3 times above the assay cut point. Further, steady state pazopanib plasma concentrations when dosed with TRC105 were similar to those reported following single agent dosing.

A TRC105 dose reduction schedule (starting with dose de-escalation to 8 mg/kg weekly) has been established to manage drug related toxicity. The majority of patients requiring a dose reduction of TRC105 dose reduced to 8 mg/kg weekly. TRC105 dose reductions have resulted in observations of improved tolerability and have not compromised response, while maintaining TRC105 concentrations necessary to avoid recurrent infusion-related reactions. All 3 patients remain in CR after reducing the TRC105 dose to 8 mg/kg weekly (3 patients) and then to 6 mg/kg weekly (1 patient). Although there is expected inter-patient and intra-patient variability, dose reductions have generally resulted in decreased serum exposures. For a dose reduction from 10 to 8 mg/kg (a 20% reduction in dose), paired before and after data are available for 13 patients and show a percent reduction in pre-dose concentration by an average of 14% (SD 83%) and median 52%. For dose reduction from 8 to 6 mg/kg (a 25% reduction in dose), paired data are available for only 2 patients and show a percent reduction in pre-dose concentration by an average of 8% (SD 52%) and median 8%. One patient required dose reduction to 4 mg/kg weekly and remained on study for 5 weeks at the reduced dose. In some cases a dose reduction did not decrease TRC105 exposure. The lack of an observed decrease in exposure in patients who had dose reduction may reflect decreased endoglin expression, consistent with a reduction in tumor burden as a result of treatment response. Because TRC105 is cleared by target mediated disposition, clearance is expected to decrease in patients with lower numbers of endoglin-expressing tumor vessels as a consequence of a reduction in tumor burden. This phenomenon may explain the variability and non-linearity of systemic exposure as a function of dose level.

Infusion-related reactions have been rare with repeat dosing in patients who have dose reduced. Two patients experienced 1 infusion-related reaction each, which was not observed on subsequent infusions: 1 patient on the day of dose reduction and the second patient on day 1 of cycle 18.

2.3.1.2.2. Study 105SAR101 Summary of Efficacy

Preliminary clinical data from the phase 1b portion of study 105SAR101 demonstrate that the combination is well tolerated with signs of clinical activity. Six of 18 soft tissue sarcoma patients (33% of those evaluable for efficacy) exhibited >10% tumor reduction by RECIST 1.1, including 1 patient with cutaneous angiosarcoma that experienced a durable CR that is ongoing for 25 months as of October, 2016. Duration of therapy ranged from 2 to 27+ cycles (in the phase 1b

portion of the study, each cycle was 28 days with the exception of cycle 1, when pazopanib was given as a single agent, for 2-4 weeks.

A total of 5 patients with angiosarcoma were initially treated in the phase 1b and 2a portions of study 105SAR101 and all 5 patients had radiographic reductions in tumor volume. Two of these 5 patients had durable CR (including the patient noted above), 1 cutaneous angiosarcoma patient had a 25% reduction in tumor volume before exiting the study at week 10 due to an unrelated AE of duodenal ulcer. The other 2 patients, both with visceral angiosarcoma, experienced tumor reductions of 7% and 14%. Notably the median PFS in these patients as of June 2016 was greater than 12.9 months as assessed by RECIST 1.1.

Data available from the patients in the angiosarcoma expansion cohorts continue to demonstrate activity and tolerability of TRC105 in combination with pazopanib.

2.4. Study 105SAR301 Rationale

The rationale for combining TRC105 with pazopanib for the treatment of angiosarcoma is three-fold. First, several nonclinical studies indicate endoglin is a dominant mechanism of escape from VEGF inhibitor therapy. Pazopanib is a VEGF inhibitor indicated for the treatment of adult patients with selective subtypes of advanced STS, including angiosarcoma, who have received prior chemotherapy for metastatic disease or who have progressed within 12 months following (neo) adjuvant therapy. Nonclinical and preliminary clinical data suggest that targeting the endoglin pathway and VEGF pathway concurrently is a more effective means of inhibiting angiogenesis than targeting either pathway alone; accordingly, the combination of TRC105 and pazopanib may be a more effective means of treating sarcoma compared to single agent pazopanib. Second, endoglin is expressed densely on tumor cells in angiosarcoma, a malignancy of endothelial cells, providing an additional mechanism of direct targeting of cancer cells (in addition to targeting proliferating tumor vasculature). Finally, because they target distinct pathways, the toxicity profile of TRC105 and pazopanib are non-overlapping and the drugs have been tolerable when given concurrently for more than 24 months.

Clinical data from Phase 1b/2 study 105SAR101 validate the biological rationale, in that robust activity, including durable complete responses, was observed in angiosarcoma. The combination of the recommended TRC105 dose of 10 mg/kg weekly with standard dose pazopanib was also shown to be well tolerated. Importantly, the tolerability of the combination allows for extended dosing durations in contrast to more toxic chemotherapy regimens.

2.5. Population to be Studied

Patients with histologically-confirmed angiosarcoma that is not amenable to curative intent surgery (e.g., metastatic or bulky disease and disease for which surgical resection would carry an unacceptable risk to the patient) who have not received pazopanib or TRC105 previously will be enrolled in this trial.

Due to the rarity of angiosarcoma, and lack of standard of care for patients 12 to 17 year of age, these patients, who are eligible only after enrollment in Cohort 1 is complete, will not be randomized and will receive only the combination TRC105 and pazopanib treatment.

2.6. Potential Risks and Benefits to Human Patients

Please refer to the current TRC105 Investigational Brochure (IB) for a complete review of potential risks and benefits of TRC105.

2.6.1. Potential Risks

2.6.1.1. TRC105

Common (≥ ~10%) TRC105 suspected AEs across all studies were headache, epistaxis, fatigue, anemia, nausea, infusion-related reaction, gingival bleeding, flushing, vomiting, hypertension, decreased appetite, telangiectasia, and diarrhea.

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

Grade 1 and 2 periodontal disease reported under various terms including gingival pain, gingival disorder, gingival swelling and gingival infection was reported in approximately 8% of patients.

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 interruption and/or reduction. The anemia related to TRC105 is hypoproliferative and non-hemolytic in nature, reversible with interruption of treatment, and may be managed with transfusion, erythropoietin or darbepoetin, and other interventions as appropriate. Anemia may also be related to blood loss from epistaxis or gingival bleeding that result from mucocutaneous telangiectasia.

Infusion-related reactions have been observed following TRC105 administration and may include one or more of the following signs or symptoms: rigors, chills, flushing, headache, bronchospasm, urticaria, fever, rash, dyspnea, nausea, vomiting, change in blood pressure, and change in heart rate. Infusion-related reactions generally occurred with the initial infusion in patients dosed at recommended phase 2 doses of 10 mg/kg or 15 mg/kg every 2 weeks, and are typically of grade 1 or 2 severity following dosing with premedication that includes glucocorticoids. All patients treated with TRC105 should receive appropriate premedication as defined in this protocol, be monitored during the TRC105 infusion, and be treated appropriately for infusion-related reactions (including possible TRC105 dose interruption). Hypersensitivity reactions with infusions are a potential risk for sensitized patients, and TRC105 should be avoided or used with caution in patients with known hypersensitivity to any component of the drug product.

Pneumothorax has been observed in trials of TRC105 administered with pazopanib in patients with lung metastases. Pneumothorax is an expected AE associated with the use of pazopanib, particularly in sarcoma patients with lung metastases. However, pneumothorax was observed in 1 patient, also with lung metastases, receiving single-agent TRC105.

2.6.1.2. Pazopanib

The most common adverse reactions in patients with advanced soft tissue sarcoma (≥ 20%) are fatigue, diarrhea, nausea, decreased weight, hypertension, decreased appetite, hair color changes, vomiting, tumor pain, dysgeusia, headache, musculoskeletal pain, myalgia, gastrointestinal pain, and dyspnea..

Further details are available in the current product labeling for pazopanib, such as the current package insert.

2.6.1.3. Other Study 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 breast-feed while on this study. Women of childbearing potential must have a negative serum 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 acceptable methods of birth control, one of which must be highly effective (see below), at the same time during study treatment (including during temporary breaks from treatment), and for at least 180 days after stopping TRC105 or pazopanib. Men with pregnant partners and men with non-pregnant partners that are of childbearing potential must agree to use a condom with spermicide, during study treatment (including during temporary breaks from treatment), and for at least 180 days after stopping TRC105 or pazopanib. The long term risk of infertility is unknown. Ovarian failure has been observed with other antiangiogenic agents. Acceptable birth control methods considered highly effective are the following:

- bilateral tubal ligation
- intrauterine device (IUD)
- vasectomy that has received medical confirmation of surgical success
- Sexual abstinence[a]

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

Acceptable birth control methods **not** considered highly effective include the following:

- male or female condom with spermicide[a]
- cap, diaphragm or sponge with spermicide

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

2.6.2. Potential Benefits

TRC105 is an investigational product, and its efficacy has not been established. Although not approved specifically for angiosarcoma, pazopanib is approved in the United States for the treatment of patients with advanced soft tissue sarcoma (including angiosarcoma) who have received prior chemotherapy and approved in Europe for adult patients with selective subtypes of advanced soft tissue sarcoma (including angiosarcoma) who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy. Together, the use of TRC105 with pazopanib may result in more effective angiogenesis inhibition and improved clinical efficacy over that seen with pazopanib alone.

2.7. Study Conduct

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying the European Union Directive 2001/20/EC and the United States Code of Federal Regulations (CFR), Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any protocol amendments and the subject informed consent must receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

3. TRIAL OBJECTIVES AND ENDPOINTS

3.1. Primary Objective

- To compare PFS of TRC105 and pazopanib vs single agent pazopanib in patients with unresectable angiosarcoma

3.2. Secondary Objectives

- To compare the objective response rate (ORR) of TRC105 and pazopanib vs single agent pazopanib in patients with unresectable angiosarcoma
- To compare overall survival (OS) of TRC105 and pazopanib vs single agent pazopanib in patients with unresectable angiosarcoma
- To assess the overall safety and tolerability of TRC105 and pazopanib vs single agent pazopanib in patients with unresectable angiosarcoma
- To characterize patient reported outcomes between the two arms of the study
- To characterize the pharmacokinetic (PK) profile of TRC105 and pazopanib between the two arms of the study
- To assess PFS and ORR by Investigator assessment between the two arms of the study
- To characterize the immunogenicity of TRC105

3.3. Exploratory Objectives

- To correlate efficacy endpoints (e.g., PFS, ORR and OS) with endoglin expression on angiosarcoma tumor samples
- To correlate efficacy endpoints (e.g., PFS, ORR and OS) with circulating angiogenic protein biomarkers
- To correlate efficacy endpoints (e.g., PFS, ORR and OS) with numbers of endoglin expressing circulating tumor cells (CTCs)

4. TRIAL ENDPOINTS

4.1. Primary Endpoint

- PFS is defined as time from randomization to either first disease progression (per independent radiology review of images by RECIST 1.1) or death from any cause. For the purpose of analysis for patients who are alive at the time of analysis and have not had disease progression, the following rules will apply: (1) The patient will be censored on the date of the last tumor assessment documenting absence of progressive disease; (2) if the patient was given antitumor treatment other than study drug treatment, the patient will be censored as of the date of the last tumor assessment prior to initiating that antitumor therapy; (3) if the patient was removed from study for toxicity or other reason, the patient will be censored as of the date of the last tumor assessment on study. With regard to missed tumor assessments, in the event of one missed tumor assessment followed by a subsequent assessment of progressive disease (PD), the subsequent PD assessment qualifies as objective tumor progression. In the event of more than one consecutive missing tumor assessment followed by a subsequent assessment of PD, the patient will be censored at the last adequate tumor assessment.

4.2. Secondary Endpoints

- Objective response rate (ORR) is defined as the number of patients with a best response of CR or PR divided by the number of randomized patients. ORR is defined as the best response designation recorded between the date of randomization and the date of documented progression, as determined by Central Radiographic Review according to RECIST 1.1, or date of subsequent therapy, whichever occurs first. For patients without documented progression or subsequent therapy, all available response designations will contribute to the ORR determination. A designation of CR or PR in this study requires confirmation at a subsequent consecutive assessment at least 4 weeks following the initial designation of CR or PR, respectively. Duration of response (DR) will be reported in patients who achieve ORR, but without a formal statistical comparison between arms.
- Overall Survival (OS) is defined as the time between the date of randomization and the date of death from any cause. Overall survival will be calculated in days as: Date of Death – Date of Randomization +1. Subjects alive or lost to follow-up at the time of analysis will be censored at the date when they were last known to be alive.
- Type, incidence, severity (graded by NCI CTCAE, Version 4.03), timing, seriousness, and relatedness of AEs and laboratory abnormalities.
- Patient reported outcomes as measured by the EuroQol five dimensions questionnaire (EQ-5D-5L) and the EORTC QLQ-C30 questionnaire.
- TRC105 and pazopanib concentrations will be measured using validated methods from peak and trough samples.

- Anti-TRC105 antibodies will be measured using validated methods and anti-drug antibody (ADA) titers will be correlated with PK parameters and AEs.

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design and Plan

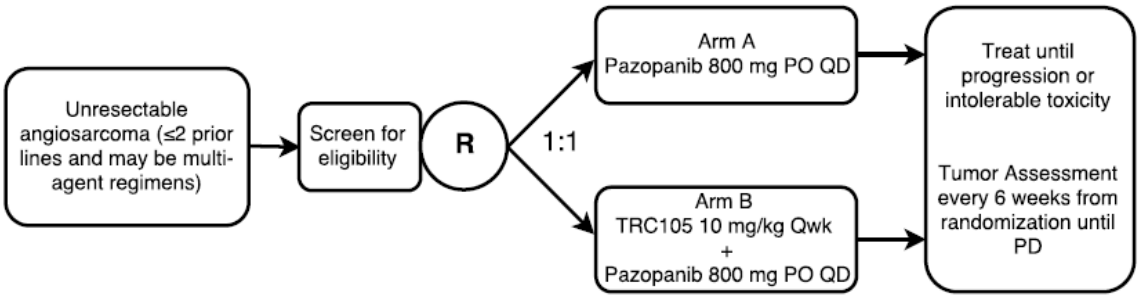
This is a multinational, multicenter, randomized, open label, parallel group, phase 3 study of TRC105 in combination with standard dose pazopanib compared to pazopanib alone in patients with angiosarcoma not amenable to curative intent surgery (e.g., metastatic or bulky disease and disease for which surgical resection would carry an unacceptable risk to the patient) who have not received pazopanib or TRC105 previously.

Adult patients will be randomized in a 1:1 ratio to TRC105 in combination with standard dose pazopanib (Arm B) vs standard dose pazopanib alone (Arm A). Patients will be stratified by angiosarcoma type (cutaneous vs non-cutaneous) and the number of lines of prior systemic therapy for angiosarcoma (0 versus 1 or 2). For the purposes of this study, cutaneous angiosarcoma will include primary skin/scalp angiosarcoma; all other angiosarcoma including primary subcutaneous angiosarcoma will be categorized as non-cutaneous (e.g., visceral, bone, soft tissue).

Due to possible differences in treatment effect on the cutaneous and non-cutaneous angiosarcoma subgroups, an adaptive enrichment design will be employed. An interim analysis is planned after 40 events or 30 days after the enrollment of 120 patients from Cohort 1 and will result in one of the following decisions: (1) no change to the study design and sample size, (2) no change to the study design but an increase in the sample size, or (3) termination of enrollment of an unresponsive non-cutaneous angiosarcoma subtype and adjustment of the sample size of the remaining cutaneous subtype. Cohort 1 is defined as the adult patients enrolled prior to the interim analysis. Enrollment at a given site will be limited to a maximum of 15% of total patients. Additionally, enrollment of Cohort 1 will be monitored to ensure that no more than 50% of the total adult patients enrolled will have the non-cutaneous subtype.

Treatment in the assigned arm must start within 3 calendar days of randomization.

Figure 2: Trial Design Schema



5.1.1. Overview

All patients must sign a consent form (and assent if under 18) prior to undertaking any protocol-specified procedures. Prospective patients will be screened to determine if they qualify for the

study within 28 days of randomization. Treatment in the assigned arm must start within 3 days of randomization. Toxicities will be graded according to the NCI CTCAE Version 4.03.

All adult and adolescent patients with a BSA > 1.8 m^2 will initially receive pazopanib 800 mg p.o. daily either as single agent or in combination with TRC105. All other patients 12-17 years of age, who are eligible for only Cohort 2, must weigh ≥ 40 kg at study enrollment will initially receive pazopanib 600 mg p.o. daily in combination with TRC105. The dose of TRC105, administered in the combination treatment arm with pazopanib (Arm B) will be the same for patients of all ages, and consist of TRC105 at 3 mg/kg on day 1, 7 mg/kg on day 4, and 10 mg/kg on day 8 and weekly thereafter.

Dose reductions of pazopanib and TRC105 are allowed per patient tolerance.

5.1.2. Trial Procedures

All on-study procedures are permitted within the time window indicated in the Schedule of Assessments (Table 3 and Table 4).

5.1.2.1. Screening

The following screening procedures must be performed within 28 days prior to the first day of study therapy and will be performed according to the Schedule of Assessments (Table 3 and Table 4), with data collected in the eCRFs (except for data pertaining to central radiographic review).

- Patient signature on current IRB/EC-approved informed consent form. Prior to undergoing any study-specific procedure, patients must read and sign the current IRB/EC-approved informed consent form. Patients may sign consent (and assent if under 18) prior to the 28-day screening period.
- Medical history, baseline signs and symptoms, prior cancer therapy (along with the best response to each prior chemotherapy regimen and the reason for discontinuation of each regimen), prior cancer surgery, prior radiation therapy, the suspected cause of the angiosarcoma (to the extent it may be known or suspected), the specific reason the angiosarcoma tumor is considered not amenable to surgery, drug allergies, primary diagnosis and demographics.
- Physical examination including examination of all major body systems, Eastern Cooperative Oncology Group (ECOG) performance status, and vital signs.
- Hematology (including serum iron, transferrin and ferritin), coagulation (INR) and serum chemistry (including thyroid stimulating hormone [TSH]) to be performed locally.
- Serum pregnancy test for all females of childbearing potential to be performed locally.
- Urinalysis (e.g., dipstick) to be performed locally. Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated.
- All patients: Computerized tomography (CT) or magnetic resonance imaging (MRI) scans of chest, abdomen and pelvis in addition to any other applicable sites of disease within 7 days of randomization. Brain and bone scans to be performed prior to starting the study if metastasis is suspected.

- Patients with cutaneous tumors: digital 2-dimensional (2D) color photography will be used to assess cutaneous lesions.
- 12-lead electrocardiogram (ECG) in triplicate (QTc, 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.
- Tumor Tissue Specimens: angiosarcoma tumor specimen for each study participant. See Section 10.1.5 and separate laboratory guide for further collection and shipment information.
- Patient questionnaires to characterize quality of life to be collected prior to randomization.
- **Pediatric patients**: plain films (anterior-posterior and lateral) of right and left distal femur to evaluate the epiphyseal plates

5.1.2.2. Trial Period

Screening radiographic and photographic assessments, qualifying hematology (including iron studies), blood chemistry (including TSH testing), coagulation, urinalysis, physical examination, ECG, pregnancy test and quality of life questionnaires do not need to be repeated on cycle 1 day 1 (C1D1) if acceptable screening assessments are performed within 7 days prior to randomization. Following randomization, C1D1 lab results do not need to re-meet eligibility criteria. However, lab abnormalities should be corrected as needed, per the investigator discretion, prior to treatment initiation. On days of TRC105 administration for patients assigned to Arm B, all assessments should be performed prior to dosing with TRC105 unless otherwise indicated in the Schedule of Assessments (Table 4).

Patients who cannot tolerate pazopanib or TRC105 therapy and who demonstrate a response of complete response (CR), partial response (PR) or stable disease (SD) with the combination and are thought to benefit from continued single agent therapy may continue on study on TRC105 or pazopanib alone. The following will be performed according to the Schedule of Assessments (Table 3 and Table 4), with data collected in the eCRFs (except for data pertaining to central radiographic review).

- Physical examination (may be performed up to 3 days prior to day 1 of each cycle) 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 (Arm B): 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-related reaction that has not yet resolved).

- Hematology, coagulation (INR) and serum chemistry (including TSH) to be performed locally.
- Serum pregnancy test for all females of childbearing potential to be performed locally.
- 12-lead ECG in triplicate (QTc, PR and QRS intervals and heart rate will be captured).
  - In case of prolongation of QTc interval > 500 msec, pazopanib will be held and appropriate investigations will be performed (e.g., cardiologist consultation, repeat ECG, continuous ECG monitoring, etc.). Rechallenge with pazopanib will be guided by cardiology input and will require authorization by TRACON.
- Urinalysis (e.g., dipstick) to be performed locally. Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated.
- Blood sampling for TRC105 and pazopanib pharmacokinetics to be analyzed by a central laboratory (see laboratory manual for specific instructions regarding collection times, procedures, processing, storage and shipment).
- Blood sampling for immunogenicity to be analyzed by a central laboratory (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).
- Blood sampling for protein biomarker analysis by a central laboratory (see laboratory manual for specific instructions regarding collection processing, storage and shipment)
- Blood sampling for CTCs by a central laboratory (see laboratory manual for specific instructions regarding collection processing, storage and shipment)
- **All patients**: CT or MRI scans of chest, abdomen and pelvis in addition to any other applicable sites of disease for all patients. Scan of the chest, abdomen, and pelvis to be performed on-study as outlined in the Schedule of Assessments. 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 scans to be performed if metastasis is detected prior to starting the study or if suspected during study conduct.
- Patients with cutaneous tumors: digital 2D color photography will be used to assess cutaneous lesions. Assessment of cutaneous lesions to be performed as outlined in the Schedule of Assessments. Known areas of disease should be consistently followed throughout the study. Assessments should be performed whenever disease progression is suspected. Allowable window is +/- 7 days.
- Tumor assessments will continue to be collected on protocol schedule for all patients who come off study drug for reasons other than RECIST 1.1 defined PD until RECIST 1.1 defined PD or start of a new therapy.
- Administration of TRC105 for patients in Arm B. TRC105 diluted in normal saline will be administered as a 1 to 4 hour infusion (+/- 15 minutes) following premedication (see Section 7.1.6) according to the Schedule of Assessments.
  - Pazopanib dosing. The oral dose of pazopanib is 800 mg for adult and for adolescent patients with a BSA > 1.8 m^2 and 600 mg for all other patients < 18 year of age (who

must weight ≥ 40 kg at study enrollment) once daily, in the evening except on cycle 1 day 15 per the footnote in the Schedule of Assessments, when the patient will be administered the pazopanib dose for that day in the clinic, without food (recommend at least 1 hour before or 2 hours after a meal) beginning on cycle 1 day 1.

- Patient questionnaires to characterize quality of life will be collected at the time points indicated in the Schedule of Assessments.
- Assessment of AEs.
- Assessment of concomitant medications and concomitant treatments.
- **Pediatric patients**: plain films (anterior-posterior and lateral) of right and left distal femur to evaluate the epiphyseal plates.

5.1.3. 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 6 weeks on study for radiologic/photographic tumor assessments). The following will be performed according to the Schedule of Assessments (Table 3 and Table 4), with data collected in the eCRFs (except for data pertaining to central radiographic review).

- Physical examination including examination of all major body systems, ECOG performance status, and vital signs.
- 12-lead ECG in triplicate (QT, PR and QRS intervals and heart rate will be captured).
- Hematology, and serum chemistry (including TSH) to be performed locally.
- Urinalysis (e.g., dipstick) to be performed locally. Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated.
- Blood sampling for TRC105 and pazopanib pharmacokinetics to be analyzed by a central laboratory (see laboratory manual for specific instructions regarding collection times, procedures, processing, storage and shipment).
- Blood sampling for immunogenicity to be analyzed by a central laboratory (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).
- Blood sampling for protein biomarker analysis by a central laboratory (see laboratory manual for specific instructions regarding collection processing, storage and shipment)
- All patients: CT or MRI scans of chest, abdomen and pelvis in addition to any other applicable sites of disease.
- Patients with cutaneous tumors: digital 2D color photography should be used to assess cutaneous lesions.
- **Tumor assessments will continue to be collected on protocol schedule for all patients who come off study drug for reasons other than RECIST 1.1 defined PD until RECIST 1.1 defined PD or start of a new therapy.**

- Assessment of AEs.
- Assessment of concomitant medications and concomitant treatments.
- **Pediatric patients**: plain films (anterior-posterior and lateral) of right and left distal femur to evaluate the epiphyseal plates.

5.1.4. Post-Treatment Follow-up

The following will be performed according to the Schedule of Assessments (Table 3 and Table 4), with data collected in the eCRFs (except for data pertaining to central radiographic review). Samples should be collected and assessments performed even if new anti-cancer therapy commences during the follow-up period.

- Assessment of AEs. The Investigator should continue to report any study treatment related or suspected AEs that occur beyond the AE reporting period.
- Blood sampling for TRC105 and pazopanib pharmacokinetics will be analyzed by a central laboratory (see laboratory manual for specific instructions regarding collection times, procedures, processing, storage and shipment).
- Blood sampling for immunogenicity to be analyzed by a central laboratory (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).
- Serum pregnancy test for all females of childbearing potential to be performed locally.
- Assessment of concomitant medications and concomitant treatments.
- Overall Survival follow-up via telephone or routine visit should occur every 3 months following the last dose of TRC105 or pazopanib until death.

Table 3: Schedule of Assessments Arm A: Single Agent Pazopanib

Protocol Activities	Screening	Cycle 1 [25]			Cycle 2 [25]			Cycle 3+ [22] [25]			End of Treatment [3]	28-Day Follow-up [23]	Overall Survival [24]
	Day -28	Day 1 [1] [2]	Day 8 [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		
Laboratory Studies													
Hematology [8]	X+Fe	X		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			X			X	X	
Urinalysis [10]	X	X			X			X			X		
Treatment w/ Study Drug													
Pazopanib [11]		**Daily**											
Tumor Assessments													
Tumor Imaging [12]	X	**Every 42 days from randomization**									X		
2D Photography [13]	X	**Every 42 days from randomization**									X		
Other Clinical Assessments													
12-Lead ECG [14]	X	X		X	X						X		
Concomitant Medications/Treatments [15]	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events [16]		X	X	X	X	X	X	X	X	X	X	X	
Special Laboratory Assessments													
Pazopanib PK [17]				X	X			Even Cycles			X	X	
Protein Biomarkers [18]		X			X			Even Cycles			X		
CTCs [19]		X						Cycle 3					
Archival Tumor Tissue [20]	X												
Other Assessments													
Patient Reported Outcomes [21]	Day -7							C3, C4 & C5					
Overall Survival													
Phone Call [24]													Every 3 Months

- Patients randomized to receive pazopanib alone (Arm A) are required to complete clinic visits only on Days 1 beyond Cycle 2 (starting with Cycle 3). Adverse events and concomitant medications/treatments assessments can be completed via documented phone call.

Arm A Schedule of Assessments Footnotes

1. **Clinic Visit Days:** All assessments should be performed prior to pazopanib dosing unless otherwise indicated. Each cycle is 21 days in duration. **If pazopanib dosing is held, all other required assessments should still be performed in accordance with the schedule of assessments.**
2. **Cycle 1 day 1: Treatment must start within 3 calendar days of randomization**. C1D1 activities should be completed prior to beginning study drug treatment. Hematology (including iron studies), blood chemistry (including TSH testing), urinalysis, physical examination, ECG, pregnancy test and quality of life questionnaires 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 (EOS) visit should generally occur within 7 days (+/- 2 days) of the last dose of study drug. Assessments other than pharmacokinetics, and protein biomarkers do not need to be repeated if performed within the previous 2 weeks (previous 6 weeks for radiologic/photographic tumor assessments). Follow-up visits should occur 28 days following the last dose of 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; may be performed up to 3 days prior to clinic visit date.
7. **Vital Signs:** Heart rate, temperature, blood pressure, respiratory rate, weight.
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 only if screening assessments were performed more than 7 days prior to cycle 1 day 1. Iron studies (Fe: serum iron, ferritin, transferrin) to be performed according to the schedule of assessments and as clinically indicated during the study. Lab assessments may be performed within 3 days prior to clinic visit. In addition to the assessments scheduled for the clinical trial, patients should undergo assessment as appropriate to ensure safe treatment. See Section 9.1.1.1 for specific panel collection requirements.
9. **Pregnancy Test:** Testing to be performed locally. All female patients of childbearing potential must have a negative serum pregnancy test within 7 days prior to cycle 1 day 1, day 1 of every cycle and 28 days following the last dose of pazopanib.
10. **Urinalysis:** To be performed locally. Cycle 1 day 1 urinalysis (e.g., dipstick) 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. **Pazopanib Dosing:** Oral pazopanib will be dosed once daily in the evening at 800 mg starting on cycle 1 day 1 in the absence of toxicity on days 1-21 of each 21-day cycle according to the pazopanib package insert. Dose reductions are allowed based on individual patient tolerability beginning with cycle 1. See Section 7.2 for specific dosing guidelines.
12. **Tumor Imaging:** All patients will undergo radiographic imaging. CT or MRI scans of chest, abdomen, and pelvis with contrast to be performed at screening within 7 days prior to randomization and every42 days from the date of randomization (+/- 7 days). If subjects are unable to receive CT contrast due to CT contrast medium allergy or renal insufficiency, enhanced MRI scans may be used. A combination of non-contrast CT and MRI studies (such as chest CT without contrast and abdominal MRI with contrast) may be used. The same method of assessment must be used throughout the course of the study thereafter. Similarly, if a subject develops a contraindication to CT contrast during the course of the study; assessments may shift to non-contrast CT of the chest and contrast-enhanced MRI of the abdomen for subsequent scans. In addition, a brain MRI or CT with contrast to be performed at screening and on study as needed if metastases are suspected. A bone scan is to be performed at screening if bone metastases is suspected. If a bone scan documents bone disease at baseline, it needs to be repeated only when complete response is identified or progression in bone is suspected. All other known areas of disease should be consistently followed throughout the study. Assessments should be performed whenever disease progression is suspected. **A designation of CR or PR in this study requires confirmation at a subsequent consecutive assessment separated by at least 4 weeks following the initial designation of CR or PR,**

respectively. **Tumor imaging will continue to be collected on protocol schedule for all patients who come off study drug for reasons other than RECIST 1.1 defined PD until RECIST1.1 defined PD or start of a new therapy**. Allowable window for tumor imaging studies is +/- 7 days.

13. **2D photography:** Patients with cutaneous tumors will undergo digital 2D color photography in addition to radiographic imaging, which will be performed at screening within 7 days prior to randomization and every 42 days from the date of randomization (+/- 7 days). Screening assessment will be centrally reviewed in real time. Assessments should be performed whenever disease progression is suspected. 2D photography will continue to be collected on protocol schedule for all patients who come off study drug for reasons other than RECIST 1.1 defined PD until RECIST1.1 defined PD or start of a new therapy Allowable window is +/- 7 days.
14. **12-Lead ECG:** Three consecutive 12-lead ECGs at least 2 minutes apart will be performed at screening, cycle 1 day 1 (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), cycle 1 day 15, day 1 of cycle 2 and EOS. **Note: on cycle 1 day 15 pazopanib dosing will occur in the clinic and ECGs will then be performed no sooner than 2 hours following pazopanib dosing (at the time of expected C_{max}). However, pazopanib dosing should not be repeated if the patient dosed within 12 hours at home.** On the ECG assessment on day 1 of cycle 2, dosing in the clinic is not required. If the patient develops an arrhythmia, the ECG should be repeated on day 1 of each subsequent cycle. In case of prolongation of QTc interval > 500 msec, pazopanib will be held and appropriate investigations will be performed (e.g., cardiologist consultation, repeat ECG, continuous ECG monitoring, etc.). Rechallenge with pazopanib will be guided by cardiology input and will require authorization by TRACON. Additional ECGs may be performed on study as clinically indicated.
15. **Concomitant Medications and Treatments:** Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and through 28 days following the last dose of study treatment.
16. **Adverse Events:** The AE reporting period for this trial begins with informed consent and ends following the completion of the 28-day-follow-up visit or at least 28 days after the last dose of pazopanib is administered, whichever occurs later. All AEs that occur in trial patients during the AE reporting period must be reported to TRACON, whether or not the event is considered study treatment-related.
17. **Pazopanib Pharmacokinetics:** A 5 mL blood sample for pazopanib concentration to be collected at the time-points indicated in the Schedule of Assessments. In addition, **on cycle 1 day 15 pazopanib dosing will occur in the clinic to assess C_{max} and the sample should be collected no sooner than 2 hours following pazopanib dosing. However, pazopanib dosing should not be repeated if the patient dosed within 12 hours at home.** On the pazopanib pharmacokinetic assessment on day 1 of cycle 2, pazopanib dosing in the clinic is not required. Samples will be stored at approximately -70°C. Samples will be batch shipped as indicated in the laboratory manual to a central 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 or after dose reductions.
18. **Protein Biomarkers:** One 10 mL purple top (K_2EDTA) 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.
19. **CTCs:** One 10 mL EDTA tube will be collected at the time-points indicated in the Schedule of Assessments and be analysed by a central laboratory. See separate laboratory guide for further collection and shipment information.
20. **Archival Tumor Tissue:** Tumor specimens (formalin-fixed, paraffin-embedded) of the primary cancer and/or metastatic cancer specimen for each study participant, if available. See Section 10.1.5 and separate laboratory guide for further collection and shipment information.
21. **Patient Reported Outcomes**: Patient questionnaires to characterize quality of life will be collected at the time-points indicated in the Schedule of Assessments. Baseline assessment must be completed prior to randomization.
22. **Cycle 3+ Treatment: Patients** who demonstrate a response of CR, PR or SD will be eligible for additional treatment until progression.
23. **28-Day Follow-up:** The follow-up visit should occur 28 days following the last dose of pazopanib. The allowable visit window is +/- 7 days.
24. **Overall Survival:** Telephone or routine visit should occur every 3 months following the last dose of TRC105 until death. Allowable window for each visit is +/- 1 week.

25. Allowable window for each visit within the cycle is +/- 2 days unless otherwise stated. **The +/-2 day window does NOT apply to randomization.** Cycle 1 day 1sets the clock for study visits, and all study visits should be scheduled in reference to cycle 1 day 1. For example, if cycle 1 day 1 was on June 1st, and patient is not able to return for C1D8 until June 10th the C1D15 visit should take place on June 15th (15 days from cycle 1 day1).

Table 4: Schedule of Assessments Arm B: TRC105 plus Pazopanib Combination Therapy

Protocol Activities	Screening	Cycle 1 [28]				Cycle 2 [28]			Cycle 3+ [25] [28]			End of Treatment [3]	28 - Day Follow -up[26]	Overall Survival [27]
	Day -28	Day 1 [1] [2]	Day 4 [1]	Day 8 [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			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			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	X			
Pazopanib [12]		**Daily**												
Tumor Assessments														
Tumor Imaging [13]	X	**Every 42 days from randomization**										X		
2D Photography [14]	X	**Every 42 days from randomization**										X		
Other Clinical Assessments														
Pediatric radiographic imaging [30]	X	**Every 42 days from enrollment via the randomization system**										X		
12-Lead ECG [15]	X	X			X	X						X		
Concomitant Medications/Treatments [16]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events [17]		X	X	X	X	X	X	X	X	X	X	X	X	
Special Laboratory Assessments														
Anti-TRC105 Antibody [18]		X				X			Even Cycles			X	X	
TRC105 PK: pre-infusion [19]			X	X	X	X		X	Even Cycles					
TRC105 PK: end of infusion [19]		X	X	X								X	X	
Pazopanib PK: pre-infusion [20]					X	X			Even Cycles			X	X	
Pediatric PK [29]		X	X	X	X	X		X	Even Cycles			X	X	
Protein Biomarkers [21]		X				X			Even Cycles			X		
CTCs [22]		X							Cycle 3					
Tumor Tissue [23]	X													
Other Assessments														
Patient Reported Outcomes [24]	Day -7								C3, C4 & C5					

Overall Survival														
Phone Call [27]														Every 3 Months

Arm B Schedule of Assessments Footnotes

1. **Days of Treatment with TRC105:** All assessments should be performed prior to TRC105 infusion and pazopanib dosing unless otherwise indicated. Each cycle is 21 days in duration. **If TRC105 dosing is held, all other required assessments should still be performed in accordance with the Schedule of Assessments.**
2. **Cycle 1 day 1: Treatment must start within 3 calendar days of randomization**. C1D1 activities should be completed prior to beginning study drug treatment except for vital signs after start of infusion. Hematology (including iron studies), blood chemistry (including TSH testing), urinalysis, physical examination, ECG, pregnancy test and quality of life questionnaires 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 (EOS) visit should generally occur within 7 days (+/- 2 day) of the last dose of study drug. Assessments other than pharmacokinetics, immunogenicity and protein biomarkers do not need to be repeated if performed within the previous 2 weeks (previous 6 weeks for radiologic/photographic tumor assessments). Follow-up visits should occur 28 days following the last dose of 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; may be performed up to 3 days prior to clinic visit date.
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-related 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: serum iron, ferritin, transferrin) to be performed according to the Schedule of Assessments and as clinically indicated during the study. Lab assessments may be performed within 3 days prior to TRC105 dosing. In addition to the assessments scheduled for the clinical trial, patients should undergo assessment as appropriate to ensure safe treatment. See Section 9.1.1.1 for specific panel collection requirements.
9. **Pregnancy Test:** Testing to be performed locally. All female patients of childbearing potential must have a negative serum pregnancy test within 7 days prior to cycle 1 day 1, day 1 of every cycle and 28 days following the last dose of TRC105.
10. **Urinalysis:** To be performed locally. Cycle 1 day 1 urinalysis (e.g., dipstick) 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 1and split into two doses whereby 3 mg/kg is administered on cycle 1 day 1 and the balance is administered on cycle 1 day 4. The entire weekly dose of TRC105 (10 mg/kg) is then given on cycle 1 day 8 and weekly thereafter. See Section 7.1.6 for specific TRC105 administration guidelines.
12. **Pazopanib Dosing:** Oral pazopanib will be dosed once daily in the evening at 800 mg for adult and for adolescent patients with a BSA > 1.8 m^2, and at 600 mg for all other patients <18 yrs of age (who must weigh ≥ 40 kg at study enrollment), starting on cycle 1 day 1 in the absence of toxicity on days 1-21 of each 21-day cycle according to the pazopanib product labelling. Dose reductions are allowed based on individual patient tolerability beginning with cycle 1. See Section 7.2 for specific dosing guidelines.

13. **Tumor Imaging:** All patients will undergo radiographic imaging. CT or MRI scans of chest, abdomen, and pelvis with contrast to be performed at screening, within 7 days prior to randomization and every 42 days from the date of randomization (+/- 7 days). If subjects are unable to receive CT contrast due to CT contrast medium allergy or renal insufficiency, enhanced MRI scans may be used. A combination of non-contrast CT and MRI studies (such as chest CT without contrast and abdominal MRI with contrast) may be used. The same method of assessment must be used throughout the course of the study thereafter. Similarly, if a subject develops a contraindication to CT contrast during the course of the study; assessments may shift to non-contrast CT of the chest and contrast-enhanced MRI of the abdomen for subsequent scans. In addition, a brain MRI or CT with contrast to be performed at screening and on study as needed if metastases are suspected. A bone scan is to be performed at screening if bone metastases is suspected. If a bone scan documents bone disease at baseline, it needs to be repeated only when complete response is identified or progression in bone is suspected. All other known areas of disease should be consistently followed throughout the study. Assessments should be performed whenever disease progression is suspected. **A designation of CR or PR in this study requires confirmation at a subsequent consecutive assessments separated by at least 4 weeks following the initial designation of CR or PR, respectively. Tumor imaging will continue to be collected on protocol schedule for all patients who come off study drug for reasons other than RECIST 1.1 defined PD until RECIST 1.1 defined PD or start of a new therapy.** Allowable window for tumor imaging studies is +/- 7 days.
14. **2D photography: Patients with cutaneous tumors** will undergo digital 2D color photography in addition to radiographic imaging, which will be performed at screening within 7 days prior to randomization and every 42 days from the date of randomization (+/- 7 days). Screening assessment will be centrally reviewed in real time**.** Assessments should be performed whenever disease progression is suspected. 2D photography will continue to be collected on protocol schedule for all patients who come off study drug for reasons other than RECIST 1.1 defined PD until RECIST1.1 defined PD or start of a new therapy Allowable window is +/- 7 days.
15. **12-Lead ECG:** Three consecutive 12-lead ECGs at least 2 minutes apart will be performed at screening, cycle 1 day 1 (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.) cycle 1 day 15, day 1 of cycle 2, and EOS. **Note: on cycle 1 day 15 pazopanib dosing should occur in the clinic (prior to TRC105 pre-medications and infusion) and ECGs will then be performed following completion of the TRC105 infusion and no sooner than 2 hours following pazopanib dosing (at the time of expected C_{max}). However, pazopanib dosing should not be repeated if the patient dosed within 12 hours at home.** On day 1 of cycle 2, pazopanib dosing in the clinic is not required and ECGs may be performed prior or following TRC105 dosing. If the patient develops an arrhythmia, the ECG should be repeated on day 1 of each subsequent cycle. In case of prolongation of QTc interval > 500 msec, pazopanib will be held and appropriate investigations will be performed (e.g., cardiologist consultation, repeat ECG, continuous ECG monitoring, etc.). Rechallenge with pazopanib will be guided by cardiology input and will require authorization by TRACON. Additional ECGs may be performed on study as clinically indicated.
16. **Concomitant Medications and Treatments:** Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and through 28 days following the last dose of study treatment. Required TRC105 premedications should be recorded on TRC105 premedications CRF.
17. **Adverse Events:** The AE reporting period for this trial begins with informed consent and ends following the completion of the 28-day follow-up visit or at least 28 days after the last dose of pazopanib or TRC105 study drug is administered, whichever occurs later. All AEs that occur in trial patients during the AE reporting period must be reported to TRACON, whether or not the event is considered study treatment-related.
18. **Anti-TRC105 Antibodies:** 5 mL blood sample will be collected to assess Anti-TRC105 Antibodies 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 central laboratory. See separate laboratory guide for further collection and shipment information. Additional Anti-TRC105 Antibody samples may also be collected at the time of unexpected clinical events.
19. **TRC105 Pharmacokinetics Concentration:** A 5 mL blood sample for TRC105 pharmacokinetics to be collected at the time-points indicated in the Schedule of Assessments. **Pre infusion**: if an acceptable window time is required to be stated, it is recommended that the samples be obtained no earlier than 6 hours prior to the start of the infusion. **Post infusion**: Sample should be collected 15 minutes after the completion of the infusion (including the flush), there is a +/- 15 minute window. A separate IV line is not required for PK blood draws if the IV line has been adequately flushed, the same line can be used for infusions and PK sampling. Samples will be stored at approximately -70°C. Samples will be batch shipped as indicated in the laboratory manual to a central 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.

20. **Pazopanib Pharmacokinetics:** A 5 mL blood sample for pazopanib concentration to be collected at the time-points indicated in the Schedule of Assessments prior to starting the TRC105 infusion. In addition, **on cycle 1 day 15 pazopanib dosing will occur in the clinic to assess C_{max} and the sample should be collected no sooner than 2 hours following pazopanib dosing. However, pazopanib dosing should not be repeated if the patient dosed within 12 hours at home.** On the pazopanib pharmacokinetic assessment on day 1 of cycle 2, pazopanib dosing in the clinic is not required. 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 or after dose reductions.
21. **Protein Biomarkers:** One 10 mL purple top (K_2EDTA) 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.
22. **CTCs:** One 10 mL EDTA tube will be collected at the time-points indicated in the Schedule of Assessments and be analysed by a central laboratory. See separate laboratory guide for further collection and shipment information.
23. **Archival Tumor Tissue:** Tumor specimens (formalin-fixed, paraffin-embedded) of the primary cancer and/or metastatic cancer specimen for each study participant, if available. See Section 10.1.5 and separate laboratory guide for further collection and shipment information.
24. **Patient Reported Outcomes**: Patient questionnaires to characterize quality of life will be collected at the time-points indicated in the Schedule of Assessments. Baseline assessment must be completed prior to randomization.
25. **Cycle 3+ Treatment:** Patients who demonstrate a response of CR, PR or SD will be eligible for additional treatment until progression.
26. **Follow-up:** The follow-up visit should occur 28 days following the last dose of TRC105 or pazopanib, whichever occurs later. Allowable visit window is +/- 7 days.
27. **Overall Survival:** Telephone or routine visit should occur every 3 months following the last dose of TRC105 until death. Allowable window for each visit is +/- 1 week.
28. **Allowable window** for each visit within the cycle is +/- 2 days unless otherwise stated. The +/-2 day window does NOT apply to randomization. Cycle 1 day 1sets the clock for study visits, and all study visits should be scheduled in reference to cycle 1 day 1. For example, if cycle 1 day 1 was on June 1st, and patient is not able to return for C1D8 until June 10th the C1D15 visit should take place on June 15th (15 days from cycle 1 day1).
29. **Pediatric PK**: TRC105: A 5 mL blood sample for TRC105 pharmacokinetics to be collected on cycle 1 day 1 and cycle 2 day 15 predose, 5 minutes post-dose and 1, 2 and 4 hours post-dose. On cycle 1 day 4, cycle 1 day 8, cycle 1 day 15, and cycle 2 day 1 samples will be collected predose and 5 minutes post-dose. Following this, samples will be collected pre-dose only day 1 of cycle 3 and subsequent even cycles. Trough concentrations will also be collected at the end of study visit and the 28-day follow-up visit. Samples will be stored at approximately -70°C. Samples will be batch shipped as indicated in the laboratory manual to a central 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. Pazopanib: A 5 mL blood sample for pazopanib pharmacokinetics to be collected on cycle 1 day 4, cycle 1 day 8, cycle 1 day 15, cycle 2 day 1 and day 1 of even cycles prior to starting the TRC105 infusion. Trough concentrations will also be collected at the end of study visit and the 28-day follow-up visit. On cycle 1 day 15 pazopanib dosing will occur in the clinic; however, pazopanib dosing should not be repeated if the patient dosed within 12 hours at home. Sample should be collected no sooner than 2 hours following pazopanib dosing. On the pazopanib pharmacokinetic assessment on day 1 of cycle 2, pazopanib dosing in the clinic is not required. 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.
30. **Pediatric radiographic imaging**: Plain films (AP and lateral) of the right and left distal femur to evaluate the epiphyseal growth plates. Pediatric patients will automatically be assigned to Arm B however they still need to be enrolled via the randomization system.

6. SELECTION AND WITHDRAWAL OF PATIENTS

6.1. Study Population

6.1.1. Inclusion Criteria

1. Histologically-confirmed angiosarcoma that is not amenable to curative intent surgery (e.g., metastatic or bulky disease and disease for which surgical resection would carry an unacceptable risk to the patient). Pathology report will be reviewed by sponsor prior to randomization.
2. Documented progression on or following most recent systemic chemotherapy regimen (not required for chemotherapy-naïve patients), within 4 months prior to screening
3. Measurable disease by RECIST v1.1
4. Age of 18 years or older; in addition, patients age 12 to 17 years may enroll beginning in Cohort 2 if weight ≥ 40 kg
5. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
6. Resolution of all acute AEs resulting from prior cancer therapies to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03) grade ≤ 1 or to that patient's pre-study baseline (except alopecia or neuropathy)
7. 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 x ULN
   - Absolute neutrophil count (ANC) ≥ 1500/μL
   - Platelets ≥ 100,000/μL (without transfusion support within 28 days prior to randomization)
   - Hemoglobin ≥ 9.0 g/dL (without transfusion support within 14 days prior to randomization; erythropoietin or darbepoetin permitted)
   - Serum creatinine ≤ 1.5 times the upper limit of normal or creatinine clearance > 30 mL/min by Cockcroft-Gault formula
   - International normalized ratio (INR) ≤ 1.2 unless the patient is receiving a direct Factor Xa inhibitor
8. Willingness and ability to consent (and assent if under age 18) for self to participate in study
9. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures

10. Angiosarcoma tumor specimen, if available
11. Men who are sterile (including vasectomy confirmed by post vasectomy semen analysis) OR agree to use a condom with spermicide (refer to Section 2.6.1.3) and to not donate sperm during the study and for at least 180 days following last dose of TRC105 or pazopanib.
12. Woman of non-child bearing potential due to surgical sterilization (at least 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by medical history or menopause (i.e., no menstrual bleeding for more than 12 months in a women aged 45 years or more), 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 acceptable methods of birth control, one of which must be highly effective, during the study and for at least 180 days after stopping TRC105 or pazopanib (refer to Section 2.6.1.3).

6.1.2. Exclusion Criteria

1. Prior treatment with TRC105
2. Prior treatment with any VEGF inhibitor
3. More than two prior lines (may be combination regimens) of chemotherapy for angiosarcoma (neoadjuvant/adjuvant treatment does not count as a line of treatment)
4. Current treatment or participation active on another therapeutic clinical trial
5. Women who are pregnant or breastfeeding
6. Receipt of systemic anticancer therapy, including investigational agents, within 5 times the agent's elimination half-life or 14 days of starting study treatment, whichever is shorter
7. Major surgical procedure or significant traumatic injury within 4 weeks prior to randomization and must have fully recovered from any such procedure or injury; planned 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 randomization: Thoracentesis, paracentesis, laparoscopy, thoracoscopy, tube thoracostomy, bronchoscopy, endoscopic ultrasonographic procedures, mediastinoscopy, skin biopsies, and imaging-guided biopsy for diagnostic purposes
8. 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 randomization
9. Uncontrolled hypertension defined as systolic > 150 or diastolic > 100 mm Hg on the average of the 3 most recent BP readings. Anti-hypertensives may be started prior to randomization.
10. Ascites or pleural effusion requiring intervention or that required intervention or recurred within three months prior to randomization

11. Pericardial effusion (except trace effusion identified by echocardiogram) within three months prior to randomization
12. 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 prior to randomization
13. Angina, myocardial infarction, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack, arterial embolism, pulmonary embolism, percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) within 6 months prior to randomization. Deep venous thrombosis within 3 months prior to randomization unrelated to a central venous catheter, unless the patient is anti-coagulated without the use of warfarin for at least 2 weeks prior to randomization. In this situation, low molecular weight heparin or a direct Factor Xa inhibitor is preferred
14. Active bleeding or pathologic condition that carries a high risk of bleeding (e.g., hereditary hemorrhagic telangiectasia). Patients with bleeding cutaneous lesions not actively requiring transfusions are eligible. Patients who have been uneventfully anti-coagulated with a direct Factor Xa inhibitor or low molecular weight heparin are eligible
15. Hemoptysis (> ½ teaspoon [2.5 mL] of bright red blood) within 6 months prior to randomization
16. Thrombolytic use (except to maintain i.v. catheters) within 10 days prior to randomization
17. Known active viral or nonviral hepatitis or cirrhosis
18. Peptic ulcer within the past 3 months of treatment, unless treated for the condition and complete resolution has been documented by esophagogastroduodenoscopy (EGD)
19. Presence of tumor(s) invading into the heart or great vessels (including carotid artery) or another location where bleeding is associated with high morbidity including patients with primary cardiac or great vessel angiosarcoma
20. Gastrointestinal perforation or fistula in the 6 months prior to randomization unless underlying risk has been resolved (e.g., through surgical resection or repair)
21. Presence of a malabsorption syndrome, gastrointestinal disorder, or gastrointestinal surgery that could affect the absorption of pazopanib
22. History of prior malignancy except adequately treated basal cell or squamous cell skin cancer or adequately treated, with curative intent, cancer from which the patient is currently in complete remission per Investigator's judgment; patients with history of breast cancer and no evidence of disease on hormonal therapy to prevent recurrence and patients with prostate cancer on adjuvant hormonal therapy with undetectable PSA are eligible
23. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness

24. Active infection that requires systemic treatment
25. Concurrent use or receipt of a strong CYP3A4 inducer within 12 days prior to randomization or a strong CYP3A4 inhibitor within 7 days prior to randomization (see Table 10)
26. History of severe hypersensitivity reaction to any monoclonal antibody
27. Other severe acute or chronic medical (including bone marrow suppressive diseases) or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation, impede the ability of the patient to complete all protocol-specified activities, or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for this study

6.2. Patient Withdrawal Criteria

Patients are eligible for treatment until disease progression, unacceptable toxicity or withdrawal of consent, or other reasons. 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 confirmed by central radiographic review.
2. A need for surgery, radiation, or for other anticancer therapy not permitted under this protocol.
3. Lost to follow-up or substantial noncompliance with the protocol.
4. Pregnancy. Pregnant patients should be followed for the duration of the pregnancy and the outcome of the pregnancy should be documented.
5. Arterial thrombosis of any grade (including that causing cerebrovascular ischemia, cardiac ischemia/infarction, or peripheral or visceral arterial ischemia) or grade 4 venous thrombosis (including grade 4 pulmonary thromboembolism).
6. Missed study drug treatment for > 8 consecutive weeks (i.e., both TRC105 and pazopanib dosing if assigned to the combination arm or pazopanib if assigned to the pazopanib alone arm). Patients in the combination arm who cannot tolerate pazopanib or TRC105 therapy and who demonstrate a response of complete response (CR), partial response (PR) or stable disease (SD) with the combination and are thought to benefit from continued single agent therapy may continue on study on TRC105 or pazopanib alone.

6.2.1. Withdrawal of Consent

Patients who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a patient specifically withdraws consent for any further contact with him/her or persons previously authorized by the patient to provide this information. Patients should notify the Investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the Investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post-treatment follow-up, and entered in the appropriate case report form

(CRF) page. In the event that vital status (whether patient is alive or dead) is being measured publicly available data should be used to determine vital status only as appropriately directed in accordance with local law.

7. STUDY TREATMENTS

7.1. Description of TRC105 Study Drug

TRC105 (carotuximab) is a genetically engineered human/murine chimeric monoclonal antibody directed against human endoglin found on the surface of proliferating endothelial cells and tumor cells of some tumor types.

7.1.1. 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.

7.1.2. TRC105 Dose Level

Each patient will be dosed with 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. 85 kg for women and 100 kg for men represent accepted maximum lean body masses for the two genders. **There is no body weight limit for enrollment purposes except for patients < 18 years of age (ages 12-17), who must weigh ≥ 40 kg at the time of study enrollment.**

The dose of TRC105, administered in the combination treatment arm with pazopanib (Arm B) will be the same for patients of all ages. The first weekly dose will be split into 2 doses whereby 3 mg/kg will be administered on cycle 1 day 1 and the balance will be administered on cycle 1 day 4. The entire weekly dose of TRC105 (10 mg/kg) is then given on cycle 1 day 8 and weekly thereafter (Table 5).

7.1.3. TRC105 Packaging and Labeling

TRC105 will be supplied at 25 mg/mL in 20 mM L-Histidine/L-Histidine Monohydrochloride, 240 mM Trehalose, 0.01% Polysorbate 20 Formulation (25 mg TRC105/mL) in one or more of the following presentations.

200 mg TRC105/8 mL single-use vial

400 mg TRC105/16 mL single-use vial

7.1.4. TRC105 Storage and Shipping

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

7.1.5. 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.
- For a 70 kg patient, for example: (70 kg x 10 mg/kg)/(25 mg/mL) = 28 mL of TRC105 product to be administered (i.e., 28 mL from the total of 32 mL from two 16-mL vails)

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. 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 TRC105 antibody into a normal saline bag in accordance with the dose needed. The final TRC105 concentration must be between 0.6 mg/mL and 10 mg/mL. The prepared TRC105 must be gently inverted several times in order to ensure a homogeneous solution. The diluted infusion solution of TRC105 must be used within 8 hours of preparation if stored at room temperature, or within 24 hours of dilution if stored at 2° to 8°C (36º to 46ºF). The expiration time should be labeled on the bag. If the diluted infusion solution of TRC105 has not been completely infused within 8 hours of preparation (i.e., the prepared infusion has been 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.

TRC105 should be diluted in ≦ 250 mL of normal saline in patients weighing less than 70 kg (this will prevent the administration of intravenous fluid in excess of 10% of blood volume during an infusion).

7.1.6. TRC105 Administration

Patients should be encouraged to drink abundant fluid (e.g., two 8 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.

In order to ameliorate the signs and symptoms of infusion-related reactions to TRC105, which are believed to be due to an ADCC mechanism of action with release of cytokines, the administration of the following TRC105 premedication regimen, including the methylprednisolone infusion, should be completed at least 30 minutes and no more than 2 hours prior to the start of TRC105 infusion as indicated below (see Table 5):

- Acetaminophen 650 mg p.o. x 1 or paracetamol 1000 mg p.o. x 1 (analgesic and antipyretic given as prophylaxis for fever and headache)
- Methylprednisolone 100 mg i.v. will be given prior to the cycle 1 day 1 and cycle 1 day 4 infusions (glucocorticoid given as prophylaxis for signs and symptoms of infusion-related reactions, including bronchospasm, urticaria, fever, and rash). Methylprednisolone may be discontinued starting with cycle 1 day 8 in the absence of infusion-related reaction with the prior dose.

- Cetirizine 10 mg i.v. or p.o. x 1 (or similar oral or intravenous H1-antihistamine) (H1-histamine antagonist given as prophylaxis for signs and symptoms of infusion-related reactions, including bronchospasm, urticaria, fever, rash, and flushing). Cetirizine (or similar oral or intravenous H1-antihistimine) may be discontinued starting with Cycle 2, in the absence of infusion-related reactions with the prior dose.
- Anti-emetic treatment, while not required, may be given prior to the initial dose and subsequent doses to reduce the frequency of nausea and vomiting that may be observed during TRC105 infusions.

As a precaution, resuscitation equipment should be immediately available at the location where TRC105 is being infused.

TRC105 will be administered intravenously utilizing an infusion pump. TRC105 has been demonstrated to be compatible with polyethylene lined, non-di(2-ethyl-hexyl)phthalate (DEHP) infusion sets and polyvinyl chloride, non-DEHP infusion sets. TRC105 is required to be administered with a 0.2 micron downstream filter. The attachment of the infusion pump administration set to the i.v. bag and transport of the TRC105 study drug to the patient will be performed as per standard study site procedures.

Following the appropriate premedication regimen, the first weekly TRC105 dose will be split into 2 administrations whereby 3 mg/kg is administered on cycle 1 day 1 over 4 hours (+/- 15 minutes) and the balance (e.g., 7 mg/kg) is administered on day 4 over 2 hours (+/- 15 minutes). Do not increase the infusion rate above 25 mg/min. Thereafter, the full dose of 10 mg/kg TRC105 dose will be administered i.v. weekly over 1 hour (+/- 15 minutes).

Patients must complete at least one 4-hour infusion without the development of any infusion-related reactions in order to reduce the duration of the subsequent TRC105 infusion to 2 hours (+/- 15 minutes) and, in turn, complete a 2-hour infusion without the development of any infusion-related reactions in order to reduce the duration of the subsequent TRC105 infusions to 1 hour (+/- 15 minutes). See Table 5 for ideal dosing schemas. **Patients with infusion-related reactions of any kind should be managed appropriately (see Section 7.1.8) 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 sufficient saline to clear the tubing. The dose level, time of transfer to i.v. bag, and the infusion start and stop times must be recorded in the source documents.

Table 5: TRC105 10 mg/kg Weekly Initial Administration Schema

Cycle/Day	C1D1	C1D4	C1D8	C1D15	C2D1 +
TRC105 Dose (mg/kg)	3	7	10	10	10
Infusion Duration (hours)	4	2	1	1	1
Premedication					
Methylprednisolone (mg) i.v.	100	100	0	0	0
Cetirizine (mg) i.v. or p.o. (or similar H1-antihistamine)	10	10	10	10	0
Acetaminophen (mg) p.o.	650	650	650	650	650

CYCLE 2 AND BEYOND: TRC105 premedication regimen should be reinstituted if a patient develops an infusion-related reaction grade ≥ 2 in association with the immediate prior infusion. Premedication, with the exception of acetaminophen, can be discontinued over time in the absence of subsequent infusion-related reaction.

7.1.7. TRC105 Dose Delay and Modification

TRC105 dose reductions and delays should be avoided, if possible. TRC105 dose must be held for grade 3 or 4 related AEs. When the event improves to grade 1 or to the patient's pre-study baseline (including anemia), TRC105 may be resumed at a reduced dose (with the exception of infusion-related reactions, which will not trigger dose reductions because infusion-related reactions could be exacerbated by dose reductions). Treatment dose delays cannot exceed 8 consecutive weeks (i.e., both TRC105 and pazopanib dosing held for patients in Arm B or pazopanib alone if in Arm A). However, patients who cannot tolerate pazopanib or TRC105 therapy and who demonstrate a response of complete response (CR), partial response (PR) or stable disease (SD) with the combination and are thought to benefit from continued single agent therapy may continue on study on TRC105 or pazopanib alone per Section 6.2.

TRC105 (and pazopanib) should be held for at least 1week prior to scheduled surgery, the decision to resume treatment after surgery should be based on clinical judgment of adequate wound healing. Port placement prior to treatment initiation does not require a 7 day wait period; treatment can be initiated as early as the following day.

TRC105 DOSING DELAY: If a patient misses a weekly TRC105 dose and dosing is resumed ≥ 10 days after the last dose, premedication and TRC105 is administered as described in Table 6. Split dosing is not required. However, it is recommended that if the patient experienced a severe headache with a previous infusion, the initial dose is split over 2 days and Table 5 is followed for premedication and TRC105 infusion.

The Schedule of Assessment should be followed with regards to visits, labs, and any other required assessments even if TRC105 dosing is held (Table 4). In cases of dosing delay of more than 3 weeks, hematology results within 3 weeks of dosing resumption should be known and within the specified protocol eligibility criteria prior to resuming treatment. In addition, in cases of dosing delay of more than 6 weeks, chemistry (including TSH) results within 6 weeks of dosing resumption should also be known and within the specified protocol eligibility criteria prior to resuming treatment.

Table 6: TRC105 10 mg/kg Weekly Administration after Missed Dose

Cycle/Day	**CxDy** (1st dose after missed dose)	**CxDy** (2nd dose after missed dose)	**CxDy** (3rd dose after missed dose)	**CxDy** (4th dose after missed dose)
TRC105 Dose (mg/kg)	10	10	10	10
Infusion Duration (hours)	4	2	1	1
Premedication				
Methylprednisolone (mg) i.v.	100	100	0	0
Cetirizine (mg) i.v. or p.o. (or similar H1-antihistamine)	10	10	10	0
Acetaminophen (mg) p.o.	650	650	650	650

Table 7: Allowable TRC105 Dose Modifications

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

[a]Patients with Grade 3 infusion-related reactions do not need to dose reduce, because infusion-related reactions could be exacerbated by dose reductions. Patients with Grade 4 infusion-related reactions should discontinue TRC105 treatment (see Table 8).

See Section 9.3.5 (Table 12) for AE grading scale.

Patients with any grade arterial thrombosis or grade 4 venous thrombosis should be discontinued from study treatment. Patients with grade 1-3 venous thrombosis who require anticoagulation will have their TRC105 therapy interrupted. TRC105 therapy for such patients 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 (e.g., no evidence of disease progression).

7.1.8. Management of TRC105 Infusion-Related 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-related reactions, the infusion may be restarted at half of the previous rate if and when the infusion-related reaction has resolved, and then increased per patient tolerance to a maximum of 25 mg/min. For grade 4 infusion-related reactions, the infusion should not be restarted and the patient should be discontinued from TRC105 treatment. Infusion-related reactions will be recorded as AEs in the CRF.

The list below provides a representative, but not exhaustive, list of some potential infusion-related adverse reactions, and any other event considered as an infusion-related event should be reported in the CRF if they occur within 24 hours following completion of the infusion:

Rigors/Chills	Pruritus
Anaphylactic reaction and symptoms	Urticaria
Nausea	Flushing
Vomiting	Rash (specify location and aspect)
Tachycardia	Hypertension/Elevated BP
Bradycardia	Hypotension/Decreased BP
Tachypnea	Headache
Dyspnea	Fever
Wheezing	Pain low back
Bronchospasm	Oedema/Swelling (specify location, e.g. swollen lips)
Anaphylactoid reaction and symptoms	Cytokine release syndrome and symptoms
Arthralgias	Diaphoresis
Myalgias	Dizziness/Syncope
Angioedema	Purpura

Interventions should be documented as concomitant medications or concomitant treatments as appropriate.

Table 8: Management of TRC105 Infusion-Related Reactions

Infusion-Related 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.** Discontinue TRC105 treatment unless other factors that contributed to the infusion-related reaction are identified and corrected
Grade 4 (life-threatening)	**1.** Discontinue infusion **2.** Treat with symptomatic medications[a] **3.** Hospitalize patient **4.** Discontinue TRC105 treatment

[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). Resuscitation equipment should be immediately available at the location where TRC105 is being infused.

7.1.9. 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.

7.1.10. TRC105 Study Drug Handling and Disposal

TRC105 vials must be stored between 2°C and 8°C (36°F to 46°F) and protected from light. The Investigator should not return or destroy clinical study materials to TRACON unless specifically instructed to do so by TRACON. Used vials do not need to be maintained. All expired vials of

TRC105 should be retained until destruction is authorized by a TRACON representative. The Site Pharmacist will be responsible for documenting the destruction (according to institutional requirements) of used or expired vials.

7.2. Description of Pazopanib

See the current approved product label.

7.2.1. Composition of Pazopanib

See the current approved product label.

7.2.2. Pazopanib Dose Level

The initial dose is pazopanib 800 mg for adult and for adolescent patients with a BSA > 1.8 m^2 and at 600 mg for patients < 18 year of age (who must weigh ≥ 40 kg at study enrollment) p.o. once daily starting on cycle 1 day 1.

7.2.3. Pazopanib Packaging and Labeling

See the current approved product label.

7.2.4. Pazopanib Storage Handling and Disposal

See the current approved product label.

7.2.5. Pazopanib Dosing

The starting dose of pazopanib for adult and adolescent patients with a BSA >1.8 m^2 is 800 mg orally once daily, in the evenings, without food (recommend at least 1 hour before or 2 hours after a meal). The dose of pazopanib will not exceed 800 mg. For all other patients < 18 years of age (who must weigh ≥ 40 kg at study enrollment) the starting dose of pazopanib is 600 mg orally once daily in the evenings. All patients age 12 to 17 year of age, who are eligible only for Cohort 2, will not be randomized and will receive treatment with TRC105 and pazopanib. Pazopanib dose reductions are allowed based on individual patient tolerability.

Do not crush tablets due to the potential for increased rate of absorption, which may affect systemic exposure.

If it is confirmed, by the patient, that a pazopanib tablet has been vomited, that amount of pazopanib can be re-dosed.
If a dose is missed, it should not be taken if it is less than 12 hours until the next dose.

7.2.6. Pazopanib Dose Modification

Dose adjustments and management of side effects of pazopanib should be guided at least in part by the applicable current approved product labeling. Dose increase or reduction is recommended based on individual safety and tolerability. Decrease or increase should be in 200-mg steps based on individual tolerability. The dose of pazopanib will not exceed 800 mg for adult and for adolescent patients with a BSA >1.8 m^2 and not exceed 600 mg for all other patients < 18 years of age, who must weigh ≥ 40 kg at study enrollment. If a dose is missed, it should not be taken if it is less than 12 hours until the next dose.

In case of prolongation of QTc interval > 500 msec, pazopanib will be held and appropriate investigations will be performed (e.g., cardiologist consultation, repeat ECG, continuous ECG monitoring, etc.). Rechallenge with pazopanib will be guided by cardiology input and will require authorization by TRACON.

The Schedule of Assessments should be followed with regards to visits, labs, and any other required assessments even if dosing is held (Table 3 and Table 4**).**

7.2.7. Pazopanib Drug Accountability

Patients will be asked to return any unused tablets from the previous cycle for proper drug accountability and destruction according to institution guidelines. A new prescription will be dispensed for the following cycle.

Investigators must maintain an accurate accounting of pazopanib lots used for this trial. During the study, the following information must also be recorded if TRACON provides the pazopanib:

- Date of purchase, quantity and lot number
- 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

Drug Accountability Logs should be maintained by the site and must be readily available for inspection.

7.3. Concomitant Medications

No approved or investigational anticancer treatment other than the 2 study drugs (i.e., TRC105 and pazopanib) 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.

Narcotic analgesics, acetaminophen, nonsteroidal anti-inflammatory drugs, and triptans (e.g., sumatriptan) may be offered as needed for relief of pain or headaches. Ketorolac may be used prophylactically following the initial dose of TRC105 to reduce the frequency and severity of headache that often occurs the evening following completion of the initial TRC105 dose. H1-antihistamines and decongestants may be offered for the treatment of conditions such as sinus congestion.

Packed red blood cells, colony stimulating factors, and platelet transfusions should be administered as clinically indicated for anemia, neutropenia, and thrombocytopenia, respectively.

QT Prolongation and torsades de pointes: pazopanib should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant pre-existing cardiac disease.

Table 9 provides a representative but not exhaustive list of medications known to prolong QT interval.

Table 9: Examples of Drugs Prolonging QT interval and/or Inducing Torsades de Pointes[a]

Class	Generic Name
Anesthetic	Sevoflurane
Anti-anginal	Ranolazine, Bepridil
Anti-arrhythmic	Sotalol, Quinidine, Amiodarone, Ibutilide, Disopyramide, Procainamide, Flecainide, Dofetilide, Dronedarone
Antibiotic	Moxifloxacin, Clarithromycin, Ciprofloxacin, Gemifloxacin, Ofloxacin Telithromycin, Levofloxacin, Roxithromycin, Trimethoprim-Sulfa, Gatifloxacin, Sparfloxacin, Azithromycin Erythromycin
Anti-cancer	Tamoxifen, Lapatinib, Nilotinib, Arsenic trioxide, Eribulin, Sunitinib, Vandetanib
Anti-convulsant	Fosphenytoin, Felbamate
Anti-depressant	Mirtazapine, Citalopram, Venlafaxine, Paroxetine, Fluoxetine, Sertraline, Trazodone, Escitalopram, Clomipramine, Amitriptyline, Imipramine, Nortriptyline, Desipramine, Doxepin, Trimipramine, Protriptyline
Anti-fungal	Voriconazole, Fluconazole, Ketoconazole, Itraconazole
Antihistamine	Astemizole, Terfenadine, Diphenhydramine, Diphenhydramine
Anti-hypertensive	Nicardipine, Isradipine, Moexipril/HCTZ
Anti-infective	Pentamidine
Antilipemic	Probucol
Anti-malarial	Artenimol + piperaquine, Chloroquine, Halofantrine
Anti-mania	Lithium
Anti-nausea/antiemetic	Granisetron, Dolasetron, Ondansetron
Anti-psychotic	Clozapine, Ziprasidone, Thioridazine, Risperidone, Mesoridazine, Quetiapine, Haloperidol, Pimozide, Amisulpride, Sertindole, Sertindole, Iloperidone, Paliperidone, Chlorpromazine
Anti-viral	Foscarnet, Ritonavir, Atazanavir
Appetite suppressant	Phentermine, Fenfluramine, Sibutramine
Bladder Antispasmodic	Tolterodine
α1-Blocker	Alfuzosin
Bronchodilator/decongestant	Albuterol, Salmeterol, Metaproterenol, Terbutaline, Metaproterenol, Levalbuterol, Ephedrine, Phenylpropanolamine, Pseudoephedrine
Cholinesterase inhibitor	Galantamine
CNS stimulant	Amphetamine, Methylphenidate, Amphetamine, Dexmethylphenidate, Methylphenidate, Lisdexamfetamine
Diuretic	Indapamide
Dopaminergic/anti-viral/anti-infective/	Amantadine
Endocrine	Ocreotide
GI stimulant	Cisapride
H2-histamine receptor antagonist	Famotidine
Imaging contrast agent	Perflutren lipid microspheres
Immunosuppressant	Tacrolimus, Fingolimod
Inotropic agent/vasconstrictor	Dopamine, Isoproterenol, Dobutamine, Epinephrine, Norepinephrine, Phenylephrine
Local anesthetic	Cocaine
Muscarinic receptor anatagonist	Solifenacin
Muscle relaxant	Tizanidine
norepinephrine reuptake inhibitor	Atomoxetine
Opiate agonist	Methadone, Levomethadyl
Oxytocic	Oxytocin
phosphodiesterase inhibitor/vasodilator	Vardenafil
Sedative	Chloral hydrate
Sedative; Anti-nausea/anesthesia adjunct	Droperidol
Uterine relaxant	Ritodrine
Vasconstrictor	Midodrine

[a]A continuously updated list of these drugs is available at www.torsades.org (accessed December 16, 2012). CNS: Central Nervous System.

Consistent with the product labeling for pazopanib, in general, short-acting antacids should be considered in place of proton pump inhibitors and H2-histamine receptor antagonists (e.g., famotidine) for patients taking pazopanib to avoid the risk of reducing pazopanib exposure.

It is recommended to separate antacid and pazopanib dosing by several hours to avoid a reduction in pazopanib exposure.

CYP3A4 Inhibitors: Avoid use of strong inhibitors (Table 10); co-administration of pazopanib with strong inhibitors of CYP3A4 increases pazopanib concentrations. Patients may not have received a strong CYP3A4 inhibitor within 7 days prior to cycle 1 day 1. If co-administration is warranted, reduce the dose of pazopanib to 400 mg. Grapefruit or grapefruit juice should be avoided as it inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib.

CYP3A4 Inducers: Consider an alternate concomitant medication with no or minimal enzyme induction potential; CYP3A4 inducers may decrease plasma pazopanib concentrations. Patients may not have received a strong CYP3A4 inducer within 12 days prior to cycle 1 day 1.

CYP Substrates: Concomitant use of pazopanib with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended.

Concomitant use of pazopanib and simvastatin increases the risk of ALT elevations and should be undertaken with caution and close monitoring.

Table 10: Examples of Strong CYP3A4 Inducers and Inhibitors[a]

Inducers:	***[a]Inhibitors:**	
	Boceprevir	Conivaptan
Phenytoin	Indinavir	Itraconazole
Carbamazepine	Nelfinavir	Ketoconazole
Rifampin	Lopinavir/ritonavir	Mibefradil
Rifabutin	Saquinavir	Nefazodone
Rifapentin	Telaprevir	Posaconazole
Phenobarbital	Ritonavir	Voriconazole
St. John's Wort	Clarithromycin	Telithromycin

[a]Because the lists of these agents are constantly changing, it is important to regularly consult a comprehensive list such as the one located at http://medicine.iupui.edu/clinpharm/ddis/.

7.4. Treatment Compliance

7.4.1. TRC105 Treatment Compliance

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

7.4.2. Pazopanib Treatment Compliance

Patients will be asked to record the day and time of pazopanib home dosing on a TRACON supplied log to be reviewed by site personnel prior to initiation of each new cycle.

7.5. Patient Randomization

Each adult patient's randomization assignment to Arm A (pazopanib alone) or Arm B (TRC105 + pazopanib), will be obtained by the investigational site after all screening procedures have

been completed. An 8 digit patient number will be assigned by the randomization system (4 digit site number + 4 digit patient number), and this 8 digit number will be used to identify patients throughout their participation in the trial. **Treatment must start within 3 calendar days of randomization.**

Detailed training and instructions for the enrollment process will be provided by TRACON.

8. ASSESSMENT OF EFFICACY

8.1. Radiological and Photographic Tumor Assessments

The primary determination of efficacy will be based on objective tumor assessments made by the independent blinded Central Radiographic Review according to RECIST version 1.1 [62] modified as noted in Section 8.1.1.1. **RECIST 1.1 PD MUST be centrally confirmed prior to withdrawing patients from the study on the basis of PD.** 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.

All patients should receive CT or MRI scans of chest, abdomen, and pelvis with contrast. If subjects are unable to receive CT contrast due to CT contrast medium allergy or renal insufficiency, enhanced MRI scans may be used. A combination of non-contrast CT and MRI studies (such as chest CT without contrast and abdominal MRI with contrast) may be used. For a given patient, the same method of assessment must be used throughout the course of the study thereafter.

Similarly, if a patient develops a contraindication to CT contrast during the course of the study, assessments may shift to non-contrast CT of the chest and contrast-enhanced MRI of the abdomen for subsequent scans. Such a situation does not imply mandatorily a non-evaluable (NE) overall response designation.

Patients with cutaneous tumors will undergo 2D color photography of all visible cutaneous lesions. In addition, a brain MRI or CT with contrast is to be performed at screening and on study as needed if metastases are suspected. A bone scan is to be performed at screening if bone metastases are suspected. If a bone scan documents bone disease at baseline, it needs to be repeated only when complete response is identified or progression in bone is suspected. All other known areas of disease should be consistently followed throughout 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 rather than clinical examination is the required technique when both could be used to assess the antitumor effect of the treatment. Radiology-based evaluation over photography-based evaluation is preferred when both could be used to assess the antitumor effect of the treatment.

Tumor evaluation by positron emission tomography (PET) scan or by ultrasound may not substitute for CT or MRI scans. The CT portion of a PET/CT could be acceptable as long as it is of diagnostic quality. (5mm slice thickness, and readable).

Tumor assessments will be performed at screening and every 6 weeks from randomization as outlined in the Schedule of Assessments (Table 3 and Table 4), and whenever disease progression is suspected. Known areas of disease should be consistently followed throughout the study. Another tumor assessment will be performed at the End of Study Visit if an assessment has not been performed within the prior 6 weeks. All patient files and radiological images must be available for CRF source verification.

8.1.1. Measurability of Tumor Lesions

Measurable disease is defined by the presence of at least 1 measurable lesion. At baseline, individual tumor lesions will be categorized by the Investigator as measurable or non-measurable according to modified RECIST 1.1 as described below.

- **Measurable** Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan or MRI (CT scan slice thickness no greater than 5 mm)
  - 10 mm cutaneous lesion measured by digital 2D color photography: lesion measurements are generated from the 2D photographs by the Independent Central Radiographic Review panel; the measurements are reported by longest diameter
  - Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in *short* axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed

  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.

- **Non-Measurable:** All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered to be truly non-measurable are bone lesions (lytic lesions or mixed osteolytic-osteoblastic lesions without identifiable soft tissue components, and osteoblastic lesions), leptomeningeal disease, ascites, pleural/pericardial effusions, cutaneous or pulmonary lymphangitis, inflammatory breast disease, abdominal masses not confirmed by imaging techniques, and cystic lesions.

8.1.1.1. Obtaining Cutaneous Lesion Measurements from 2D Photography

The following modifications will be applied when using RECIST 1.1 criteria to evaluate visible cutaneous lesions via 2D color photography.

- Up to 5 target cutaneous lesions
- 2D color photographs are reviewed by independent medical experts.
- The reviewer determines whether each lesion can best be measured digitally or via a tape measure included in the lesion photograph.
- For each lesion, the Central Radiographic Review panel is provided with all available photographs.
- The Central Radiographic Review panel incorporates the measurements into their RECIST 1.1 assessment.

8.1.1.2. Recording Tumor Measurements

Measurable lesions up to a maximum of 10 total, including 5 cutaneous lesions and up to 5 non-cutaneous lesions representative of all involved organs (with a maximum of 2 lesions per organ, other than skin, where up to 5 target lesions may be used) should be identified as target lesions and measured and recorded at baseline and at the stipulated intervals during treatment. Target lesions should be selected on the basis of their size (lesions with the longest diameters) and their suitability for accurate repetitive measurements (by the selected imaging techniques). Target lesions may include lymph nodes with a short axis $\geq$ 15 mm and cutaneous lesions $\geq$ 10 mm in at least 1 dimension.

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 diameters for all target lesions at baseline 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 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."

8.1.2. Definitions of Tumor Response

8.1.2.1. Target Lesions

- **Complete response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- **Partial response (PR):** A least a 30% decrease in the sum of diameters of the target lesions, taking as a reference the baseline sum diameters.
- **Progressive disease (PD):** At least 20% increase in the sum of diameters of target lesions, taking as a reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.
- **Stable disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

8.1.2.2. Non-Target Lesions

- **Complete response (CR):** Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- **Non-CR/non-PD:** Persistence of $\geq$ 1 non-target lesion(s).
- **Progressive disease (PD):** Unequivocal progression of existing non-target lesions, or the appearance of $\geq$ 1 new lesion.

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.

8.1.2.3. Determination of Overall Response

8.1.2.3.1. RECIST 1.1

When both target and non-target lesions are present, individual assessments will be recorded separately. The overall assessment of response will involve all parameters as depicted in Table 11. A designation of CR or PR in this study requires confirmation at a subsequent consecutive assessments separated by at least 4 weeks following the initial designation of CR or PR, respectively. Per RECIST 1.1, a modest increase in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

Table 11: Response Evaluation Criteria in Solid Tumors

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

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

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.

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.

8.1.3. Central Review of Disease Assessments

Independent blinded central review of imaging studies, photographs and clinical information documenting disease status will be performed in real time to verify disease response and progression during study. It is important to the integrity of the study that all imaging studies and

clinical information, including photographs, are forwarded to the review center as each patient enrolls and progresses through the study.

Materials for central review are the following:

1. All imaging studies performed on study, preferably in digital format on compact disc or optical disc. All digital media must be in DICOM format. Films may be forwarded for review if necessary; all films must be originals (second original films acceptable) rather than copies of films.
2. 2D photographs of sites of all target and non-target lesions. It is important to the integrity of the study that all 2D photographs, including annotation of baseline 2D photographs with target lesion border demarcation, are forwarded to the review laboratory as each patient enrolls and progresses through the study.

Details concerning clinically assessed lesions will be collected on the CRFs.

Further information on materials to be forwarded for central review is provided in separate manuals provided by the vendors.

8.2. Primary Endpoint

PFS is defined as time from randomization to either first disease progression (per independent radiology review of images by RECIST 1.1) or death from any cause. For the purpose of analysis for patients who are alive at the time of analysis and have not had disease progression, the following rules will apply: (1) The patient will be censored on the date of the last tumor assessment documenting absence of progressive disease; (2) if the patient was given antitumor treatment other than study drug treatment, the patient will be censored as of the date of the last tumor assessment prior to initiating that antitumor therapy; (3) if the patient was removed from study for toxicity or other reason, the patient will be censored as of the date of the last tumor assessment on study. With regard to missed tumor assessments, in the event of one missed tumor assessment followed by a subsequent assessment of progressive disease (PD), the subsequent PD assessment qualifies as objective tumor progression. In the event of more than one consecutive missing tumor assessment followed by a subsequent assessment of PD, the patient will be censored at the last adequate tumor assessment.

Rarely, a patient not amenable to curative intent surgery enrolled onto study therapy may become amenable due to treatment effect. Patients who undergo surgery with curative intent will be censored at the time of surgery in the primary endpoint of PFS. These patients will continue to be evaluated with tumor assessments, as scheduled, until progression, death, or receipt of other anti-cancer therapy. A secondary analysis of the data will be conducted without censoring such patients.

Pediatric patients will not be randomized and will not be analyzed in the determination of primary or secondary endpoints. Individual efficacy data will be reported for pediatric patients who enroll in the trial.

8.3. Secondary Endpoints

8.3.1. Objective Response Rate

Objective response rate (ORR) is defined as the number of patients with a best response of CR or PR divided by the number of randomized patients. ORR is defined as the best response designation recorded between the date of randomization and the date of documented progression, as determined by Central Radiographic Review and Central Photographic Review according to RECIST 1.1 criteria, or date of subsequent therapy, whichever occurs first. For patients without documented progression or subsequent therapy, all available response designations will contribute to the ORR determination. A designation of CR or PR in this study requires confirmation at a subsequent consecutive assessments separated by at least 4 weeks following the initial designation of CR or PR, respectively.

Patients who undergo curative intent surgery on study due to treatment response and are determined to have a pathologic CR, best overall response for these patients will be CR. If patients do not have pathologic CR, best overall response is that determined prior to the surgery.

Duration of response (DR) is defined as the time from first objective response (CR or PR) to the date of the first documented tumor progression, as determined by Central Radiographic Review and Central Photographic Review according to RECIST 1.1 criteria or date of death due to any cause, whichever occurs first. For subjects who neither progress nor die, the duration of response will be censored at the same time they were censored for the definition of PFS. This endpoint will only be evaluated in subjects with objective response of CR or PR and without a formal statistical comparison between treatment arms

8.3.2. Overall Survival

Overall survival (OS) is defined as the time from randomization to the date of death. A patient who has not died will be censored from OS analysis as of the last known alive date.

8.3.3. Safety

Safety will be analyzed through incidence of AEs, both serious and non-serious, ECGs, physical examinations and vital signs, ECOG performance status, and specific laboratory abnormalities in each treatment arm. See Section 9 Assessment of Safety.

9. ASSESSMENT OF SAFETY

9.1. Safety Parameters

Adverse events (AEs) will be characterized in terms of the type, timing, frequency, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.03), seriousness, and relatedness to study therapy (individually to TRC105 and to pazopanib). In addition, physical examination, vital signs, and ECOG performance status will be serially monitored. Laboratory safety analyses will be based on the local laboratory data, and will include hematology, serum chemistry (including liver and kidney function), urinalysis, and serum or urine pregnancy testing. Serum will also be assessed for immunogenicity to TRC105 (including anti-TRC105 antibody titers). In addition, 12-lead ECGs will be performed at the time points indicated in the Schedule of Assessments (Table 3 and Table 4).

9.1.1. Laboratory Safety Assessments

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

9.1.1.1. Hematology, Serum Chemistry, Coagulation, and Pregnancy Test

Assessments will be performed at the time points indicated in the Schedule of Assessments (Table 3 and Table 4) and analyzed at local laboratories. Investigators may have additional blood tests performed for the purpose of planning treatment administration, or for following AEs as clinically indicated.

- Hematology: Complete blood count (CBC) with differential and platelet count. Iron studies (serum iron, transferrin and ferritin) are obtained only a Screening, and then on study only if clinically indicated.
- 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 or serum urea, creatinine, magnesium, TSH, and glucose
- Pregnancy Test: Serum pregnancy tests will be performed locally on all female patients of childbearing potential.

9.1.1.2. Urinalysis

Urinalysis (without microscopic analysis, unless indicated) will be performed at time points indicated in the Schedule of Assessments (Table 3 and 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.

9.1.1.3. Physical Examination

A physical examination including, but not limited to, general appearance, head, eyes, ears, nose, throat, neck, heart, chest, abdomen, musculoskeletal, extremities, skin, lymph nodes, neurological genitourinary (as appropriate), and rectal (as appropriate) will be assessed at time points indicated within the Schedule of Assessments (Table 3 and Table 4). The physical examination will include examination of known and suspected sites of disease.

9.1.1.4. Vital Signs

Heart rate, temperature, blood pressure, respiratory rate and weight will be assessed at time points indicated within the Schedule of Assessments (Table 3 and Table 4). Heart rate, temperature, blood pressure, and respiratory rate will also be assessed during TRC105 infusions as described in Section 5.1.2.2 and the footnotes of Table 3 and Table 4 (Schedule of Assessments).

9.1.1.5. Performance Status

The ECOG scale (Section 21.2) will be used to assess performance status at Screening.

9.1.1.6. ECG

Three consecutive 12-lead ECGs at least 2 min apart will be performed. 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 3 and Table 4) and as clinically indicated throughout the study.

Prolonged QT intervals and torsades de pointes have been observed in association with pazopanib administration. Pazopanib is absorbed orally with median time to achieve peak concentrations of 2 to 4 hours after the dose. The timing of the ECG at day 15 should reflect the cardiac status at the anticipated maximal plasma concentrations of pazopanib based on the protocol-specified timing of pazopanib dosing on the days when ECG is performed.

9.1.1.7. Patient Reported Outcomes

Patient reported outcome questionnaires will be performed at the time points indicated in the Schedule of Assessments (Table 3 and Table 4).

The EuroQol Group Patient Questionnaire (EQ-5D-5L) quality of life questionnaire comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. On the EQ-5D-5L, each dimension has 5 levels (e.g., no problems, slight problems, moderate problems, severe problems, and unable). EQ-5D is one of a handful of measures recommended for use in cost-effectiveness analyses by the Washington Panel on Cost Effectiveness in Health & Medicine. In the UK, NICE has issued revised guidance that argues for the use of measures like EQ-5D that have been weighted according to the social preferences of the UK population. The more specific ways in which EQ-5D is being used:

- Monitoring the health status of patient groups at different moments in time, e.g. referral, admission, discharge, follow-up of outpatients.

- Evaluation and audit of health care, by measuring changes in health status in individual patients and in groups of patients.
- Assessing the seriousness of conditions at different moments in time.
- Providing relevant information for resource allocation at a variety of levels.
- Assisting in providing evidence about medical effectiveness in processes where drugs or procedures have to be approved.

Establishing levels of population health status both locally and nationally. Examples include health surveys carried out in Canada, Finland, Spain (1994 Catalan health survey interview) UK (UK Department of Health Omnibus Sample Survey 1996, Health Survey for England) and the US (current Medical Expenditure Panel Survey by the Agency for Healthcare Research and Quality) [63-66].

EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients. The QLQ-C30 is composed of both functional scales and symptom scales. All the scales range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning, while a high score for a symptom scale / item represents a high level of symptomatology / problems.

9.2. Adverse Events

All observed or volunteered AEs regardless of suspected causal relationship to TRC105 and/or pazopanib study drugs will be reported as described below. The CRF page will collect onset time and signs and symptoms of infusion-related reactions. Medications administered and all other actions taken to treat the event, the outcome, and any recurrence upon re-challenge will be captured.

9.2.1. Definition of Adverse Event

An AE 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 AEs include, but are not limited to the following:

- Clinically significant symptoms and signs including:
  - 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 AEs.
  - 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 AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.):
  - 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 AE by the Investigator or TRACON

9.2.2. Serious Adverse Events

An AE that meets one or more of the following criteria/outcomes is classified as a serious AE (SAE):

- 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 a regulatory authority 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 an AE unless the outcome is fatal during the trial or within the safety reporting period, in which case it should be reported as an SAE. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the patient expires during the trial or within the safety reporting period, then the event leading to death must be recorded as an SAE with NCI CTC grade 5.

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

9.2.2.1. Hospitalization

AEs 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 situations **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 AEs as follows:
  - Admission for treatment of preexisting condition not associated with the development of a new or worsened AE
  - 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 AE (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 AEs. The medical condition for which the procedure was performed should be reported if it meets the definition of an AE (e.g., acute appendicitis that begins during the AE reporting period should be reported as an AE and the appendectomy should be recorded as a Concomitant Procedure).

9.3. Reporting Adverse Events

9.3.1. Eliciting Adverse Event Information

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

9.3.2. Adverse Event Reporting Period

The AE reporting period for this trial begins with informed consent and ends following the completion of the 28-day follow-up visit or at least 28 days after the last dose of pazopanib or TRC105 study drug is administered, whichever occurs later. Data for patients who screen fail will not be collected in the clinical database. However, if a screen fail patient experiences an AE that is considered related to study conduct or study procedures during the screening period, the event will be tracked on the Screening Log and the event will be assessed for reportability. All events that occur following randomization, even if the patient does not go on to receive study treatment, will be entered on CRFs. AEs occurring prior to the initiation of the study treatment will be considered "baseline-emergent adverse events" and will be recorded on the corresponding CRFs.

All AEs that occur in trial patients during the AE 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 AE reporting period that the Investigator assesses as a suspected adverse reaction to the investigational medications/products should also be reported as an AE.

9.3.3. Reporting Requirements

Each AE is to be classified by the Investigator as SERIOUS or NONSERIOUS (Section 9.2.2 for serious adverse event definition). This classification 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 AE 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 adverse events (e.g., change in seriousness criteria, relationship to study drug etc.) should also be communicated to TRACON immediately. This notification should be made to:

PRIMARY MEDICAL MONITOR

Charles Theuer, MD PhD
TRACON Pharmaceuticals Inc.
4350 La Jolla Village Drive, Suite 800
San Diego, California 92122
Email: ctheuer@traconpharma.com
Cell Phone: 1.858.344.9400
Office Phone: 1.858.550.0780 x233

SECONDARY MEDICAL MONITOR

James Freddo, MD
TRACON Pharmaceuticals Inc.
4350 La Jolla Village Drive, Suite 800
San Diego, California 92122
Email: jfreddo@traconpharma.com
Cell Phone: 1.858.472.2330

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

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, returns to the patient's pre-treatment baseline status, or until such time as the Investigator determines that it has become stable. Information pertaining to follow-up of SAEs should also be sent to the TRACON Pharmaceuticals Inc.

SAEs that are unexpected and reported as associated with use of the study drugs TRC105 or pazopanib will be submitted to the US Food and Drug Administration (FDA), Competent Authorities and Ethics Committees in other countries taking part in the study, as well as all participating clinical sites in all countries as required by applicable regulatory authorities. Investigators should report to their local IEC/IRB as dictated by their board's policies and procedures. For events which are fatal or life-threatening, unexpected, and reported as associated with use of the investigational products, a 7-Day Alert Report will be submitted to the regulatory authorities within 7 calendar days of receipt of the SAE information. For all other AEs that are serious, unexpected, and reported as associated with use of the investigational products, 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 AEs, including SAEs, are to be reported on the AE CRFs.

9.3.4. Recording Adverse Events in the Case Report Forms

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

9.3.5. Grading of Adverse Event Severity

To report AEs on the CRFs, the Investigator will use the severity grading as described in NCI CTCAE (Version 4.03).

Every effort should be made by the Investigator to assess the AE according to CTCAE criteria. However, the diagnosis term should not be altered to accommodate the CTCAE dictionary. If the Investigator is unable to assess severity because the term is not described in NCI CTCAE (Version 4.03), severity of MILD, MODERATE, SEVERE, LIFE-THREATENING, or FATAL may be used to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

Table 12: 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	That event results in immediate risk of patient's death
5	Fatal	That event results in patient's death

Note the distinction between the severity and the seriousness of an AE. 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 1 of the criteria for serious events.

9.3.6. Relationship of Adverse Event to TRC105 and Pazopanib Study Drugs

In this study, TRC105 study drug may be given in combination with pazopanib. The relationship of an AE to TRC105 study drug and pazopanib should be classified by the Investigator independently using the following guidelines:

- Suspected Adverse Reaction to TRC105: There is a reasonable possibility that TRC105 caused the AE (i.e., there is evidence to suggest a causal relationship between TRC105 and the AE). See Section 2.6.1.1 for common TRC105 adverse reactions; however, the most current version the TRC105 IB should be referenced.
- Suspected Adverse Reaction to pazopanib: There is a reasonable possibility that pazopanib caused the AE (i.e., there is evidence to suggest a causal relationship between pazopanib and the AE). Section 2.6.1.2 for a list of common pazopanib adverse reactions; however, the most current version the pazopanib product labeling should be referenced.

- Not Related: There is no reasonable possibility that the AE is associated with TRC105 study drug or pazopanib.

Causality assessment should be reported for every AE. An AE could be reported as related to one study drug, both study drugs or not related to any study drug. Please refer to Section 2.6.1.1 and Section 2.6.1.2 for the most common TRC105 and pazopanib adverse reactions; for complete reference, please use the most current version the TRC105 IB and the most current version the pazopanib product labeling. Note: an AE could be considered as related or possibly related to study drug(s) even if not referenced in the IB or the product labeling if in the opinion of the investigator there is a reasonable possibility that the drug(s) may have caused the AE.

9.3.7. Expectedness Assessment

All TRC105 AEs and suspected adverse drug reactions are considered "unexpected" if not listed in the applicable section of the current TRC105 Investigator Brochure (IB) or not listed at the specificity or severity that has been observed and listed in the IB. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB 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.

For the expectedness assessment of AEs related to pazopanib, the most recent product labeling will be referenced.

9.3.8. Exposure *in Utero*

A pregnant patient will be withdrawn from the study. If any trial patient (or partner of a trial patient) becomes or is found to be pregnant during the study or within 180 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 AE 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.

For pregnancies of partners of male participating in the study: all partners who become pregnant and provide appropriate consent to TRACON will be monitored to the completion or termination of the pregnancy as described above.

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

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

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

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

9.3.9. Follow-up of Unresolved Adverse Events

All AEs should be followed until they are resolved or return to the patient's pre-treatment baseline, or the Investigator assesses them as stable; every effort should be made to make this determination by the 28-day follow-up visit. Any increase or decrease in AE grade should be recorded as a new AE.

All serious and those non-serious events assessed by the Investigator as suspected adverse reaction to the investigational medication/product must continue to be followed even after the patient's participation in the trial is over, until the event is either resolved, improved to the patient's pre-treatment baseline or better, stable without anticipated future change or the patient is lost to follow-up, or in the case of a suspected adverse reaction, later determined to be not related to the investigational medicinal product.

9.4. Safety Monitoring

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

- Surveillance and reporting of SAEs according to regulatory guidelines as outlined in the safety plan
- Routine monitoring of non-serious AEs as they are recorded in the CRFs and the source documents at study sites
- Periodic teleconferences with the Principal Investigators to share experiences and ensure communication
- New 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
- An Independent Data Monitoring Committee (IDMC) will review the data from the trial. The IDMC will periodically review the progress of the study and accumulating safety and efficacy data. Following each review, the IDMC will recommend to the Sponsor (TRACON Pharma) whether to continue the trial unchanged, modify the conduct of the study, or terminate the study early. The DMC will be comprised of 3 voting members

external to the Sponsor, including a clinician specializing in the treatment of angiosarcoma, a clinician with broader specialty in oncology clinical studies, and a biostatistician with expertise in the design, analysis, and interpretation of oncology clinical studies.

- There are 2 committees monitoring safety across all studies of TRC105, a separate charter for each committee will define the roles and responsibilities.
  - A formally chartered external Safety Review Team
  - A formally chartered TRACON in-house Safety Review Team

9.5. Steering Committee

An external steering committee comprised of sarcoma experts assisted with study design and will review study amendments as needed.

10. OTHER ASSESSMENTS

10.1. Other Laboratory Assessments

10.1.1. Pharmacokinetics

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

10.1.1.1. TRC105 and Pazopanib Concentrations

A 5 mL blood sample for each TRC105 and pazopanib pharmacokinetics (PK) to be collected at the time points indicated in the Schedule of Assessments (Table 3 and Table 4) (if applicable). Samples will be stored at approximately -70°C. Samples will be batch shipped as indicated in the laboratory manual to a central 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.

10.1.2. TRC105 Immunogenicity

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

Anti-TRC105 antibody concentrations will be measured using validated enzyme-linked immunosorbent assay (ELISA) methods at the time points specified in the Schedule of Assessments (Table 4) in all patients. Anti-TRC105 antibody concentrations will be evaluated in the context of PK/pharmacodynamics parameters and AE profiles. Samples will be separated and stored at approximately -70 °C. See separate laboratory guide for further collection and shipment information.

10.1.3. Protein Biomarkers

One 10 mL purple top (K_2EDTA) tube of blood will be collected on the days indicated within the Schedule of Assessments (Table 3 and Table 4). Samples will be stored at approximately -70°C and shipped to Fisher BioServices Inc. for storage until the time of analysis. Protein biomarkers to be analyzed include, but are not limited to, VEGF, VEGF-R2, placental growth factor (PIGF), and sCD105. Please see the separate laboratory guide for further collection and shipment information.

10.1.4. Circulating Tumor Cells

One 10 mL EDTA tube of blood for circulating tumor cells (CTCs) will be collected on the days indicated within the Schedule of Assessments (Table 3 and Table 4). Samples will be shipped to Apocell Inc. for analysis. Please see the separate laboratory guide for further collection and shipment information.

10.1.5. Archival Tumor Specimens

Specimens (formalin-fixed, paraffin-embedded) of the primary cancer and/or metastatic angiosarcoma tumor for each study participant will be obtained and centrally reviewed,

retrospectively, to corroborate diagnosis of angiosarcoma. Other markers that may relate to efficacy or toxicity of TRC105 may also be explored.

It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 10 unstained slides are requested for immunohistochemical analysis (sections of ~ 5 microns are preferred).

Samples will be stored at room temperature and shipped to Fisher BioServices Inc. for storage until the time of analysis. See separate laboratory guide for further collection and shipment information.

11. STATISTICS

11.1. Sample Size

A hazard ratio (HR) of 0.55 is considered to be clinically relevant. Based on 1:1 randomization and the use of log-rank test at the 2-sided alpha of 0.05 level of significance, 95 events provides 83% power to detect a HR of 0.55.

The expected PFS of angiosarcoma patients treated with pazopanib who have progressed following first line treatment is 4 months. A HR of 0.55 corresponds to an improvement of median PFS from 4 months to 7.27 months. Due to the uncertainty of the treatment effect, and heterogeneity among the cutaneous and non-cutaneous subgroups, an adaptive enrichment design will be employed. The adaptive design calls for enrolling two cohorts, with 120 adult patients in Cohort 1, and 70 adult patients in Cohort 2. The initially planned final analysis will be conducted when 60 events are observed from Cohort 1 and 35 events are observed from cohort 2, whichever comes at a later time. A projection of events in Cohort 1 will be done prior to the interim analysis, and the sample size of Cohort 1 may be increased by no more than 20% to compensate for a lack of expected events. Similarly, a projection of events in Cohort 2 will be done at 55 events in Cohort 1 and the sample size and number of events in Cohort 2 only may be increased by no more than 20% to compensate for a lack of or expected time frame of events.

A formal interim analysis will be performed after observing 40 events or 30 days after enrolling 120 patients in cohort 1. Based on the results obtained at this interim analysis, the trial will be classified into one of four zones: favorable, promising, enrichment, and unfavorable. The future course of the trial may be modified in one of the following ways (Figure 3):

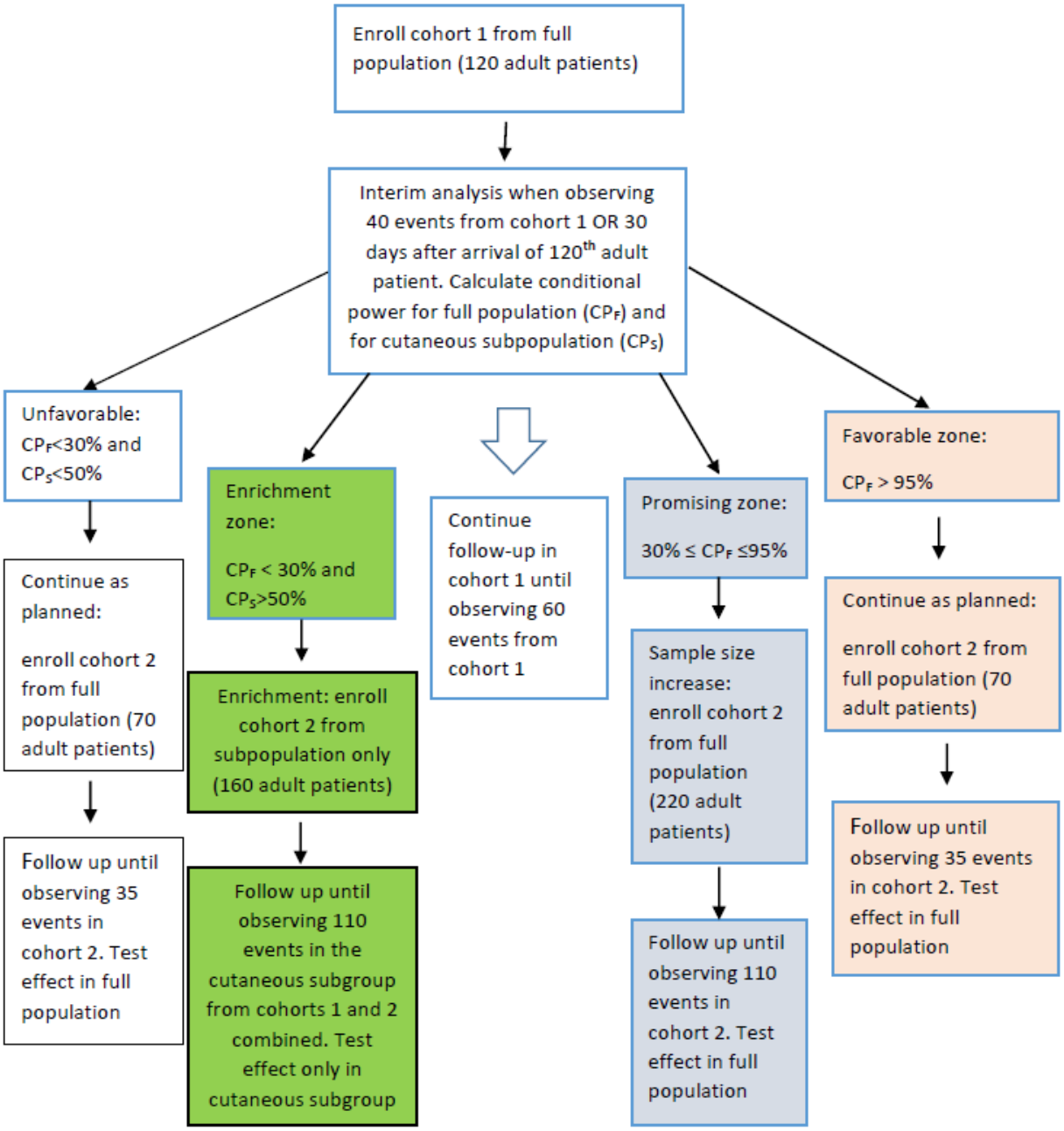
1. Favorable Zone: If the conditional power of demonstrating treatment effect with full population is high, i.e., $CP_F > 95\%$, the trial is considered to fall into the favorable zone. In this case, it will continue with the initially planned enrolment of 120 adult patients for Cohort 1 and 70 adult patients for Cohort 2 from both cutaneous and non-cutaneous patients. The final analysis will be performed on the full population when 60 events are observed for Cohort 1 and 35 events for Cohort 2, whichever comes later.
2. Promising Zone: If the conditional power of demonstrating treatment effect with full population is between 30% and 95% inclusive, the trial is considered to fall into the promising zone. If the trial falls into promising zone, enrollment into Cohort 2 will be increased from 70 adult patients to 220 adult patients from the full population and the events in Cohort 2 will be increased from 35 to 110. The final analysis will be performed on the full population when 60 events are observed from the 120 adult patients in Cohort 1 and 110 events are observed from the 220 adult patients in Cohort 2, whichever comes later.
3. Enrichment Zone: If the conditional power for the full population is < 30% and the conditional power for the cutaneous subgroup is > 50%, the enrollment for Cohort 2 will be restricted to the cutaneous subgroup only and 160 adult patients will be enrolled. The final analysis will be performed on the cutaneous subgroup only, when 60 events are observed from the 120 adult patients in Cohort 1 and when 110 events are observed in cutaneous subgroup from both cohorts combined.

4. Unfavorable Zone: If the conditional power for the full population is < 30% and the conditional power for cutaneous subgroup is ≤ 50%, the trial is considered to fall into the unfavorable zone. In this case, the trial will remain unchanged, enrolling 120 adult patients for Cohort 1 and 70 adult patients for Cohort 2 from the full population. The final analysis will be performed on full population when 60 events are observed from the 120 adult patients in Cohort 1 and 35 events are observed from the 70 adult patients whichever comes later.

The IDMC might recommend termination of the trial for futility by exercising its judgment based on the totality of the data at interim time if TRC105 seems doing worse than the control group.

In order to preserve the statistical integrity of the adaptive design it is **pre-specified** that 120 subjects will be enrolled in Cohort 1, and followed until 60 events are obtained. This specification was based on initial assumptions about patient enrollment rates and HRs. The actual rates could vary from these initial assumptions. In addition it has not been factored in the impact of possible patient drop-outs. If there are too many drop-outs from Cohort 1, it may either become impossible to obtain the required 60 events or the duration of patient follow-up may become excessively prolonged. To mitigate these risks, the sample size of Cohort 1 and Cohort 2 may increase by a maximum of 20% as detailed in the statistical analysis plan (SAP) in a manner that does not increase the Type 1 error rate.

Figure 3: Schematic Representation of Adaptive Trial Design



11.1.1. 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 either TRC105 or pazopanib. If a patient actually received study drug not according to their randomized treatment arm, they will be analyzed for safety in the treatment arm according to the study drug they actually received.

- The study population for efficacy will include all randomized adult patients (intent-to-treat, ITT).

11.2. Data Analysis

Descriptive statistics (such as means, medians, standard deviations and ranges for continuous data and percentages for categorical data) will be used to summarize patient characteristics, treatment administration/compliance, immunogenicity (anti-TRC105 antibodies), efficacy, PK parameters, protein biomarkers, and archival tumor tissue. Data will also be displayed graphically, where appropriate. Additional details of data analyses for the study may be found in the statistical analysis plan (SAP).

11.2.1. Analysis of Primary Objective

PFS is defined as time from randomization to either first disease progression (per independent radiology review of images by RECIST 1.1) or death from any cause. For the purpose of analysis for patients who are alive at the time of analysis and have not had disease progression, the following rules will apply: (1) The patient will be censored on the date of the last tumor assessment documenting absence of progressive disease; (2) if the patient was given antitumor treatment other than study drug treatment, the patient will be censored as of the date of the last tumor assessment prior to initiating that antitumor therapy; (3) if the patient was removed from study for toxicity or other reason, the patient will be censored as of the date of the last tumor assessment on study. With regard to missed tumor assessments, in the event of one missed tumor assessment followed by a subsequent assessment of progressive disease (PD), the subsequent PD assessment qualifies as objective tumor progression. In the event of more than one consecutive missing tumor assessment followed by a subsequent assessment of PD, the patient will be censored at the last adequate tumor assessment.

The primary efficacy analysis will test the null hypothesis that the HR of the experimental arm relative to the control arm is 1 against the alternative hypothesis that the HR is less than 1, at the 2-sided 0.05 level of significance. The hypothesis test will be based on the method of Jenkins, Stone and Jennison [67], thereby ensuring strong control of Type 1 error for this adaptive design. Additional supportive analyses will include Kaplan-Meier plots for each treatment arm and the p-value and confidence interval for the HR, unadjusted for the adaptive nature of the design.

A pre-planned assessment of the primary endpoint will additionally be done to determine the primary endpoint of PFS without censoring patients with tumor response who undergo curative intent surgical resection. A Cox regression model will be used to explore the potential influences of the stratification factors on the primary PFS endpoint. In addition, the potential influences of baseline patient characteristics will be evaluated.

An exploratory, sensitivity analysis will be conducted that will apply the modified RECIST 1.1 separately to cutaneous lesions and to non-cutaneous lesions for each patient with both cutaneous and non-cutaneous sites of disease.

The secondary endpoints will be tested in a hierarchical order only if the test for primary endpoint is significant at 2-sided significance level 0.05. More specifically, if the test for PFS is significant at the final analysis time, the objective response rate (ORR) will be tested next at the same 2-sided 0.05 level followed by the test for overall survival (OS) at the same level.

11.2.2. Analysis of Pharmacokinetics

Serum TRC105 and plasma pazopanib concentrations will be measured using validated methods and assessed for potential correlations with response, PFS, survival, AEs, and baseline characteristics using descriptive statistics and models as appropriate. To the extent possible potential PK drug interaction between pazopanib and TRC105 and the relationship between pazopanib exposure and efficacy/safety endpoints in the pazopanib alone arm will be explored, and examine the assumption that the exposure-response relationship for pazopanib is flat and that there is no drug interaction between pazopanib and TRC105 in the combination arm. Intensive pharmacokinetic data collection with additional analyses will be done for patients 12-17 years of age to provide data in support of extrapolation of the treatment effects of TRC105 and pazopanib from adults to this pediatric population.

11.2.3. Analysis of Protein Biomarkers

Angiogenic protein biomarker data for each patient who received at least 1 dose of TRC105 or pazopanib will be listed.

11.2.4. Analysis of Circulating Tumor Cells

Endoglin expressing circulating tumor cell data for each patient who received at least 1 dose of TRC105 or pazopanib will be listed.

11.2.5. Analysis of Immunogenicity

Anti-TRC105 antibody responses will be measured using a validated bridging electrochemiluminescent (ECL) assay format (on the MesoScale Discoveries platform) at the time points specified in the Schedule of Assessments (Table 4). This method employs an initial acid dissociation step to increase drug tolerance of TRC105 to > 400 µg/mL. A three-tiered approach will be utilized for sample analysis: screening, confirmatory, and titration assays. Samples that are above the cutpoint in the initial screening assay will be considered potentially positive. The potentially positive samples will then be tested in a confirmatory assay, where they will be assessed in the presence or absence of TRC105 to establish whether a sample is a true positive or false positive. Samples determined to be true positives in the confirmatory assay will be taken to the third tier assay where they will be titrated until the signal falls below the assay cutpoint in order to determine a titer for the sample, which reflects the magnitude of response.

Anti-TRC105 antibody responses will be evaluated in the context of PK parameters and AE profiles. To the extent possible as provided by the available data, the effect of anti-TRC105 antibodies on the PK, pharmacodynamics (PD), efficacy, and safety of TRC105 will be evaluated.

12. 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.

13. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

Protocol deviations will be captured in TRACONs electronic data capture system.

14. ETHICS

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

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

All correspondence and other evidence of appropriate and timely communications with the IRB/IEC should be retained in the Investigator/site files. Copies of all IRB/IEC approvals should also be forwarded to TRACON.

The only circumstance in which an amendment may be initiated prior to 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.

14.2. 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 Harmonisation (ICH) 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).

14.3. 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.

14.4. Patient Compensation

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

15. DATA HANDLING AND RECORDKEEPING

15.1. Inspection of Records

CRFs are required and should be completed for each patient who receives any treatment with either TRC105 or pazopanib. Screen failure CRFs 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 a Regulatory Authority and in accordance with Health Portability and Accountability Act (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 CRFs and that the information is complete, accurate, and true. At all times, the Investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

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

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

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

15.2. Retention of Records

To allow for appropriate evaluations and/or audits by regulatory authorities or TRACON, the Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, source documents, and detailed records of treatment disposition.

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

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

If the Investigator relocates, retires, or for any reason withdraws from the study, then TRACON should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator or 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.

16. DEFINITION OF END OF TRIAL

16.1. 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 the follow up period, all data collection and clean-up activities have been completed, including all query resolution.

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

16.2. TRACON Study Discontinuation Criteria

Premature termination of this trial may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, study drug safety problems or availability, 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 ongoing 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.

17. PUBLICATION OF TRIAL RESULTS

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

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

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

18. FINANCING AND INSURANCE

Financing and Insurance are discussed in the Investigators' Clinical Trial Agreement.

19. INVESTIGATOR PROTOCOL AGREEMENT: 105SAR301

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, all protocol amendments, and all materials provided to potential study patients must be submitted to and approved by the appropriate IRB/IEC prior to implementation.

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required): _____

Name (typed or printed): _____

Institution and Address: _____

_____

Signature Date (Day Month Year)

Principal (Site) Investigator: _____

Name (typed or printed): _____

Institution and Address: _____

Telephone Number: _____

_____

Signature Date (Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor.

Please sign and return this agreement to:

TRACON Pharmaceuticals, Inc.
Attn: Clinical Operations
4350 La Jolla Village Drive, Suite 800
San Diego, CA 92122
Please keep a copy for your records.

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21. APPENDICES

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

The NCI CTCAE (Version 4.03) should be used to assess AEs and may be reviewed on-line at the following NCI website:

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

21.2. 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.

21.3. Appendix 3: Quality of Life Questionnaire - EQ-5D-5L Example

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

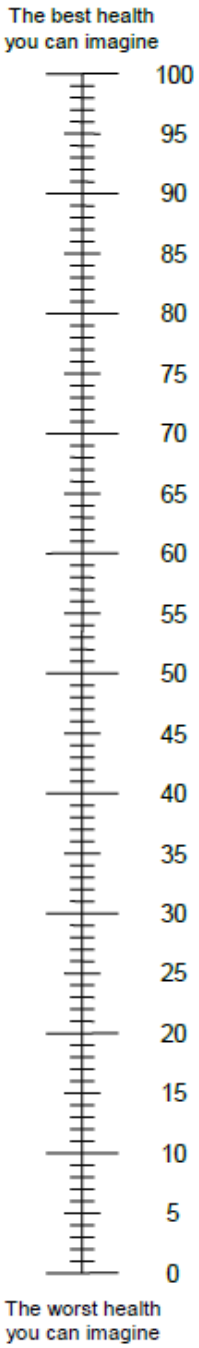
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

21.4. Appendix 4: Quality of Life Questionnaire – EORTC QLQ-C30 Example

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): 31 _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent