CLINICAL PROTOCOL

Title:	A RANDOMIZED PHASE 2 TRIAL OF AXITINIB AND TRC105 VERSUS AXITINIB ALONE (INCLUDING A LEAD-IN PHASE 1B DOSE-ESCALATION PORTION) IN PATIENTS WITH ADVANCED OR METASTATIC RENAL CELL CARCINOMA
Protocol Number:	105RC101
Study Sponsor:	TRACON Pharmaceuticals, Inc. 8910 University Center Lane, Suite 700 San Diego, CA 92122 Phone: 858.550.0780 Facsimile: 858.550.0786
Medical Monitor:	Ronald Shazer, M.D., M.B.A. 8910 University Center Lane, Suite 700 San Diego, CA 92122 Direct Phone: 858.550.0780, Ext. 230 Fax: 858.550.0786 Cell Phone: 310.922.8039 Email: rshazer@traconpharma.com
Signature and Date:	Signed: _____ Print: RONALD SHAZER Dated: 15MAR2016

CLINICAL PROTOCOL

Version Date:	Original Version: February 4th, 2013 Amendment #1: April 2nd, 2013 Amendment #2: June 25th, 2013 Amendment #3: July 28th, 2014 Amendment #4: December 2nd, 2014 Amendment #5: April 17th, 2015 Amendment #6: September 2nd, 2015 Amendment #7: December 7th, 2015 Amendment #8: February 22nd, 2016

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone number
Primary Medical Monitor	Ronald Shazer, M.D., MBA	8910 University Center Lane, Suite 700 San Diego, CA 92122 Office: 1.858.550.0780, Ext. 230 Mobile Phone: 1.310.922.8039 Email: rshazer@traconpharma.com
Secondary Medical Monitor	Charles Theuer M.D., PhD	8910 University Center Lane, Suite 700 San Diego, CA 92122 Office: 1.858.550.0780, Ext. 230 Mobile Phone: 1.858.344.9400 Email: ctheuer@traconpharma.com

1. SYNOPSIS

Name of Sponsor/Company: TRACON Pharmaceuticals, Inc.

Name of Investigational Product: TRC105

Name of Active Ingredient: TRC105

Title of Study:
A RANDOMIZED PHASE 2 TRIAL OF AXITINIB AND TRC105 VERSUS AXITINIB ALONE (INCLUDING A LEAD-IN PHASE 1B DOSE-ESCALATION PORTION) IN PATIENTS WITH ADVANCED OR METASTATIC RENAL CELL CARCINOMA

Study center(s): This study will be performed at approximately:
Phase 1b: 5 US Centers
Phase 2: approximately 30 US centers and 20 centers in the EU (sites to be determined).

Investigators: To be determined

Studied period (years):	**Phase of development:** 1b/2
Date first patient enrolled phase 1b portion: March 2013 Date phase 1b MTD obtained: February 2014 Estimated date first patient enrolled phase 2 portion: Sept 2014 Estimated date phase 2 endpoint obtained: June 2016 Estimated date last patient completed: December 2016	

Rationale:

Axitinib 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. Axitinib is approved for the treatment of advanced renal cell carcinoma, following progression on one prior systemic therapy. TRC105 is an antibody to CD105, an important angiogenic target on vascular endothelial cells that is distinct from VEGFR. TRC105 inhibits angiogenesis, tumor growth and metastases in preclinical models and complements the activity of bevacizumab and multi-kinase inhibitors that target VEGFR. In a phase 1 study of advanced solid tumors, TRC105 therapy caused a global reduction in angiogenic biomarkers and reduced tumor burden at doses that were well-tolerated. By targeting a non-VEGF pathway that is upregulated following VEGF inhibition, TRC105 has the potential to complement VEGF inhibitors and could represent a major advance in cancer therapy. TRC105 potentiates bevacizumab and VEGFR tyrosine kinases (VEGFR TKI) in preclinical models. In a phase 1b study, the combination of TRC105 and bevacizumab produced radiographic reductions in tumor burden in bevacizumab refractory patients. Together, the use of TRC105 with axitinib may result in more effective angiogenesis inhibition and improved clinical efficacy over that seen with axitinib alone. In the phase 1b portion of the study, TRC105 at its recommended phase 2 dose of 10 mg/kg given by weekly intravenous infusion was combined with axitinib given at 5 mg p.o. BID, without the development of dose limiting toxicity (DLT). Tumor

reductions, including response by RECIST 1.1, were observed in renal cell carcinoma patients who had progressed on prior VEGFR TKI treatment.

Objectives:

Phase 1b:

Primary:

- To evaluate safety and tolerability and determine a recommended phase 2 dose for TRC105 when added to standard dose axitinib in patients with advanced renal cell carcinoma

Secondary:

- To look for preliminary evidence of antitumor activity when TRC105 is added to axitinib, by assessing overall response rate and progression-free survival
- To characterize the pharmacokinetic profile of TRC105 when given with axitinib
- To evaluate TRC105 immunogenicity by measuring Anti-Product Antibody (APA) formation
- To explore the pharmacodynamic changes in circulating angiogenic biomarkers following treatment with TRC105 and axitinib

Phase 2:

Primary:

- To estimate the PFS of patients with advanced or metastatic RCC by RECIST 1.1 criteria in patients treated with axitinib and TRC105 compared to those treated with axitinib alone, following failure of one prior VEGF inhibitor.

Secondary:

- To estimate overall response rate by RECIST 1.1 and Choi criteria, including duration of response by RECIST 1.1
- To estimate the disease control rate (CR + PR + SD) at 16 weeks by RECIST 1.1 and Choi criteria
- To determine the frequency and severity of adverse events as assessed by NCI CTCAE (Version 4.0)
- To evaluate TRC105 immunogenicity as measured by Anti-Product Antibody (APA) concentrations
- To explore the effects of TRC105 on circulating angiogenic protein biomarkers
- To characterize the pharmacokinetic profile of TRC105 and axitinib

Methodology:

Phase 1b:

This is a multicenter, open-label, nonrandomized, phase 1b, dose-finding study of TRC105 in combination with standard dose axitinib in patients with advanced renal cell carcinoma. Escalating doses of i.v. TRC105 will be administered weekly beginning with Dose Level 1 in combination with oral axitinib given twice daily of each 28 day cycle. Additional intermediate doses (below the MTD established during the trial) may be explored based upon clinical, PK, and/or biomarker data.

Cohort	Number of Evaluable Subjects	Axitinib mg p.o., BID days 1-28	TRC105 mg/kg IV
-1	3-6	5	6[a]
1 (starting dose)	3-6	5	8[a]
2	3-6	5	10[a]
Expanded Cohort 1	9-12 (up to 15 total at the MTD)	5	10[a]
3	3-6	5	• 10 mg/kg weekly during cycle 1[b] • 15 mg/kg every two weeks beginning with cycle 2 day 1[b]
4	3-6	5	• 10 mg/kg weekly during cycle 1[b] • 20 mg/kg every two weeks beginning with cycle 2 day 1[b]
Expanded Cohort 2	At least 6 patients will be treated at the MTD (either cohort 3 or cohort 4 dose level)	5	• 10 mg/kg weekly during cycle 1[b] • Either 15 or 20 mg/kg every two weeks beginning cycle 2 day 1[b]

[a] In cohort -1, 1, 2 and expanded cohort 1 TRC105 will be given weekly.

[b] In cohorts 3 and 4 and Expanded Cohort 2, axitinib dosing will begin on cycle 1 day 1 and twice daily thereafter, and TRC105 will be administered weekly during cycle 1. The first weekly TRC105 dose will be 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. Starting on cycle 2 day 1 and beyond, TRC105 will be administered every two weeks on days 1 and 15.

For cohorts 1 and 2, the DLT evaluation period, for purposes of dose expansion, will be the first 28 days of dosing axitinib and TRC105 together (e.g., from cycle 1 day 1 through cycle 1 day 28) . Cycles are 28 days in duration.

For cohorts 3 and 4, the DLT evaluation will be the first 28 days of dosing axitinib with TRC105 every 2 weeks (e.g., from cycle 2 day 1 through cycle 2 day 28). Cycles are 28 days in duration.

Three patients will be initially enrolled and treated at each dose level. If none of these 3 patients experiences a dose-limiting toxicity (DLT) during the 28-day evaluation period, dose escalation will proceed following review of safety data with appropriate site staff including the principal investigators at all sites.

If 1 of 3 patients experiences DLT, the dose level will be expanded to 6 patients. The maximum tolerated dose (MTD) will have been exceeded if ≥ 33% of patients experience DLT at a given dose level. DLT will have occurred when a patient has 1 or more toxicity listed in the table below that is at least possibly related to the combination of axitinib and TRC105 during the 28 day DLT evaluation period. Patients who exit the study for reasons other than DLT or any TRC105 dose delay > 2 days in cycle 2 (phase 1b cohort 3 and 4 only) prior to completion of the 28-day DLT evaluation period will be replaced to ensure an adequate safety assessment at each dose level. Patients who experience DLT and those without DLT who receive less than the prescribed dose of TRC105 or axitinib due to documented toxicity in Cycle 1 (for cohorts -1, 1, and 2) and in Cycle 2 (for cohorts 3 and 4) will be considered evaluable for dose escalation purposes. Upon agreement of the study investigators, a given TRC105 dose level may be reenrolled at ≥ 60% of the axitinib dose intensity and/or the first dose of TRC105 may be delayed by one week (i.e., delayed to cycle 1 day 8).

Toxicity Category	**Drug-Related Toxicity/Grade**
Hematologic	Grade 4 neutropenia for ≥ 5 days
	Febrile neutropenia: grade 4 neutropenia with fever > 38.5 ºC both sustained over a 24 hour period.
	Neutropenic infection: grade ≥ 3 neutropenia with grade ≥ 3 infection
	Anemia ≥ grade 3
	Grade > 4 thrombocytopenia or grade ≥ 3 thrombocytopenia and grade ≥ 3 hemorrhage
Nonhematologic	Grade 3 or 4 nonhematologic toxicity with the following exceptions: • Nausea, vomiting or diarrhea for < 48 hours[a] • Asymptomatic electrolyte abnormalities that are corrected to grade 1 or better in < 48 hours[b]

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

Up to 15 patients with advanced renal cell carcinoma will be treated at the weekly dosing MTD (or top dose level if a MTD is not determined) to further characterize safety and tolerability. At least 6 patients with advanced renal cell carcinoma will be treated at the every two week dosing MTD (or top dose level if a MTD is not determined).

Phase 2:

This is a multicenter, randomized, phase 2 study of TRC105 in combination with standard dose axitinib in patients with advanced or metastatic renal cell carcinoma. Patients will be stratified by performance status (PS = 0 vs. PS = 1) and centrally randomized in a 1:1 ratio to one of the following treatment arms: TRC105 in combination with standard dose axitinib vs. standard dose axitinib, following documented progression on one prior VEGF inhibitor. All patients will initially receive axitinib 5 mg twice daily; patients randomized to receive TRC105 will receive TRC105 at 3 mg/kg on day 1, 7 mg/kg on day 4, and 10 mg/kg on day 8 and weekly thereafter.

TRC105 may be administered every two weeks starting with cycle 2 day 1 but **ONLY AFTER COHORT 3 AND 4 IN THE PHASE 1B ARE COMPLETE AND THE SPONSOR SENDS NOTIFICATION TO PROCEED WITH EVERY TWO WEEK DOSING**.

- Axitinib dosing will begin on cycle 1 day 1 and twice daily thereafter.
- TRC105 will be administered weekly during cycle 1.
    - The first weekly TRC105 dose will be 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.
- Starting on cycle 2 day 1 and beyond, TRC105 may be administered every two weeks on days 1 and 15.

Patients **in both arms** who tolerate axitinib for at least two consecutive weeks with no adverse reactions > Grade 1 considered clinically significant (according to the Common Toxicity Criteria for Adverse Events [CTCAE]), will, at the discretion of their treating physician, have the axitinib dose increased to 7 mg twice daily beginning on **cycle 2 day 1**, unless the patient's blood pressure is > 150/90 or the patient is receiving more than one antihypertensive medication. Subsequently, with the same criteria, patients who tolerate the axitinib dose of 7 mg twice daily for at least two consecutive weeks may have the axitinib dose increased to a maximum of 10 mg twice daily beginning with **cycle 3 day 1**. Dose reductions of axitinib and TRC105 are allowed per patient tolerance. Each cycle is 28 days.

Number of patients (planned):

Approximately 30 patients with advanced renal cell carcinoma will be enrolled in the phase 1b portion and approximately 150 patients with advanced or metastatic renal cell carcinoma will be enrolled in the phase 2 portion.

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

1. **PHASE 2 ONLY:** Histologically confirmed advanced or metastatic renal cell carcinoma with a clear cell component that has progressed by investigator assessment on treatment with one and only one multi-targeted tyrosine kinase inhibitor (TKI) other than axitinib that targets the VEGF receptor (VEGFR) (e.g., sunitinib, pazopanib, sorafenib, tivozanib, cabozantinib) **OR** bevacizumab. Patients who received VEGF inhibitor treatment for ≤ one month due to documented intolerance in the absence of progression, and were started on a second VEGF inhibitor within one month of discontinuing the initial VEGF inhibitor are eligible. One prior immunotherapy (interleukin-2 or interferon-alpha or immune checkpoint inhibitor or tumor vaccine) and one prior mTOR inhibitor treatment are allowed. Prior adjuvant therapy is permitted in the absence of disease progression during treatment, but no further VEGF treatment is allowed if progression occurred on adjuvant VEGF inhibitor treatment.
2. **PHASE 1B COHORT 3 AND 4 ONLY:** Histologically confirmed advanced or metastatic renal cell carcinoma that has progressed by investigator assessment on treatment with at least **TWO** VEGF inhibitors (e.g., sunitinib, pazopanib, sorafenib, tivozanib, cabozantinib, bevacizumab). Prior immunotherapy (interleukin-2 or interferon-alpha or immune checkpoint inhibitor or tumor vaccine), or mTOR inhibitor treatment is allowed.
3. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission per investigators' clinical judgment.
4. Measurable disease by RECIST 1.1 criteria
5. Age of 18 years or older
6. ECOG performance status ≤ 1
7. Resolution of all acute adverse events resulting from prior cancer therapies to NCI CTCAE grade ≤ 1 or baseline (except alopecia)
8. Adequate organ function as defined by the following criteria:
   - AST and ALT ≤ 2.5 x ULN **OR** ≤ 5 x ULN in cases of liver metastases
   - Total serum bilirubin ≤ 1.5 times the upper limit of normal
   - Absolute neutrophil count (ANC) ≥ 1500/μL
   - Platelets ≥ 100,000/μL without transfusion support within the past 28 days
   - Hemoglobin ≥ 9.0 g/dL without transfusion support within the past 14 days (erythropoietin or darbepoetin permitted)

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

9. Willingness and ability to consent for self to participate in study
10. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures
11. Men who are sterile (including vasectomy confirmed by post vasectomy semen analysis) OR agree to use a condom with spermicide (refer to Section 2.3.6.1) and to not donate sperm during the study and for at least 180 days following last dose of TRC105 or axitinib.
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 two acceptable methods of birth control, one of which must be highly effective during the study and for at least 180 days after stopping TRC105 or axitinib (refer to Section 2.3.6.1).

Exclusion Criteria:

1. **PHASE 2:** Prior treatment with TRC105 or axitinib or any agent targeting the endoglin pathway (including a fusion protein that binds bone morphogenic protein)
2. **PHASE 1B COHORT 3 & 4 ONLY:** Prior treatment with TRC105
3. Grade 3 or 4 toxicity related to prior VEGF inhibitor that did not resolve to grade 1
4. Current treatment on another therapeutic clinical trial
5. Receipt of systemic anticancer therapy, including investigational agents, within 28 days of starting study treatment. If anticancer therapy was given within 28 days of starting study treatment, patients may be included if 5 times the elimination half-life of the drug passed.
6. Prior radiation therapy within 28 days of starting the study treatment, except radiation therapy for bone metastases or radiosurgery is permitted up to 14 days of starting treatment
7. No major surgical procedure or significant traumatic injury within 6 weeks prior to study registration, and must have fully recovered from any such procedure; date of surgery (if applicable). Note: the following are **not** considered to be major procedures and are permitted up to 7 days before therapy initiation: Thoracentesis, paracentesis, port placement, laparoscopy, thoracoscopy, tube thoracostomy, bronchoscopy, endoscopic ultrasonographic procedures, mediastinoscopy, skin biopsies, incisional biopsies, imaging-guided biopsy for diagnostic purposes, and routine dental procedures
8. Uncontrolled chronic hypertension defined as systolic > 150 or diastolic > 90 despite optimal therapy (initiation or adjustment of BP medication prior to study entry is allowed provided that the average of 3 BP readings at a visit prior to enrollment is < 150/90 mm Hg)
9. History of brain involvement with cancer, spinal cord compression, or carcinomatous meningitis, or new evidence of brain or leptomeningeal disease. Patients with radiated or

resected lesions are permitted, provided the lesions are fully treated and inactive, patients are asymptomatic, and no steroids have been administered for at least 28 days.

10. Angina, MI, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack, arterial embolism, pulmonary embolism, PTCA or CABG within the past 6 months. Deep venous thrombosis within 6 months unless the patient is anticoagulated without the use of warfarin for at least 2 weeks. In this situation, low molecular weight heparin is preferred.
11. Active bleeding or pathologic condition that carries a high risk of bleeding (e.g. hereditary hemorrhagic telangiectasia).
12. Thrombolytic use (except to maintain i.v. catheters) within 10 days prior to first day of study therapy
13. Known active viral or nonviral hepatitis or cirrhosis
14. History of hemorrhage or hemoptysis (> ½ teaspoon bright red blood) within 3 months of starting study treatment
15. History of peptic ulcer disease within 3 months of treatment, unless treated for the condition and complete resolution has been documented by esophagogastroduodenoscopy (EGD) within 28 days of starting study treatment
16. History of gastrointestinal perforation or fistula in the past 6 months, or while previously on antiangiogenic therapy, unless underlying risk has been resolved (e.g., through surgical resection or repair)
17. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness
18. Receipt of a strong CYP3A4/5 inducer within 12 days prior to cycle 1 day 1 or a strong CYP3A4/5 inhibitor within 7 days prior to cycle 1 day 1 (Table 18)
19. Other severe acute or chronic medical (including bone marrow suppressive diseases) or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for this study
20. Patients with known hypersensitivity to Chinese hamster ovary products or other recombinant human, chimeric, or humanized antibodies
21. Significant ascites or pericardial or pleural effusion
22. Patients with hereditary problems of galactose intolerance, including Lapp lactase deficiency or glucose-galactose malabsorption

TRC105 investigational product dose and mode of administration:

Phase 1b:

Dosing will begin at 8 mg/kg (cohort 1); however a -1 cohort has also been included (6 mg/kg) and will be enrolled if 8 mg/kg is found to exceed the MTD. Following the appropriate premedication regimen, the first weekly TRC105 dose (cycle 1 day 1) will be split into two doses whereby 3 mg/kg is administered on cycle 1 day 1 and the balance (e.g., 5 mg/kg for Dose Level 1) is administered on

cycle 1 day 4. Thereafter, the TRC105 dose will be administered i.v. weekly during each 28-day cycle.

In cohort 3 (10 mg/kg weekly during cycle 1; 15 mg/kg every two weeks beginning with cycle 2 day 1) and cohort 4 (10 mg/kg weekly during cycle 1; 20 mg/kg every two weeks beginning with cycle 2 day 1) the first weekly TRC105 dose will also be 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. Starting on cycle 2 day 1 and beyond, TRC105 will be administered every two weeks on days 1 and 15.

Phase 2:

Weekly Dosing:

Following the appropriate premedication regimen, TRC105 is to be administered intravenously over 1 to 4 hours on days 1 (3 mg/kg), 4 (7 mg/kg), 8 (10 mg/kg), 15 (10 mg/kg) and 22 (10 mg/kg) of cycle 1 and 10 mg/kg on days 1, 8, 15, and 22 of subsequent 28 day cycles.

Every Two Week Dosing:

TRC105 10 mg/kg weekly during cycle 1as described above. Starting on cycle 2 day 1 and beyond, TRC105 may be administered every two weeks on days 1 and 15 at either 15 mg/kg or 20 mg/kg based on the every two week dosing MTD determined in Phase 1b (Cohort 3 & 4).

Axitinib dose and administration:

Axitinib will be initially dosed orally at its approved dose of 5 mg p.o. BID daily.

Duration of treatment:

Patients are eligible for treatment until disease progression, unacceptable toxicity or withdrawal of consent, or other reasons. Phase 1b patients may be withdrawn for DLT, but DLT does not mandate withdrawal if the DLT resolves and can be treated (i.e., a first dose infusion reaction). A patient should be withdrawn from study treatment if, in the opinion of the Investigator, it is medically necessary, or if it is the wish of the patient. In addition, patients will be withdrawn from treatment in the case of:

1. RECIST 1.1-defined disease progression. In cases where RECIST cannot be applied, progression should be based on unequivocal evidence of progressive disease sufficient to require a change in therapy.
2. A need for anticancer surgery, radiation, or for other anticancer therapy not specified in the protocol.
3. Lost to follow-up or noncompliant.
4. Any TRC105 dose delay > 2 days in cycle 1 (phase 1b cohorts -1, 1, and 2 only)
5. Pregnancy. Pregnant patients should be followed for the duration of the pregnancy and the outcome of the pregnancy should be documented.
6. Arterial thrombosis of any grade (including cerebrovascular ischemia, cardiac ischemia/infarction, or peripheral or visceral arterial ischemia), grade 3 or 4 venous thrombosis (including pulmonary embolism), grade $\geq$ 2 intracranial hemorrhage, grade 3 or 4 non-CNS hemorrhage. Grade 2 non-CNS hemorrhage does not mandate withdrawal if the underlying condition is treatable. Grade 1 intracranial hemorrhage does not

mandate withdrawal and may be treated with dose interruption if the patient is benefitting from treatment.

7. Missed study drug treatment for > 8 consecutive weeks (i.e., both TRC105 and axitinib dosing held if assigned to the combination arm or axitinib held if assigned to axitinib alone arm). However, patients assigned to the combination arm who cannot tolerate axitinib 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 axitinib alone.

Parameters to be assessed:

Safety:

Safety assessments will include physical exams, performance status, laboratory results (complete blood counts and serum chemistry) and 12-lead ECG's, and additional studies as clinically indicated. Safety parameters will be reviewed by a chartered Safety Review Team that reviews data for all TRC105 studies quarterly and a chartered Data Monitoring Committee (DMC) that will periodically review accumulating safety and efficacy data from this study. In addition, recurring teleconferences will be held with Investigators at all clinical sites (Section 8.4).

Pharmacokinetics:

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

Immunogenicity:

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

Exploratory Biomarkers:

Concentrations of a panel of angiogenic protein biomarkers in plasma will be measured at baseline and during treatment to explore TRC105 pharmacodynamics. Archival tumor specimens will be collected for assessment of endoglin expression (Phase 2 Only).

Efficacy:

RECIST 1.1 criteria will be applied to measurable disease to assess response and progression.

Statistical methods:

Evaluable Study Population:

Phase 1b:

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

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

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

of escalating. Conversely, for a common toxicity that occurs with a rate of 70%, the probability of escalating is < 5%.

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

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

Expanded Cohort 1

The probability of failing to observe toxicity in a sample size of 3 patients given various true underlying toxicity rates is shown in the table below. Following identification of the MTD using 3 or 6 patients, an additional 9 patients will be enrolled to further assess safety. If MTD was determined using 3 patients, then a total of 12 patients will be enrolled at the MTD, whereas, if the MTD was determined using 6 patients, then 15 patients will be enrolled at the MTD. The MTD will be exceeded if more than 33% of patients enrolled at the MTD experience DLT. In the case of 12 patients treated at the MTD, the chance of seeing no DLT, given a true underlying DLT rate of 30% is 1.4%. In the case that 15 patients are treated at the MTD, the chance of seeing one or fewer DLT, given a true underlying DLT rate of 30%, is 3%.

Expanded Cohort 2:

The probability of failing to observe toxicity in a sample size of 3 patients given various true underlying toxicity rates is shown in the table below. Following identification of the MTD using 3 patients, at least 3 additional patients will be enrolled to further assess safety.

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

True Underlying DLT Rate	5%	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of Failing to Observe Toxicity, N = 3	0.86	0.73	0.51	0.34	0.22	0.13	0.006	0.027	0.008	0.001

Phase 2:

Efficacy Analyses

The study population for safety will include all patients receiving at least a portion of one dose of TRC105. The study population for efficacy will include all randomized patients (intention to treat). The primary endpoint is PFS and the primary analysis will compare the TRC105 and control groups using a one-sided, stratified (by performance status) log rank test at the alpha=0.10 level of significance. The primary analyses of efficacy endpoints dependent on disease assessments (PFS, ORR and DR) will be performed in the intent-to-treat (ITT) population based on results of the central review of disease response and progression. Supportive analyses will be performed based on investigator assessments of disease response and progression. Pre-planned assessments of the primary endpoint will additionally be done based on number of prior therapies (one, two or three).

Sample Size Justification

A hazard ratio of 0.67 is considered to be clinically relevant. Based on 1:1 randomization and the use of a one-sided log-rank test at the alpha=0.10 level of significance, 115 events are required in order to have 80% power to detect a hazard ratio of 0.67.

The expected PFS of patients treated with axitinib who have progressed following first line treatment with a VEGFR TKI is 4.8 months. Based on a planned accrual period of 12 months, and a minimum follow-up period of 4.3 months, approximately 150 patients will be required.

Interim Analysis for Futility

An interim analysis for futility will be conducted by the DMC when 55 events have occurred. At the interim analysis, the conditional power based on the observed hazard ratio will be estimated. If the conditional power is less than 25%, the DMC may recommend to the sponsor that the study be terminated for futility. However, this interim analysis will not consider the possibility of early termination on the basis of superior efficacy.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Table 2: Abbreviations and Specialist Terms

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

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

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

2. BACKGROUND

2.1. Angiogenesis and Cancer

Angiogenesis is required for the survival and growth of solid cancers [1, 2]. It is generally accepted that solid cancers have two phases, an avascular phase and a vascular phase [2]. During the initial avascular phase, tumors exist as small aggregates of malignant cells supported by simple diffusion of oxygen and nutrients. The progressive growth of solid cancers beyond clinically occult sizes requires the continuous formation of new blood vessels, a process known as tumor angiogenesis. Tumor growth and metastasis require angiogenesis. Therefore, inhibition of tumor angiogenesis and selective inhibition of the tumor vasculature represent potentially effective strategies for the prevention and treatment of solid cancers.

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

Indeed, agents that target pathways required for tumor angiogenesis have an important role in the therapy of cancer patients. The monoclonal antibody bevacizumab, which binds to the angiogenic cytokine VEGF, significantly prolongs overall survival for patients with advanced colorectal cancer or non-small cell lung cancer when added to standard chemotherapy regimens [3, 4]. Bevacizumab is also effective therapy for renal cell cancer and malignant glioma [5-7]. 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, sarcoma and colorectal cancer [8-11].

2.1.1. Angiogenesis and Advanced Renal Cell Carcinoma

The treatment of RCC has changed dramatically since the approval of VEGF inhibitors. Both sunitinib and sorafenib are VEGF receptor tyrosine kinase inhibitors (VEGFR TKI) that were approved as single-agents for cytokine-refractory metastatic renal cell cancer in 2006 [13]. Other VEGF inhibitors approved more recently in the first-line setting are pazopanib and bevacizumab [11, 14], and the VEGFR TKI tivozanib is likely to be approved soon. Axitinib is a relatively pure VEGFR TKI that was approved on the basis of superior progression-free survival in second-line renal cell cancer compared to sorafenib (Table 3) [15]. Inhibitors of mTOR have also demonstrated a survival advantage in RCC. Everolimus is an mTOR inhibitor approved for recurrent metastatic renal cell cancer after failing prior anti-VEGF therapy [16] and temsirolimus is an mTOR inhibitor approved as first-line treatment for poor-risk metastatic RCC [17].

Table 3: Key Phase 3 Studies in Renal Cell Cancer Leading to Drug Approval

Population	Agents	N	PFS (months)	ORR
First-line	Sunitinib vs. interferon	750	11 vs. 5	31% vs. 6%
First-line	Temsirolimus vs. temsirolimus + interferon vs. interferon	626	5.5 vs. 4.7 vs. 3.1	8.6% vs. 8.1% vs. 4.8%
First-line	Sorafenib vs. best supportive care	769	5.5 vs. 2.8	2% vs. 0%
First-line	Pazopanib vs. best supportive care	435	9.2 vs. 4.2	30% vs. 3%
First-line	Bevacizumab + IFN vs. IFN	732	8.5 vs. 5.2	25.5% vs. 13.1%
Second-line	Everolimus vs. best supportive care	416	4.9 vs. 2.9	2% vs. 0%
Second-line	Axitinib vs. sorafenib	723	6.7 vs. 4.7	19.4% vs. 9.4%

RCC is considered fertile ground for the development of TRC105 for the same reason that is was fertile ground for the development of VEGF inhibitors. Both targets are strongly expressed in RCC due to HIF-α dysregulation. Trials combining different VEGF inhibitors (or even VEGF and mTOR inhibitors) in RCC have not been successful due to severe toxicities and there remains a need for agents that complement approved agents targeting the VEGF pathway as well as the mTOR pathway. Initial studies in patients who have failed frontline VEGFR TKI have the advantage of a short time to endpoint. Initial approval in the second- or third-line setting would set the stage for trials in the front-line setting.

Axitinib was approved in a trial of patients who failed one systemic treatment for advanced RCC. While there was an improvement in PFS versus sorafenib, (6.7 versus 4.7 month; hazard ratio = 0.67), many of the patients had not received prior therapy directed at the VEGFR. The results in patients who had failed prior sunitinib were more modest (PFS of 4.8 with axitinib versus 3.4 months with sorafenib; hazard ratio = 0.74). It is clear that further improvement in survival will depend upon addressing targets other than those in the VEGF axis. Beyond the VEGF axis, angiogenesis is dependent upon multiple growth factors and stromal elements [18]. Upregulated non-VEGF pathways may include the IL-6, TGF-β, PDGF, bFGF, c-Met, and angiopoietin axes [19] [20] [21]. In particular, the TGF-β axis, including the soluble bone morphogenic proteins (BMP), and the endoglin and ALK1 receptors, may provide an escape pathway for tumor angiogenesis [22] [23]. Notably, a recent study that examined putative escape pathways following VEGF inhibition indicated the endoglin ligand TGF-β was the most significantly upregulated angiogenic factor examined [24]. Notably, levels of TGF-β increased by a factor of 16.8; in comparison, other angiogenic factors increased by less than 4-fold, if at all. Collectively, these data suggest that targeting non-VEGF angiogenic factors in general, and TGF-β family members in particular, may complement the activity of anti-VEGF therapy.

2.2. CD105 and Angiogenesis

CD105 (endoglin) is a homodimeric cell membrane glycoprotein that was initially identified as a human leukemia-associated antigen [25] and later also found on endothelial cells [26, 27]. CD105 is a TGF-β coreceptor that is essential for angiogenesis [28, 29] and CD105 is strongly expressed on the proliferating vascular endothelium of solid tumors [27, 30]. All of these properties make CD105 an attractive target for the antiangiogenic therapy of cancer [31]. Vascular targeted therapy may more effectively address large established tumors than

conventional antiangiogenic therapy such as anti-VEGF therapy [32]. In animal models, CD105 targeted therapy has demonstrated both vascular targeting effects and antiangiogenic effects by inducing regression of established tumors as well as by preventing new tumor formation and inhibiting expansion of existing tumors [27, 33-36]. Therefore, CD105 offers a novel alternative target relative to the VEGF inhibitors currently available for antiangiogenesis therapy.

CD105 acts to modulate signaling of multiple kinase receptor complexes of the TGF-β superfamily, including TGF-β receptors, activin receptor-like kinases (ALKs) and activin receptors [37]. In the absence of CD105, activation of TGF-β receptors results in phosphorylation of SMAD proteins that inhibit endothelial cell growth. However, activation of CD105 by TGF-β modulates SMAD protein phosphorylation. The end result is release of the growth inhibitory effects of TGF-β receptor activation on endothelium. Not surprisingly, prevention of CD105 activation by anti-CD105 antibody acts synergistically with TGF-β to inhibit endothelial cell growth [38].

CD105 expression is required for endothelial cell proliferation, and CD105 is upregulated in the setting of hypoxia through the induction of hypoxia-inducible factor-1-α (HIF-1-α) [39, 40]. CD105 has also been shown to protect hypoxic cells from apoptosis [41]. The expression of CD105 by endothelial cells is essential for the development of new vasculature. Targeted inactivation (knockout) of murine CD105 results in defective vascular development. Mice lacking CD105 die *in utero* from defective vascular development by gestational day 11 [29].

CD105 is critical for normal human blood vessel development [42]. CD105 haplotype insufficiency causes a well-described syndrome known as hereditary hemorrhagic telangiectasia type 1 (HHT-1 or Rendu-Osler-Weber Syndrome). HHT-1 is a rare autosomal dominant genetic disorder characterized by localized angiodysplasia involving the nasal, buccal, gastrointestinal mucosa and skin microvasculature. Angiodysplasia also occurs in vessels from internal organs including the lungs, liver and brain [43]. The genotype is manifested *in utero*, but the phenotype does not become apparent for many years following birth. Affected patients commonly present with epistaxis in the second decade of life. The phenotype of this disorder is limited to vascular effects, indicating the specific role of CD105 in the vasculature [44].

CD105 is highly expressed on the proliferating endothelial cells of tumor vessels including lung, breast, colorectal, gastric, liver, endometrial, renal cell, head and neck, and ovarian cancers. In adults, CD105 expression is limited to vascular endothelial cells and proerythroblasts, a red blood cell precursor [45].

CD105 expression is a prognostic factor in solid tumor patients. High microvessel density of CD105-positive vessels has been correlated with poor prognosis in clinical studies of breast cancer [46, 47], lung cancer [48], prostate cancer [49, 50], colorectal cancer [51, 52], ovarian cancer [53, 54], gastric cancer [55], endometrial cancer [56], astrocytic brain tumors [57], hepatocellular carcinoma [58], esophageal adenocarcinoma [59], and head and neck cancer [60, 61].

Plasma CD105 levels are prognostic in retrospective studies of cancer patients. In one study, the mean plasma CD105 concentration in 76 patients with colorectal cancer was 4-fold higher than the mean value in 40 healthy subjects without cancer [51]. In the study, a positive correlation was observed between plasma CD105 concentration and stage of disease.

Importantly, CD105 expression is upregulated in tumor endothelial cells following inhibition of the VEGF pathway. CD105 expression increased more than 2-fold in human pancreatic cancers grown in mice treated with an antibody that binds VEGF [62]. As well, treatment of human bladder cancers grown in mice with an antibody that blocks activation of the VEGF receptor increased CD105 expression within the core tumor vasculature [63].

TRC105 is a novel IgG1 that binds CD105 with high avidity. Recent studies at Duke University explored the *in vitro* effects of dual angiogenesis inhibition using bevacizumab and TRC105 in human umbilical vein endothelial cells (HUVEC). Combination therapy was found to be more potent in decreasing HUVEC proliferation, migration, and tubular network formation than bevacizumab or TRC105 treatment alone (manuscript in preparation). Furthermore, TRC105 induced apoptosis in HUVEC, while promoting SMAD2/3 phosphorylation and inhibiting SMAD1/5/8 signaling, confirming its anti-angiogenic properties. Finally, antibody to mouse CD105 potentiates the activity of multitargeted kinase inhibition that targets the VEGFR-2, in mouse bearing cancer grafts (manuscript in preparation). For these reasons, CD105 blockade using TRC105 in combination with VEGF inhibition by axitinib may provide greater clinical benefit than would be seen with either drug alone.

2.3. TRC105 Background

TRC105 is a genetically engineered human/murine chimeric monoclonal antibody directed against human CD105 [64], a growth proliferation receptor found on the surface of normal and proliferating endothelial cells [27, 33, 40].

The antibody is an IgG1 kappa immunoglobulin containing murine variable region sequences and human constant region sequences [64]. TRC105 has an approximate molecular weight of 148 kDa. TRC105 has a binding avidity for human CD105 of approximately 5 pM. TRC105 is formulated as a phosphate-buffered saline (PBS) solution at a concentration of 5 mg/mL or 7 mg/mL.

SN6j, the murine parent antibody of TRC105, binds to human umbilical vein endothelial cells (HUVECs) with nearly identical avidity as TRC105. SN6j has been shown to bind the tumor vasculature of malignant tissues including breast, colon, rectum, kidney and lung cancers and to inhibit the growth of tumor xenografts [34]. Reactivity with tumor tissues is restricted to the tumor endothelium, as CD105 is not generally expressed on epithelial tumor cells [33]. TRC105 induces ADCC on proliferating HUVECs at low concentrations and induces apoptosis and growth inhibition at higher concentrations.

2.3.1. Phase 1 TRC105 Monotherapy Study Design for Solid Cancers

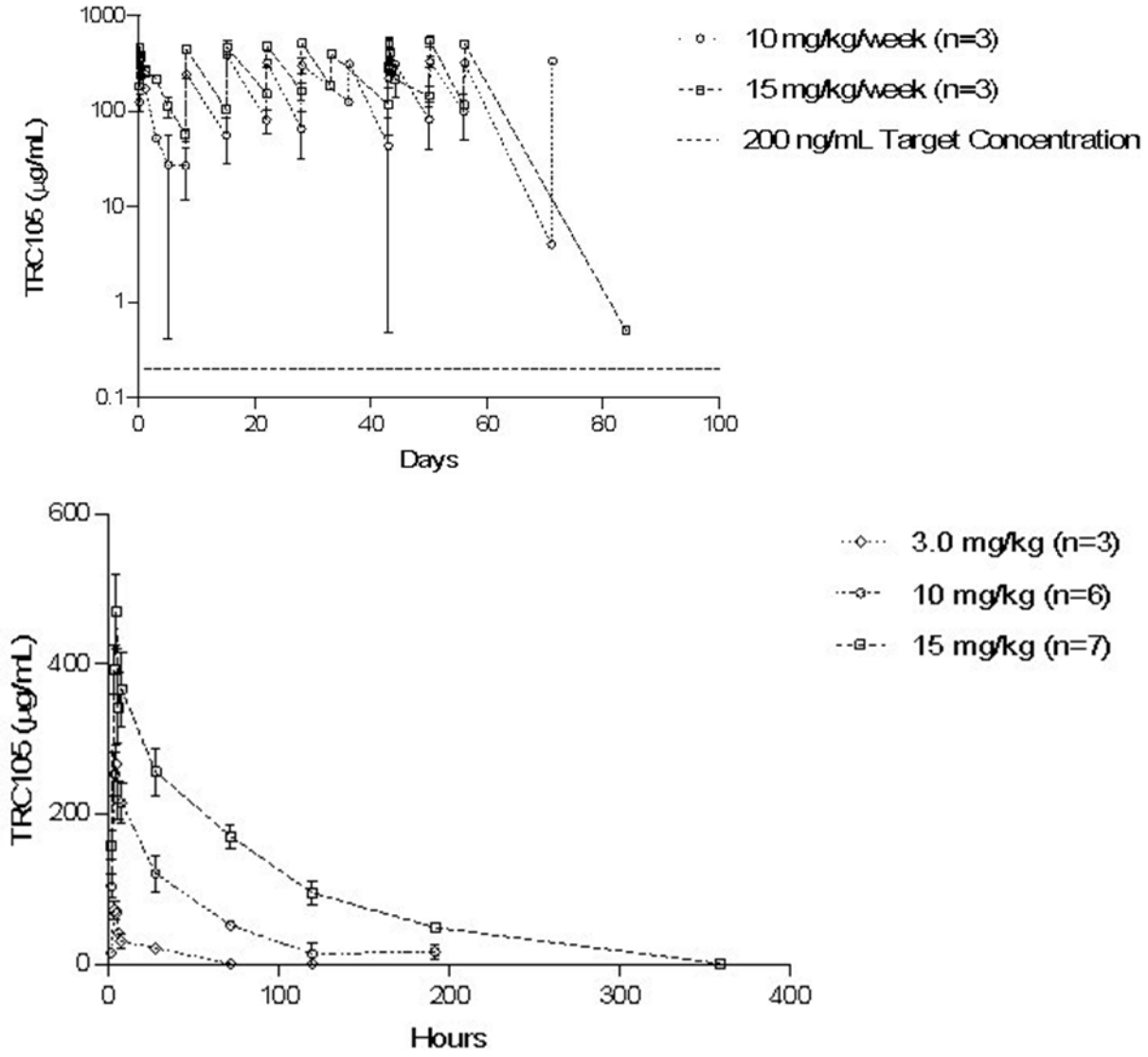
Several studies with TRC105 are underway or have completed. An open-label, phase 1, multicenter study of TRC105 (Study 105ST101) is complete. Fifty patients were treated until disease progression with TRC105 at 0.01-15 mg/kg/q2wk or 10-15 mg/kg/wk.

2.3.1.1. Phase 1 TRC105 Monotherapy Pharmacokinetics

In Study 105ST101, TRC105 pharmacokinetics were assessed on patients enrolled at doses up to 15 mg/kg weekly. Circulating TRC105 was not measurable above the lower limit of quantitation

of the assay (78 ng/mL) in patients receiving doses below 0.3 mg/kg. TRC105 was measurable above the target concentration based on preclinical data (200 ng/mL) for 4 hours at 0.3 mg/kg, 1 day at 1 mg/kg, 5 days at 3 mg/kg, 7 days at 10 mg/kg TRC105 dosed every two weeks. Serum concentrations expected to saturate CD105 binding sites (≥ 200 ng/mL) were achieved continuously at 15 mg/kg q2wk and 10 mg/kg weekly, and TRC105 accumulated at 15 mg/kg weekly (Figure 1).

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



2.3.1.2. Phase 1 TRC105 Monotherapy Immunogenicity

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

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

2.3.1.3. Phase 1 TRC105 Monotherapy Safety

A total of 50 patients were treated on Study 105ST101 with escalating doses of TRC105 at 0.01, 0.03, 0.1, 0.3, 1, 3, 10 and 15 mg/kg every two weeks and then 10 and 15 mg/kg weekly. Dose escalation proceeded stepwise until the top dose was reached. The maximum tolerated dose was exceeded at 15 mg/kg weekly and the recommended phase 2 dose of TRC105 was therefore determined to be 10 mg/kg weekly or 15 mg/kg every two weeks. Three of 4 patients at 15 mg/kg weekly developed grade 3 hypoproliferative anemia (without leucopenia or thrombocytopenia) in cycle 2, and one of the three progressed to grade 4 in cycle 3. Anemia was associated with accumulation of TRC105 and characterized by a low reticulocyte production index. Additional laboratory and clinical evaluations excluded common causes of anemia including blood loss, hemolysis, plasma volume expansion, inadequate erythropoietin, iron deficiency, and vitamin B-12 or folate deficiency. The anemia is believed to result from TRC105-mediated suppression of proerythroblasts, the only cells in the bone marrow known to express substantial levels of CD105 [45]. Anemia was reversible and manageable with dose reduction and standard supportive measures including erythropoietin and blood transfusion.

Treatment related adverse events occurring in more than one patient and all grade 3 and higher adverse events are listed by dose level in Table 4. Infusion reactions, anemia, fatigue, epistaxis and headache were the most frequently observed adverse events considered related to TRC105. The majority of treatment-related adverse events were grade 1 or 2.

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

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

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

Grade 1 or 2 headaches were observed, mainly in patients treated at doses of TRC105 above 3 mg/kg (Table 4). Headaches began the day following infusion and were generally manageable with acetaminophen. However, grade 2 headache in one patient at 15 mg/kg weekly prompted discontinuation prior to completion of the dose-limiting toxicity evaluation period. Fatigue was one of the more common adverse events attributable to TRC105 and was more prevalent at doses above 3 mg/kg (Table 4).

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

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

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

TRC105 Dose	Preferred Term	Gr 1	Gr 2	Gr 3	Gr 4	Gr 5
0.01 mg/kg q2 weeks (NS0, n=3)	Vaginal hemorrhage	1				
0.03 mg/kg q2 weeks (NS0, n=3)	Fatigue		2			
	Dysgeusia	1				
0.1 mg/kg q2 weeks (NS0, n=6)	GI hemorrhage				1	
	Anemia		1			
	Proteinuria		1			
	Diarrhea	1				
	Flushing	1				
0.3 mg/kg q2 weeks (NS0, n=3)	Diarrhea	1				
	Arthralgia	1				
1 mg/kg q2 weeks (NS0, n=6)	Infusion related reaction		1	1		
	Fatigue		1			
	Hyperuricemia	1				

TRC105 Dose	Preferred Term	Gr 1	Gr 2	Gr 3	Gr 4	Gr 5
	Nausea	1				
	Vomiting	1				
0.3 mg/kg q2 weeks (CHO, n=6)	Infusion related reaction		2	1		
	Headache	1				
1 mg/kg q2 weeks (CHO, n=6)	Infusion related reaction			1		
	Blood bilirubin increased		1			
	Constipation	1				
	Flushing	1				
	Micturition urgency	1				
3 mg/kg q2 weeks (CHO, n=3)	None					
10 mg/kg q2 weeks (CHO, n=3)	Infusion related reaction		2			
	Cough		1			
	Tinnitus		1			
	Chills	1				
	Epistaxis	1				
	Fatigue	1				
	Vision blurred	1				
15 mg/kg q2 weeks (CHO, n=4)	Anemia			1		
	Malaise		1			
	Fatigue	1				
	Pain	1				
10 mg/kg q1 week (CHO, n=3)	Fatigue	1	1			
	Anemia		1			
	Dyspnea		1			
	Gingival bleeding		1			
	Headache	3				
	Pyrexia	2				
	Bone pain	1				
	Dysesthesia	1				
	Epistaxis	1				
	Gingival pain	1				
	Hot flash	1				
	Night sweats	1				
	Musculoskeletal pain	1				
	Pruritis	1				
	Telangiectasia	1				
15 mg/kg q1 week (CHO, n=4)	Anemia			2	1	
	Adrenal insufficiency		1			

TRC105 Dose	Preferred Term	Gr 1	Gr 2	Gr 3	Gr 4	Gr 5
	Infusion related reaction		1			
	Constipation		1			
	Dehydration		1			
	Fatigue		1			
	Gastritis		1			
	Headache		1			
	Hypertension		1			
	Dry mouth	1				
	Epistaxis	1				
	Gingival bleeding	1				
	Mucosal inflammation	1				
	Muscle spasms	1				
	Hemoccult positive	1				
	Telangiectasia	2				

2.3.1.4. Phase 1 TRC105 Monotherapy Efficacy

In study 105ST101 stable disease ≥ 2 months was observed in 21 of 45 patients (47%) and stable disease ≥ 4 months in 6 of 44 patients (14%). Decreases in CEA, PSA, or CA-125 were noted in 7 of 21 patients (33%) and a global decrease in key angiogenic biomarkers was observed with treatment. One patient with castrate-refractory prostate cancer remains on TRC105 treatment after 6 years at a TRC105 dose of 0.01 mg/kg every 2 weeks. He has an ongoing complete PSA response, with resolution of bone pain and bone scan normalization. One uterine cancer patient remained on TRC105 treatment for 20 months with a minor radiographic response. TRC105 treatment duration of the patient with carcinosarcoma of the uterus exceeded prior treatment duration with all prior therapies including a carboplatin/paclitaxel, anastrozole and ifosfamide.

2.3.2. Study with Bevacizumab

2.3.2.1. Summary of Safety

Administration of TRC105 at a dose of 3 mg/kg weekly in combination with bevacizumab was well tolerated by three patients without the development of dose limiting toxicity (DLT) and dose escalation occurred per the protocol to cohort 2 (6 mg/kg TR105 weekly) [65]. However, the concurrent administration of 6 mg/kg TRC105 and bevacizumab on day 1 resulted in the development of moderate or severe headaches (including two grade 3 headaches) in four of five treated patients. The 6 mg/kg dose of TRC105 was tolerated when the initial TRC105 dose was delayed one week following bevacizumab dosing at 10 mg/kg every two weeks. Tolerability was further improved when the initial dose of TRC105 was given over two days during the first week of TRC105 dosing, and dose escalation proceeded to the recommended phase 2 dose of 10 mg/kg TRC105 weekly. At the recommended phase 2 dose of both drugs (10 mg/kg), TRC105 serum concentration were present above target concentration continuously and immunogenicity was rarely observed.

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

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

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

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

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

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

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

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

2.3.2.2. Summary of Efficacy

The combination of TRC105 and bevacizumab was active in patients with advanced refractory cancer who had progressed on prior bevacizumab or other VEGF inhibitor treatment. Thirty-three patients had measurable disease (31 patients) or evaluable disease (2 patients) at baseline and received at least one follow up scan and were evaluable for the primary efficacy outcome of ORR by RECIST 1.1. Eighteen patients with measureable disease (58%) had a best response of stable disease or partial response. Two patients (6%), both of whom had been treated with bevacizumab and chemotherapy prior to study entry and were then treated at the top dose level of TRC105 and bevacizumab, had RECIST 1.1- defined partial responses, including one patient with colorectal cancer who continues on treatment for more than 24 months. A total of 14 patients (45%) had decreases in overall tumor burden, of whom 10 received prior VEGF inhibitor treatment (usually bevacizumab with chemotherapy). Notably, the duration of treatment with TRC105 and bevacizumab of six patients (19% of those with measureable disease) exceeded the duration of treatment of the most recent treatment regimen containing a VEGF inhibitor (i.e., VEGFR TKI or bevacizumab), received prior to study entry. These six patients had decreases in tumor burden and several were responders by Choi criteria or RECIST. Time to progression ranged from 0 to 437+ days. Reductions in tumor markers ranging from 5% to 85% were observed in 15 of 28 (54%) patients with relevant tumor markers. Three patients demonstrated clinical benefit throughout the study (patient 10038102 at cycle 12 day 22, patient 10018106 at cycle 7 day 22 and patient 10028101 at cycle 17 day 1), two of them continue to receive treatment under a continuation protocol (105CON101).

2.3.3. Study Rationale

Given the novel mechanism of action and safety profile in early phase clinical studies, TRC105 is a logical therapy for use with axitinib. Axitinib inhibits angiogenesis through the inhibition of VEGFR tyrosine kinases. TRC105 is an antibody to CD105, an important angiogenic target on proliferating endothelial cells that is distinct from VEGFR. TRC105 inhibits angiogenesis,

tumor growth and metastases in preclinical models and complements the activity of bevacizumab and multi-kinase inhibitors that target VEGFR. In a phase 1 study of advanced solid tumors, TRC105 therapy caused a global reduction in angiogenic biomarkers and reduced tumor burden at doses that were well-tolerated. In a phase 1b study, the combination of TRC105 and bevacizumab produced radiographic reductions in tumor burden in bevacizumab refractory patients. Together, the use of TRC105 with axitinib may result in more effective angiogenesis inhibition and improved clinical efficacy over that seen with axitinib alone in advanced patients with RCC who have progressed following treatment with a VEGF TKI.

Advanced RCC represents a well aligned setting to test novel anti-angiogenic combination regimens. Angiogenesis inhibition has been shown to be useful with multiple agents across multiple lines of therapy in the treatment of RCC. The large number of patients with RCC and unfortunate short time to progression for most patients treated in the 2nd line setting mean that study conduct will be efficient. These features also allow for efficient biomarker evaluations. In addition, it is anticipated that axitinib will have a unique indication and broad clinical adoption, making it a popular regulatory standard upon which to build.

This is a phase 2, randomized, open label study of axitinib alone versus TRC105 plus axitinib including a lead-in phase 1b dose escalation study of axitinib in combination with TRC105. The phase 1b portion is a standard "3+3" dose- escalation design of patients with advanced RCC followed by an expanded cohort to further assess the safety and tolerability of the recommended phase 2 dose (RPTD) of TRC105. The purpose of the dose escalation portion is to determine the maximum tolerated dose (MTD) of TRC105 with axitinib and determine the dose limiting toxicities. Patients included in the phase 1b portion of the study will have RCC that has progressed following VEGFR TKI treatment. Secondary endpoints will be progression free survival (PFS) and response rate (RR), safety, and correlative studies of plasma angiogenic biomarkers. The maximum tolerated dose from the phase 1b portion will be studied in the phase 2 portion. The phase 2 portion is a multicenter, randomized, phase 2 study of TRC105 in combination with standard dose axitinib versus axitinib alone in patients with advanced or metastatic renal cell carcinoma. Patients will be stratified by performance status (PS = 0 vs. PS = 1) and centrally randomized in a 1:1 ratio to one of the following treatment arms: TRC105 in combination with standard dose axitinib vs. standard dose axitinib, following documented progression on one prior VEGFR TKI. The primary endpoint is PFS and secondary endpoints will evaluate safety, immunogenicity and correlative studies of plasma angiogenic biomarkers.

2.3.4. Phase 1b 105RC101 Study Results

All eighteen planned patients have been treated in the phase 1 portion of this study as of the time of this protocol amendment (3 at 8 mg/kg and 15 at 10 mg/kg).

2.3.4.1. Phase 1b 105RC101 Safety

Patients experienced expected TRC105 related adverse events of grade 2 infusion reaction and grade 1 epistaxis, gingival bleeding, headache, rash, and fatigue; and expected axitinib adverse events of grade 1-3 hypertension, grade 1 hand-foot syndrome and grade 1 proteinuria. Two patients dosed with TRC105 at 8 mg/kg with axitinib developed grade 2 creatinine elevations that reversed with hydration. Adverse events characteristic of each drug were not increased in

frequency or severity when both drugs were administered concurrently. Patients in the Phase 1b portion of the trial initially received axitinib at 5 mg p.o. BID and intrapatient dose escalation of axitinib was performed to 7 mg p.o. BID and 10 mg p.o. BID, without the development of dose limiting toxicity. Ongoing patients have received TRC105 and axitinib for up to 12 months of treatment.

2.3.4.2. Phase 1b 105RC101 Efficacy

Eleven of 17 evaluable VEGFR TKI refractory patients demonstrated decreases in tumor burden ranging from 1.2% to 50% (including five partial responses per RECIST 1.1, four of which were in the fourth line setting).

2.3.5. Population to be Studied

Patients with histologically confirmed advanced clear cell RCC will be enrolled in the phase 2 portion of this trial. All histologies are eligible for participation in the Phase 1b portion.

2.3.6. Potential Risks and Benefits to Human Patients

2.3.6.1. Potential Risks

TRC105

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

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

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

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

grade 1 and 2 severity. Potential infusion reactions seen with other therapeutic antibodies include angioedema, asthenia, throat irritation, rhinitis, vomiting, joint pain, fatigue and neurologic disorders including inflammation of the spine and/or brain.

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

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

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

Adult respiratory distress syndrome that required temporary intubation occurred in one patient who received TRC150 with pazopanib, from which the patient recovered. Of note, interstitial lung disease has been added as an adverse drug reaction and warning/precaution to the core safety information for pazopanib. Pneumothorax (collapsed lung) has been observed in trials of TRC105 administered with a VEGFR TKI in patients with lung metastases.

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

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

infection and ulceration has also been observed. Overall, infections have been observed in fewer than 5% of patients and have largely been considered unrelated to treatment with TRC105.

Reversible grade 3 colitis was reported in a patient treated with TRC105 and pazopanib

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

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

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

Axitinib

The most common (≥20%) adverse reactions associated with axitinib use are diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome, weight decreased, vomiting, asthenia, and constipation. Other rare but significant adverse events include hypertension and hypertensive crisis, hemorrhage, arterial and venous thromboembolism, reversible posterior leukoencephalopathy syndrome (RPLS), thyroid dysfunction, liver function abnormalities, proteinuria and gastrointestinal perforation or fistula. Further details are available in the package insert (Section 20.3).

Computed Tomography (CT) Scans

Patients will be exposed to a small amount of radiation as a result of the CT scans required in this study. This degree of exposure has not been associated with harmful health effects. In addition, the frequency of CT scans performed in this study is similar to the standard of care frequency. Patients with a medical contraindication to CT scans or known Iodinated contrast allergies may undergo MRI. There is minimal risk of MRI imaging in patients able to undergo this type of exam including very rare reports of gadolinium-induce nephrogenic systemic fibrosis in patients with poor renal function.

Magnetic Resonance Imaging (MRI):

MRI is a noninvasive imaging test used to diagnose and evaluate medical conditions. MRI does not use radiation and there are no known harmful side-effects. However, MRI may cause anxiety for people due to the loud banging made by the machine and the confined space of the testing

area. People with pacemakers, aneurysm clips, artificial heart valves, ear implants, or metal implants or foreign objects in their body are not permitted to have an MRI.

Bone Scans:

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

Venipuncture

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

Other Risks

This study treatment may involve risks to unborn children therefore patients should not become pregnant or father a baby while participating in this study. Patients should not nurse while on this study. Women of childbearing potential must have a negative pregnancy test before taking part in this study. Woman 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 axitinib. 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 axitinib. The long term risk of infertility is unknown. Ovarian failure has been observed with other antiangiogenic agents.

Acceptable birth control methods considered highly effective:

- bilateral tubal ligation
- intrauterine device (IUD)
- vasectomy that has received medical assessment of surgical success
- Sexual abstinence*

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

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

- male or female condom with spermicide*
- cap, diaphragm or sponge with spermicide

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

2.3.6.2. Potential Benefits

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

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

The dose and schedule of TRC105 (8 mg/kg weekly up to 10 mg/kg weekly, 15 mg/kg every 2 weeks, and 20 mg/kg every 2 weeks) were selected based on safety, pharmacokinetics and early evidence of activity in the phase 1 study of TRC105 for patients with solid tumors (Study 105ST101) and in the Phase 1b study of TRC105 with bevacizumab. In phase 1, a weekly dose of 10 mg/kg and a dose of 15 mg/kg every two weeks were well tolerated and associated with clinical activity. Dose reduction was possible for treatment of anemia. In total, 15 patients have been treated at 15 mg/kg administered every two weeks and 4 patients have been treated at 20 mg/kg administered every two weeks; both doses were well tolerated. Doses of 8 and 10 mg/kg TRC105 weekly were tolerated in combination with bevacizumab, pazopanib and axitinib (in cohorts 1 and 2 of this study) and doses of TRC105 of 15 mg/kg every 2 weeks were tolerated in combination with sorafenib. Notably, while the initial schedule of TRC105 was adjusted to decrease the frequency of headaches, there was no potentiation of life threatening toxicities associated with bevacizumab, nor potentiation of common VEGF inhibitor toxicities (e.g., hypertension and proteinuria).

Given the limited experience dosing TRC105 with VEGF inhibitors, it is possible that TRC105 toxicities will potentiate axitinib toxicities, and vice versa. Therefore a TRC105 starting dose of 8 mg/kg weekly, which is 20% lower than the single-agent TRC105 MTD identified in the phase 1 single agent study and phase 1b study with bevacizumab, was selected. In addition a 6 mg/kg (-1) dose level has also been included and will be enrolled should 8 mg/kg of TRC105 in combination with axitinib exceed the MTD. As an added precaution, the first dose of TRC105 will be split and administered over 2 days (cycle 1 day 1 and cycle 1 day 4).

2.3.8. Conduct

The 105RC101 clinical trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirements.

3. TRIAL OBJECTIVES AND PURPOSE

3.1. Purpose

The purpose of this study is to evaluate the safety and effectiveness of TRC105 in combination with axitinib.

3.1.1. Phase 1b Trial Objectives

3.1.1.1. Primary objectives

- To evaluate safety and tolerability and determine a recommended phase 2 dose for TRC105 when added to standard dose axitinib in patients with advanced renal cell carcinoma

3.1.1.2. Secondary objectives

- To look for preliminary evidence of improved antitumor activity when TRC105 is added to axitinib, by assessing overall response rate and progression-free survival
- To characterize the pharmacokinetic profile of TRC105 when given with axitinib
- To evaluate TRC105 immunogenicity by measuring Anti-Product Antibody (APA) formation
- To explore the pharmacodynamic changes in circulating angiogenic biomarkers involved in angiogenesis associated following treatment with TRC105 and axitinib

3.1.2. Phase 2 Trial Objectives

3.1.2.1. Primary Objective:

- To estimate the PFS of patients with advanced or metastatic RCC by RECIST 1.1 criteria in patients treated with axitinib and TRC105 compared to those treated with axitinib alone, following failure of one prior VEGF inhibitor.

3.1.2.2. Secondary Objectives:

- To estimate overall response rate by RECIST 1.1 and Choi criteria, including duration of response by RECIST 1.1
- To estimate the disease control rate (CR + PR + SD) at 16 weeks by RECIST 1.1 and Choi criteria
- To determine the frequency and severity of adverse events as assessed by NCI CTCAE (Version 4.0)
- To evaluate TRC105 immunogenicity as measured by Anti-Product Antibody (APA) concentrations
- To explore the effects of TRC105 on circulating angiogenic protein biomarkers

- To characterize the pharmacokinetic profile of TRC105 and axitinib

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

4.1.1. Overview

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

4.1.1.1. Phase 1b Overview

This is a multicenter, open-label, nonrandomized, phase 1b, dose-finding study of TRC105 in combination with standard dose axitinib in patients with advanced RCC. Escalating doses of i.v. TRC105 will be administered weekly beginning with Dose Level 1 in combination with oral axitinib given as 5 mg p.o. BID daily. Intermediate dose TRC105 (below the MTD established during the trial) may be explored based upon clinical, PK, and/or biomarker data.

Weekly Dosing:

Dosing will begin at 8 mg/kg (cohort 1) however a -1 cohort has also been included (6 mg/kg) and will be enrolled if 8 mg/kg TRC105 plus axitinib exceeds the MTD. The first weekly TRC105 dose will be 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 (6, 8 or 10 mg/kg) is then given on cycle 1 day 8 and weekly thereafter in combination with oral axitinib given as 5 mg p.o. BID. Those who tolerate TRC105 without any infusion reactions may be eligible for reduced infusion durations and decreased premedication (see Section 6.1.6).

Every Two Week Dosing:

In cohort 3 (10 mg/kg weekly during cycle 1; 15 mg/kg every two weeks beginning with cycle 2 day 1) and cohort 4 (10 mg/kg weekly during cycle 1; 20 mg/kg every two weeks beginning with cycle 2 day 1) the first weekly TRC105 dose will also be 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. Starting on cycle 2 day 1 and beyond, TRC105 will be administered every two weeks on days 1 and 15.

After 2 cycles of treatment, patients who demonstrate a response of complete response (CR), partial response (PR) or stable disease (SD) will be eligible for additional treatment until progression.

Patients who exit the study for reasons other than drug-related dose-limiting toxicity prior to completion of the first 28-day cycle will be replaced. Intrapatient dose escalation of TRC105 is not allowed.

Table 5: Dose Levels

Cohort	Number of Evaluable Subjects	Axitinib mg p.o., BID days 1-28	TRC105 mg/kg IV
-1	3-6	5	6[a]

Cohort	Number of Evaluable Subjects	Axitinib mg p.o., BID days 1-28	TRC105 mg/kg IV
1 (Starting Dose)	3-6	5	8[a]
2	3-6	5	10[a]
Expanded Cohort 1	9-12 (up to 15 total at the MTD)	5	10[a]
3	3-6	5	• 10 mg/kg weekly during cycle 1[b] • 15 mg/kg every two weeks beginning with cycle 2 day 1[b]
4	3-6	5	• 10 mg/kg weekly during cycle 1[b] • 20 mg/kg every two weeks beginning with cycle 2 day 1[b]
Expanded Cohort 2	At least 6 patients will be treated at the MTD (either cohort 3 or cohort 4 dose level)	5	• 10 mg/kg weekly during cycle 1[b] • Either 15 or 20 mg/kg every two weeks beginning cycle 2 day 1[b]

[a] In cohort -1, 1, 2 and Expanded Cohort 1 TRC105 will be given weekly.

[b]In cohorts 3 and 4 and Expanded Cohort 2, axitinib dosing will begin on cycle 1 day 1 and twice daily thereafter, and TRC105 will be administered weekly during cycle 1. The first weekly TRC105 dose will be 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. Starting on cycle 2 day 1 and beyond, TRC105 will be administered every two weeks on days 1 and 15.

For cohorts 1 and 2, the DLT evaluation period, for purposes of dose expansion, will be the first 28 days of dosing axitinib and TRC105 together (e.g., from cycle 1 day 1 through cycle 1 day 28) . Cycles are 28 days in duration.

For cohorts 3 and 4, the DLT evaluation will be the first 28 days of dosing axitinib with TRC105 every 2 weeks (e.g., from cycle 2 day 1 through cycle 2 day 28). Cycles are 28 days in duration.

Three patients will be initially enrolled and treated at each dose level. If none of these 3 patients experiences a dose-limiting toxicity (DLT) during the 28-day evaluation period, dose escalation will proceed following review of safety data with appropriate site staff including the principal investigators at all sites.

If 1 of 3 patients experiences DLT, the dose level will be expanded to 6 patients. The maximum tolerated dose (MTD) will have been exceeded if ≥ 33% of patients experience DLT at a given dose level. DLT will have occurred when a patient has 1 or more toxicity listed in the table below that is at least possibly related to the combination of axitinib and TRC105 during the 28 day DLT evaluation period. Patients who exit the study for reasons other than DLT or any TRC105 dose delay > 2 days in cycle 2 (phase 1b cohort 3 and 4 only) prior to completion of the 28-day DLT evaluation period will be replaced to ensure an adequate safety assessment in each cohort. Patients who experience DLT and those without DLT who receive less than the prescribed dose of TRC105 or axitinib due to documented toxicity in Cycle 1 (for cohorts -1, 1, and 2) and in Cycle 2 (for cohorts 3 and 4) will be considered evaluable for dose escalation purposes. Upon agreement of the study investigators, a given TRC105 dose level may be reenrolled at ≥ 60% of the axitinib dose intensity and/or the first dose of TRC105 may be delayed by one week (i.e., delayed to cycle 1 day 8).

Table 6: Dose Limiting Toxicity Definition and Criteria

Toxicity Category	**Drug-Related Toxicity/Grade**
Hematologic	Grade 4 neutropenia for ≥ 5 days
	Febrile neutropenia: grade 4 neutropenia with fever > 38.5 ºC both sustained over a 24 hour period.
	Neutropenic infection: grade ≥ 3 neutropenia with grade ≥ 3 infection
	Anemia ≥ grade 3
	Grade > 4 thrombocytopenia or grade ≥ 3 thrombocytopenia and grade ≥ 3 hemorrhage
Nonhematologic	Grade 3 or 4 nonhematologic toxicity with the following exceptions: • Nausea, vomiting or diarrhea for < 48 hours[a] • Asymptomatic electrolyte abnormalities that are corrected to grade 1 or better in < 48 hours[b]

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

Up to 15 patients with advanced renal cell carcinoma will be treated at the weekly dosing MTD (or top cohort if a MTD is not determined) to further characterize safety and tolerability. At least 6 patients with advanced renal cell carcinoma will be treated at the every two week dosing MTD (or top cohort if a MTD is not determined).

The recommended phase 2 dose for the combination will be determined by the study investigators, medical monitor, and TRACON after reviewing the toxicity and pharmacokinetic profile of the study combination.

4.1.1.2. Phase 2 Overview

This is a multicenter, randomized, phase 2 study of TRC105 in combination with standard dose axitinib in patients with advanced or metastatic renal cell carcinoma. Patients will be stratified by performance status (PS = 0 vs. PS = 1) and centrally randomized to one of the following treatment arms: TRC105 in combination with standard dose axitinib vs. standard dose axitinib, following documented progression on one prior VEGF inhibitor. All patients will initially receive axitinib 5 mg twice daily; patients randomized to receive TRC105 will receive TRC105 at 3 mg/kg on day 1, 7 mg/kg on day 4, and 10 mg/kg on day 8 and weekly thereafter.

TRC105 may be administered every two weeks starting with cycle 2 day 1 but **ONLY AFTER COHORT 3 AND& 4 IN THE PHASE 1B ARE COMPLETE AND THE & SPONSOR SENDS NOTIFICATION TO PROCEED WITH EVERY TWO WEEK DOSING**.

- Axitinib dosing will begin on cycle 1 day 1 and twice daily thereafter
- TRC105 at 10 mg/kg will be administered weekly during cycle 1.
    - The first weekly TRC105 dose will be 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.
- Starting on cycle 2 day 1 and beyond, TRC105 may be administered every two weeks on days 1 and 15 at either 15 mg/kg or 20 mg/kg

Patients **in both arms** who tolerate axitinib for at least two consecutive weeks with no adverse reactions > Grade 1 considered clinically significant (according to the Common Toxicity Criteria for Adverse Events [CTCAE]), will, at the discretion of their treating physician, have the axitinib dose increased to 7 mg twice daily beginning on cycle 2 day 1, unless the patient's blood pressure is > 150/90 or the patient is receiving more than one antihypertensive medication. Subsequently, with the same criteria, patients who tolerate the axitinib dose of 7 mg twice daily for at least two consecutive weeks may have the axitinib dose increased to a maximum of 10 mg twice daily beginning with cycle 3 day 1. Dose reductions of axitinib and TRC105 are allowed per patient tolerance.

4.1.2. Trial Procedures

All on-study procedures are permitted within the time window indicated in the Schedule of Assessments (see Table 7, Table 8, Table 9, Table 10 , and Table 11).

4.1.2.1. Screening

The following screening procedures must be performed within 28 days prior to the first day of study therapy. Qualifying hematology (including Fe studies), serum chemistry (including TSH testing), coagulation, physical examination, ECG, pregnancy and urinalysis collected within 7 days of cycle 1 day 1 do not need to be repeated. The following will be performed according to the Schedule of Assessments (see Table 7, Table 8, Table 9, Table 10 , and Table 11).

- Patient signature on current approved informed consent form. Prior to undergoing any study-specific procedure, patients must read and sign the current approved informed consent form. Patients may sign consent prior to the 28 day screening period.
- Medical history, prior cancer therapy, prior cancer surgery, prior radiation therapy, drug allergies, primary diagnosis and demographics.
- Physical examination including examination of all major body systems, ECOG performance status, and vital signs.
- Hematology (including serum iron, ferritin and total iron binding capacity), coagulation (INR) and serum chemistry (including thyroid stimulating hormone (TSH)) to be performed locally.
- Serum or urine pregnancy test for all females of childbearing potential to be performed locally.
- Urinalysis to be performed locally. Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated.
    - Imaging: CT or MRI scans of chest, abdomen and pelvis in addition to any other applicable sites of disease. Brain MRI or CT with contrast to be performed at screening to assure absence of CNS metastases and confirm eligibility. Bone scans to be performed at screening to determine presence of bone metastases.
- Single tracing 12-Lead ECG (QT, PR and QRS intervals and heart rate will be captured).
- Assessment of baseline emergent Adverse Events (serious and nonserious) from the date of informed consent.
- Assessment of concomitant medications and treatments from 28 days prior to the start of study treatment.
- Archival Tumor Tissue Specimens: Archival specimens (formalin-fixed, paraffin-embedded) of the primary cancer specimen and/or metastatic cancer specimen for each study participant, if they are available. It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 20 unstained slides are requested for immunohistochemical analysis (sections of ~ 5 microns are preferred). Patients without available archival tumor tissue specimens are still eligible to participate in the study. See separate laboratory guide for further collection and shipment information

4.1.2.2. Trial Period

Qualifying hematology (including Fe studies), blood chemistry (including TSH testing), coagulation, urinalysis, physical examination, ECG, and pregnancy test do not need to be repeated on cycle 1 day 1 if acceptable screening assessments are performed within 7 days prior to the start of study therapy. On days of dosing, all assessments should be performed prior to dosing with TRC105 unless otherwise indicated in the Schedule of Assessments. Patients will receive 2 cycles (approximately 8 weeks) of treatment. Patients who demonstrate a response of CR, PR or SD, will be eligible for additional treatment until progression. Each cycle is 4 weeks in duration. The following will be performed according to the Schedule of Assessments (see Table 7, Table 8, Table 9, Table 10 , and Table 11).

- Physical examination including examination of all major body systems, ECOG performance status, weight and vital signs (heart rate, temperature, blood pressure, respiratory rate).
  - Assessment of vital signs during TRC105 infusion: Vital signs are to be assessed pre-infusion (i.e., within 30 minutes of starting infusion), every 30 minutes during the infusion (+/- 15 minutes), and at the end of infusion (i.e., within 30 minutes after completing infusion). Vital signs should be monitored more frequently and/or beyond the completion of the infusion if medically indicated (e.g. if the patient experiences an infusion reaction that has not yet resolved).
- Hematology, coagulation (INR) and serum chemistry (including TSH) to be performed locally.
- Serum or urine pregnancy test for all females of childbearing potential to be performed locally.
- Single tracing 12-Lead ECG (QT, PR and QRS intervals and heart rate will be captured).
- Urinalysis to be performed locally. Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated.
- Phase 1b **cohorts -1, 1, 2, and Expanded Cohort 1**: Blood sampling for TRC105 pharmacokinetics will include a pre-infusion trough sample and an end-of-infusion peak sample to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection times, procedures, processing, storage and shipment).
- Phase 1b **cohorts 3, 4 and expanded cohort 2**: Blood sampling for TRC105 and axitinib pharmacokinetics will include a pre-infusion trough sample to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection times, procedures, processing, storage and shipment)
- Phase 2: Blood sampling for TRC105 and axitinib pharmacokinetics will include pre-dose trough samples to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection times, procedures, processing, storage and shipment).

- Phase 1b and Arm B of Phase 2 Only: Blood sampling for immunogenicity (APA concentrations) to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).
- Blood sampling for protein biomarker analysis by a third party laboratory (see laboratory manual for specific instructions regarding collection processing, storage and shipment)
- Imaging: CT or MRI scans of chest, abdomen and pelvis in addition to any other applicable sites of disease. Scan of the chest, abdomen, and pelvis to be performed on-study as outlined in the assessment table. Known areas of disease should be consistently followed throughout the study. Bone scans are to be performed at screening and throughout the study at the time of CT assessments if bone metastases are present and cannot be followed by CT. Brain MRI or CT with contrast to be performed at screening to assure absence of CNS metastases and on study as needed if metastases are suspected.
  - **For phase 1b:** scans will be performed on day 22 of cycle 2, 4, and 6. Beyond cycle 6 scans will be performed every 3 cycles (Day 22 of cycle 9, 12, 15, etc.).
  - **For Phase 1b Cohort 3, 4 and Expanded Cohort 2:** scans will be performed on every 56 days from cycle 1 day 1.
  - **For phase 2:** scans will be performed every 56 days from date of randomization. Assessments should be performed whenever disease progression is suspected. Allowable window for tumor imaging studies is +/- 7 days.
- Administration of TRC105. TRC105 diluted in normal saline will be administered as a 1 to 4 hour infusion (+/- 15 minutes) following premedication (see Section 6.1.6) according to the pertinent schedule of assessment.
  - Phase 1b Cohorts -1, 1, 2 and Expanded Cohort 1: The first TRC105 dose will be 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 (6, 8 or 10 mg/kg) is then given on cycle 1 day 8 and weekly thereafter (e.g., if TRC105 is given at 3 mg/kg on cycle 1 day 1 and at 7 mg/kg on cycle 1 day 4, then 10 mg/kg is given on cycle 1 day 8).
  - Phase 1b Cohorts 3, 4 and Expanded Cohort 2: TRC105 dosing will start on cycle 1 day 1 and the first dose will be 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, cycle 1 day 15 and on cycle 1 day 22. Beginning with cycle 2 day 1, TRC105 will be dosed at 15mg/kg or 20 mg/kg and every two weeks thereafter (days 1 and 15).
  - Phase 2 **WEEKLY DOSING**: The first TRC105 dose will be 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.
  - Phase 2 **EVERY TWO WEEK DOSING (after notification from sponsor):** TRC105 dosing will start on cycle 1 day 1 and the first dose will be 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, cycle 1 day 15 and on cycle 1 day 22. Starting on cycle 2 day 1 and beyond, TRC105 may be administered every two weeks on days 1 and 15 at either 15 mg/kg or 20 mg/kg as determined by cohort 3 and 4 of the phase 1b.

TRC105 will be administered intravenously utilizing an infusion pump. TRC105 has been demonstrated to be compatible with polyethylene lined, non-DEHP infusion sets and polyvinyl chloride, non-DEHP infusion sets. TRC105 is required to be administered with a 0.2 micron downstream filter. Duration of infusion administration may be increased as medically necessary.

- Axitinib dosing. The oral dose of axitinib is 5 mg twice daily. Administer axitinib doses approximately 12 hours apart with or without food. Axitinib should be swallowed whole with a glass of water. If the patient vomits or misses a dose (i.e., more than 6 hours elapses from the time of the usual dose), an additional dose should not be taken. The next prescribed dose should be taken at the usual time.
- Assessment of adverse events.
- Assessment of concomitant medications and concomitant treatments.

4.1.3. End of Study Assessments

Assessments other than TRC105 pharmacokinetics (phase 1b and Arm B of phase 2), immunogenicity, and protein biomarkers only need to be completed if they were not completed during the previous 2 weeks on study (during the last 8 weeks on study for radiologic tumor assessments). The following will be performed according to the Schedule of Assessments (Table 7, Table 8, Table 9, Table 10, and Table 11).

- Physical examination including examination of all major body systems, ECOG performance status, and vital signs.
- Single tracing 12-Lead ECG (QT, PR and QRS intervals and heart rate will be captured).
- Thyroid function tests (i.e., thyroid stimulating hormone)
- Hematology and serum chemistry (including TSH) to be performed locally.
- Urinalysis to be performed locally. Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated.
- Phase 1b **cohorts -1, 1, 2, and Expanded Cohort 1**: Blood sampling for TRC105 pharmacokinetics will include a pre-infusion trough sample and an end-of-infusion peak sample to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection times, procedures, processing, storage and shipment).
- Phase 1b **cohorts 3, 4 and Expanded Cohort 2**: Blood sampling for TRC105 and axitinib pharmacokinetics will include a trough sample to be analyzed by a third party

laboratory (see laboratory manual for specific instructions regarding collection times, procedures, processing, storage and shipment)

- Phase 2: Blood sampling for TRC105 and axitinib pharmacokinetics will include pre-dose trough samples to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection times, procedures, processing, storage and shipment).
- Phase 1b and Arm B of Phase 2: Blood sampling for immunogenicity to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).
- Blood sampling for protein biomarker analysis by a third party laboratory (see laboratory manual for specific instructions regarding collection processing, storage and shipment)
- Imaging: CT or MRI scans of chest, abdomen and pelvis in addition to any other applicable sites of disease. Bone scans to be performed throughout the study at the time of CT assessments if screening scans are positive and/or if bone metastases are identified that cannot be followed by CT. Brain scans to be performed if metastasis is suspected.
- Assessment of adverse events.
- Assessment of concomitant medications and concomitant treatments.

4.1.4. Post Treatment Follow-up

The following will be performed according to the Schedule of Assessments (Table 7, Table 8, Table 9, Table 10, and Table 11). Samples should be collected and assessments performed even if new anti-cancer therapy commences during the follow-up period.

- Assessment of adverse events. The Investigator should continue to report any related or possibly related adverse events that occur beyond the adverse event reporting period.
- Phase 1b **cohorts -1, 1, 2, and Expanded Cohort 1**: Blood sampling for TRC105 pharmacokinetics will include a pre-infusion trough sample and an end-of-infusion peak sample to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection times, procedures, processing, storage and shipment).
- Phase 1b **cohorts 3, 4 and Expanded Cohort 2**: Blood sampling for TRC105 and axitinib pharmacokinetics will include a trough sample to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection times, procedures, processing, storage and shipment).
- Phase 2: Blood sampling for TRC105 and axitinib pharmacokinetics will include pre-dose trough samples to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection times, procedures, processing, storage and shipment).
- Phase 1b and Arm B of Phase 2: Blood sampling for immunogenicity (APA concentrations) to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection, processing, storage and shipment).

- Assessment of concomitant medications and concomitant treatments.
- Serum or urine pregnancy test for all females of childbearing potential to be performed locally.

Table 7: Schedule of Assessments Phase 1b: Cohorts -1, 1, 2, and Expanded Cohort 1

Protocol Activities	Screening	Cycle 1 and 2 [23]					Cycle 3+ [21] [23]				End of Study [3]	28 Day Follow-up [22]
	Day -28	Day 1 [1,2]	Day 4 (Cycle 1) [1]	Day 8 [1]	Day 15 [1]	Day 22 [1]	Day 1 [1]	Day 8 [1]	Day 15 [1]	Day 22 [1]		
Baseline Documentation												
Informed Consent [4]	X											
Medical/Oncology History [5]	X											
Physical Examination [6]	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 + Fe (C1)			X		X		X		X	
Coagulation [8]	X	X										
Blood Chemistry [8]	X + TSH	X + TSH			X		X + TSH				X + TSH	
Pregnancy Test [9]	Day -7											X
Urinalysis [10]	X	X					X				X	
Treatment w/ Study Drug												
TRC105 Dosing [11]		X C1 Split	X C1 Split	X	X	X	X	X	X	X		
Axitinib [12]		Day 1				Day 28	Day 1			Day 28		
Tumor Assessments												
CT or MRI Scans [13]	X Including Brain					Cycle 2				Cycle 4 Cycle 6 Cycle 9, 12, 15 etc.	X	
Bone Scans [13]	X											
Other Clinical Assessments												
12-Lead ECG [14]	X	X					X				X	
Concomitant Medications/Treatments [15]	X	X	X		X		X		X		X	X
Baseline-Emergent Adverse Events [16]	X											
Adverse Events [16]		X	X		X		X		X		X	X
Special Laboratory Assessments												
TRC105 PK Pre-Dose PK [17]		Cycle 2			X				Even Cycles			
TRC105 PK Post-Dose PK [17]		Cycle 2			X				Even Cycles		X	X
Anti-Product Antibody Testing [18]		Cycle 1									X	X
Protein Biomarkers [19]		X							Even Cycles		X	
Archival Tumor Tissue [20]	X											

Schedule of Assessments Footnotes Phase 1b

1. **Days of Treatment with TRC105:** All assessments should be performed prior to the TRC105 infusion unless otherwise indicated. Each cycle is 28 days in duration.
2. **Cycle 1 day 1:** Hematology (including Fe studies), blood chemistry (including TSH testing), coagulation, urinalysis, physical examination, ECG and pregnancy test not required if acceptable screening assessment is performed within 7 days prior to the start of treatment on cycle 1 day 1.
3. **End of Study:** Visit should generally occur within 7 days (+/- 1 day) of the last dose of TRC105. Assessments other than TRC105 pharmacokinetics, immunogenicity and protein biomarkers do not need to be repeated if performed within the previous 2 weeks (previous 8 weeks for radiologic tumor assessments). Follow-up visits should occur 28 days following the last dose of TRC105 study drug as outlined in the Schedule of Assessments.
4. **Informed Consent:** Must be obtained prior to undergoing any study specific procedure and may occur prior to the 28-day screening period.
5. **Medical/Oncologic History and Demographics:** To include information on prior anticancer therapy.
6. **Physical Examination:** Examination of major body systems and ECOG performance status.
7. **Vital Signs:** Heart rate, temperature, blood pressure, respiratory rate, weight. Assessment of vital signs during TRC105 Infusions: Vital signs are to be assessed pre-infusion (i.e., within 30 minutes of starting infusion), every 30 minutes during the infusion (+/- 15 minutes) and at the end of infusion (i.e., within 30 minutes after completing infusion). Vital signs should be monitored more frequently and/or beyond the completion of the infusion if medically indicated (e.g. if the patient experiences an infusion reaction that has not yet resolved).
8. **Hematology, Chemistry and 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. Iron studies to be performed at screening, cycle 1 day 1 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 8.1.1.1 for specific panel collection requirements.
9. **Pregnancy Test:** Testing to be performed locally. All female patients of childbearing potential must have a negative serum or urine pregnancy test within 7 days of cycle 1 day 1 and 28 days following the last dose of TRC105.
10. **Urinalysis:** To be performed locally. 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 (cycle 1 day 1) will 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 (6, 8 or 10 mg/kg) is then given on cycle 1 day 8 and weekly thereafter. See Section 6.1.6 for specific TRC105 administration guidelines.
12. **Axitinib Dosing:** Oral axitinib will be dosed twice daily on days 1-28 of each 28 day cycle according to the axitinib package insert. Patients who tolerate the starting dose with no adverse reactions above grade 2 for four weeks will have the axitinib dose increased. See Section 6.2 for specific dosing guidelines.
13. **Imaging:** CT or MRI Images of the chest, abdomen, and pelvis to be performed at screening, and on-study as outlined in the assessment table. In addition, a brain MRI or CT with contrast to be performed at screening to assure absence of CNS metastases and on study as needed if metastases are suspected. Bone scans are to be performed at screening and throughout the study at the time of CT assessments if bone metastases are present

and cannot be followed by CT. Known areas of disease should be consistently followed throughout the study. Assessments should be performed whenever disease progression is suspected. Allowable window for tumor imaging studies is +/- 7 days. Scans will be performed on day 22 of cycle 2, 4, and 6. Beyond cycle 6 scans will be performed every 3 cycles (Day 22 of cycle 9, 12, 15, etc.).

14. **12-Lead ECG:** Single tracing 12-lead ECG will be performed at screening and at time points indicated in the Schedule of Assessments (pre-dose). For a QTc > 500 ms, a repeat ECG for confirmation and evaluation of the ECG by a cardiologist is recommended. 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 up to 28 days following the last dose of study treatment. Required TRC105 premedications should be recorded on TRC105 premedications CRF.
16. **Baseline Emergent Adverse Events/Adverse Events:** Patients must be followed for safety from the day of informed consent until at least 28 days after the last dose of study treatment, or until all serious or TRC105 related toxicities have resolved or are determined to be “chronic” or “stable”, whichever is later. Adverse events occurring prior to the initiation of the study treatment will be considered "Baseline-Emergent Adverse Events” and will be recorded on corresponding case report forms. Events that occur from the time the patient has taken the first dose of TRC105 study drug through 28 days after the last dose of TRC105 study drug will be recorded on “Adverse Event” CRFs. Any serious AE that is possibly related to TRC105 occurring from the time of first dose or at any point after the reporting period must be promptly reported to TRACON.
17. **TRC105 Pharmacokinetics Trough Concentration:** A 5 mL blood sample to be collected at the time-points indicated in the Schedule of Assessments, prior to starting the TRC105 infusion. Samples will be stored at approximately -70°C. Samples will be batch shipped as indicated in the laboratory manual to a third-party laboratory. See separate laboratory guide for further collection and shipment information. Additional PK samples may also be collected at the time of unexpected clinical events.
    TRC105 Pharmacokinetics Peak Concentrations: A 5 mL blood sample to be collected within 10 minutes of the completion of the TRC105 infusion at the time-points indicated in the Schedule of Assessments. 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.
18. **Anti-Product Antibody Testing:** 5 mL blood sample will be collected to assess APA at the time-points indicated in the schedule of assessments and stored at approximately -70°C to be analysed by a central laboratory. Samples will be batch shipped as indicated in the laboratory manual to a third-party laboratory. See separate laboratory guide for further collection and shipment information. Additional APA samples may also be collected at the time of unexpected clinical events.
19. **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.
20. **Archival Tumor Tissue:** Archival specimens (formalin-fixed, paraffin-embedded) are required of the primary cancer and/or metastatic cancer specimen for each study participant, if they are available. It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 20 unstained slides are requested for immunohistochemical analysis (sections of 5 microns are preferred). Patients without available archival tumor tissue specimens are still eligible. See separate laboratory guide for further collection and shipment information.
21. **Cycle 3+ Treatment:** Patients who demonstrate a response of CR, PR or SD will be eligible for additional treatment until progression.

22. **Follow-up:** The follow-up visit should occur 28 days following the last dose of TRC105. The allowable visit window is +/- 7 days.
23. Allowable window for each visit within the cycle is +/- 2 days unless otherwise stated.

Table 8: Schedule of Assessments Phase 1b: Cohorts 3, 4 and Expanded Cohort 2

Protocol Activities	Screening	Cycle 1[23]					Cycle 2[23]			Cycle 3 and Odd Cycles ONLY[21,23]		Cycle 4 and Even Cycles ONLY[21,23]			End of Study [3]	28 Day Follow-up [22]
	Day - 28	Day 1[1,2]	Day 4[1]	Day 8[1]	Day 15 [1]	Day 22 [1]	Day 1 [1]	Day 15 [1]	Day 22 [1]	Day 1[1]	Day 15[1]	Day 1[1]	Day 15[1]	Day 22[1]		
Baseline Documentation																
Informed Consent[4]	X															
Medical/Oncology History[5]	X															
Physical Examination[6]	X	X					X			X		X			X	
Vital Signs[7]	X	X	X	X	X	X	X	X		X	X	X	X		X	
Laboratory Studies																
Hematology[8]	X + Fe	X			X		X	X		X	X	X	X		X	
Coagulation[8]	X	X					X									
Blood Chemistry[8]	X + TSH	X + TSH			X		X + TSH	X		X + TSH		X + TSH			X + TSH	
Pregnancy Test[9]	Day -7	X					X			X		X				X
Urinalysis[10]	X	X					X			X		X			X	
Treatment w/ Study Drug																
TRC105 Dosing[11]		X C1 Split	X C1 Split	X	X	X	X	X		X	X	X	X			
Axitinib[12]		28 Day Cycle					28 Day Cycle			28 Day Cycle		28 Day Cycle				
Tumor Assessments																
CT or MRI Scans[13]	X Including Brain	EVERY 56 DAYS FROM CYCLE 1 DAY 1													X	
Bone Scans[13]	X															
Other Clinical Assessments																
12-Lead ECG[14]	X	X					X			X		X			X	
Concomitant Medications/Treatments[15]	X	X	X		X		X	X		X	X	X	X		X	
Baseline-Emergent Adverse Events[16]	X															X
Adverse Events[16]		X	X		X		X	X		X	X	X	X		X	
Special Laboratory Assessments																X
TRC105 & Axitinib Pre-Dose PK[17]		X					X	X		X	X	X	X		X	X
Anti-Product Antibody Testing[18]		X					X					X			X	X
Protein Biomarkers[19]		X					X					X			X	
Archival Tumor Tissue[20]	X															

Schedule of Assessments Footnotes Phase 1b COHORTS 3 and 4 ONLY

1. **Days of Treatment with TRC105:** All assessments should be performed prior to the TRC105 infusion unless otherwise indicated. Each cycle is 28 days in duration.
2. **Cycle 1 day 1:** Hematology (including Fe studies), blood chemistry (including TSH testing), coagulation, urinalysis, physical examination, ECG and pregnancy test not required if acceptable screening assessment is performed within 7 days prior to the start of treatment on cycle 1 day 1.
3. **End of Study:** Visit should generally occur within 7 days (+/- 1 day) of the last dose of TRC105. Assessments other than TRC105 pharmacokinetics, immunogenicity and protein biomarkers do not need to be repeated if performed within the previous 2 weeks (previous 8 weeks for radiologic tumor assessments). Follow-up visits should occur 28 days following the last dose of TRC105 study drug as outlined in the Schedule of Assessments.
4. **Informed Consent:** Must be obtained prior to undergoing any study specific procedure and may occur prior to the 28-day screening period.
5. **Medical/Oncologic History and Demographics:** To include information on prior anticancer therapy.
6. **Physical Examination:** Examination of major body systems and ECOG performance status.
7. **Vital Signs:** Heart rate, temperature, blood pressure, respiratory rate, weight. Assessment of vital signs during TRC105 Infusions: Vital signs are to be assessed pre-infusion (i.e., within 30 minutes of starting infusion), every 30 minutes during the infusion (+/- 15 minutes) and at the end of infusion (i.e., within 30 minutes after completing infusion). Vital signs should be monitored more frequently and/or beyond the completion of the infusion if medically indicated (e.g. if the patient experiences an infusion reaction that has not yet resolved).
8. **Hematology, Chemistry and 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. Iron studies to be performed at screening, cycle 1 day 1 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 8.1.1.1 for specific panel collection requirements.
9. **Pregnancy Test:** Testing to be performed locally. All female patients of childbearing potential must have a negative serum or urine pregnancy test within 7 days of cycle 1 day 1, day 1 of every cycle starting with cycle 2, and 28 days following the last dose of TRC105.
10. **Urinalysis:** To be performed locally. 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 is diluted in normal saline. TRC105 will be administered weekly during cycle 1. The first weekly TRC105 dose will be 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. Starting on cycle 2 day 1 and beyond, TRC105 will be administered every two weeks on days 1 and 15. See Section 6.1.6 for specific TRC105 administration guidelines.
12. **Axitinib Dosing:** Oral axitinib will be dosed twice daily on days 1-28 of each 28 day cycle according to the axitinib package insert. Patients who tolerate the starting dose with no adverse reactions above grade 2 for four weeks will have the axitinib dose increased. See Section 6.2 for specific dosing guidelines.
13. **Imaging:** CT or MRI Images of the chest, abdomen, and pelvis to be performed at screening, and on-study as outlined in the assessment table. In addition, a brain MRI or CT with contrast to be performed at screening to assure absence of CNS metastases and on study as needed if metastases are suspected. Bone scans are to be performed at screening and throughout the study at the time of CT assessments if bone metastases are present

and cannot be followed by CT. Known areas of disease should be consistently followed throughout the study. Assessments should be performed whenever disease progression is suspected. Allowable window for tumor imaging studies is +/- 7 days. Scans will be every 56 days from cycle 1 day 1.

14. **12-Lead ECG:** Single tracing 12-lead ECG will be performed at screening and at time points indicated in the Schedule of Assessments (pre-dose). For a QTc > 500 ms, a repeat ECG for confirmation and evaluation of the ECG by a cardiologist is recommended. 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 up to 28 days following the last dose of study treatment. Required TRC105 premedications should be recorded on TRC105 premedications CRF.
16. **Baseline Emergent Adverse Events/Adverse Events:** Patients must be followed for safety from the day of informed consent until at least 28 days after the last dose of study treatment, or until all serious or TRC105 related toxicities have resolved or are determined to be “chronic” or “stable”, whichever is later. Adverse events occurring prior to the initiation of the study treatment will be considered "Baseline-Signs and Symptoms” and will be recorded on “Medical History and Baseline Signs and Symptoms” case report forms. Events that occur from the time the patient has taken the first dose of TRC105 study drug through 28 days after the last dose of TRC105 study drug will be recorded on “Adverse Event” CRFs. Any serious AE that is possibly related to TRC105 occurring from the time of first dose or at any point after the reporting period must be promptly reported to TRACON.
17. **TRC105 and Axitinib Pharmacokinetic Trough Concentration:** Two (i.e., one for TRC105 and one for Axitinib) 5 mL blood samples to be collected at the time-points indicated in the Schedule of Assessments, prior to dosing with axitinib and prior to starting the TRC105 infusion. The morning dose of axitinib should be taken after the PK draw. This dose will still need to be taken 30 minutes before TRC105 dosing. 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.
18. **Anti-Product Antibody Testing:** 5 mL blood sample will be collected to assess APA at the time-points indicated in the schedule of assessments and stored at approximately -70°C to be analysed by a central laboratory. Samples will be batch shipped as indicated in the laboratory manual to a third-party laboratory. See separate laboratory guide for further collection and shipment information. Additional APA samples may also be collected at the time of unexpected clinical events.
19. **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.
20. **Archival Tumor Tissue:** Archival specimens (formalin-fixed, paraffin-embedded) are required of the primary cancer and/or metastatic cancer specimen for each study participant, if they are available. It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 20 unstained slides are requested for immunohistochemical analysis (sections of 5 microns are preferred). Patients without available archival tumor tissue specimens are still eligible. See separate laboratory guide for further collection and shipment information.
21. **Cycle 3+ Treatment:** Patients who demonstrate a response of CR, PR or SD will be eligible for additional treatment until progression.
22. **Follow-up:** The follow-up visit should occur 28 days following the last dose of TRC105. The allowable visit window is +/- 7 days.

23. Allowable window for each visit within the cycle is +/- 2 days unless otherwise stated.

Table 9: Schedule of Assessments Phase 2: Arm A Axitinib Alone

Protocol Activities	Screening	Cycle 1 and 2 [21]			Cycle 3+ [19] [21]		End of Study [3]	28 Day Follow-up [20]
	Day -28	Day 1 [1,2]	Day 15 [1]	Day 22 [1]	Day 1 [1]	Day 22 [1]		
Baseline Documentation								
Informed Consent [4]	X							
Medical/Oncology History [5]	X							
Physical Examination [6]	X	X			X		X	
Vital Signs [7]	X	X	X		X		X	
Laboratory Studies								
Hematology [8]	X + Fe	X + Fe (C1)	X		X		X	
Coagulation [8]	X	X						
Blood Chemistry [8]	X + TSH	X + TSH	X		X + TSH		X + TSH	
Pregnancy Test [9]	Day -7	X			X			X
Urinalysis [10]	X	X			X		X	
Treatment w/ Study Drug								
Axitinib Dosing [11]		Day 1-28	Day 1-28	Day 1-28	Day 1-28	Day 1-28		
Tumor Assessments								
CT or MRI Scans [12]	X Including Brain	EVERY 56 DAYS FROM DATE OF RANDOMIZATION					X	
Bone Scans [12]	X							
Other Clinical Assessments								
12-Lead ECG [13]	X	X			X		X	
Concomitant Medications/Treatments [14]	X	X	X		X		X	X
Baseline-Emergent Adverse Events [15]	X							
Adverse Events [15]		X	X		X		X	X
Special Laboratory Assessments								
Pre-Dose PK [16]		X			Even Cycles		X	X
Protein Biomarkers [17]		X			Even Cycles		X	
Archival Tumor Tissue [18]	X							

Schedule of Assessments Footnotes Arm A (Axitinib Alone):

1. All assessments should be performed prior to axitinib dosing unless otherwise indicated. Each cycle is 28 days in duration.
2. **Cycle 1 day 1:** Hematology (including Fe studies), blood chemistry (including TSH testing), coagulation, urinalysis, physical examination, ECG and pregnancy test not required if acceptable screening assessment is performed within 7 days prior to the start of treatment on cycle 1 day 1.
3. **End of Study:** Visit should generally occur within 7 days (+/- 1 day) of the last dose of axitinib. Assessments other than pharmacokinetics, immunogenicity and protein biomarkers do not need to be repeated if performed within the previous 2 weeks (previous 8 weeks for radiologic tumor assessments). Follow-up visits should occur 28 days following the last dose of axitinib as outlined in the Schedule of Assessments.
4. **Informed Consent:** Must be obtained prior to undergoing any study specific procedure and may occur prior to the 28-day screening period.
5. **Medical/Oncologic History and Demographics:** To include information on prior anticancer therapy.
6. **Physical Examination:** Examination of major body systems and ECOG performance status.
7. **Vital Signs:** Heart rate, temperature, blood pressure, respiratory rate, weight.
8. **Hematology, Chemistry and Coagulation:** Testing to be performed locally (pre-dose). Thyroid stimulating hormone to be tested at screening, day 1 of each cycle and at the end of study visit. Iron studies to be performed at screening, cycle 1 day 1 and as clinically indicated during the study. Lab assessments may be performed within 3 days prior to axitinib dosing. In addition to the assessments scheduled for the clinical trial, patients should undergo assessment as appropriate to ensure safe treatment. See Section 8.1.1.1 for specific panel collection requirements.
9. **Pregnancy Test:** Testing to be performed locally. All female patients of childbearing potential must have a negative serum or urine pregnancy test within 7 days of cycle 1 day 1, day 1 of every cycle starting with cycle 2, and 28-days following last dose of axitinib.
10. **Urinalysis:** To be performed locally (pre-dose). Microscopic analysis and/or urine protein creatinine ratio or 24-hour urine protein collection should be performed as clinically indicated.
11. **Axitinib Dosing:** Oral axitinib will be dosed twice daily on days 1-28 of each 28 day cycle according to the axitinib package insert. Patients who tolerate the starting dose with no adverse reactions above grade 2 for four weeks will have the axitinib dose increased. See Section 6.2 for specific dosing guidelines.
12. **Imaging:** CT or MRI scans of chest, abdomen, and pelvis with contrast to be performed at screening, and on-study as outlined in the assessment table. 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 to assure absence of CNS metastases and on study as needed if metastases are suspected. Bone scans are to be performed at screening and throughout the study at the time of CT assessments if bone metastases are present and cannot be followed by CT. Known areas of disease should be consistently followed throughout the study. Assessments should be performed whenever disease progression is suspected. Allowable window for tumor imaging studies is +/- 7 days. Scans will be performed every 56 days from the date of randomization.

13. **12-Lead ECG:** Single tracing 12-lead ECG will be performed at screening and at time points indicated in the Schedule of Assessments (pre-dose). For a QTc >500 ms, a repeat ECG for confirmation and evaluation of the ECG by a cardiologist is recommended. Additional ECGs may be performed on study as clinically indicated.
14. **Concomitant Medications and Treatments:** Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 28 days following the last dose of study treatment.
15. **Baseline Emergent Adverse Events/Adverse Events:** Patients must be followed for safety from the day of informed consent until at least 28 days after the last dose of study treatment, or until all serious or axitinib related toxicities have resolved or are determined to be "chronic" or "stable", whichever is later. Adverse events occurring prior to the initiation of the study treatment will be considered "Baseline-Emergent Adverse Events" and will be recorded on corresponding case report forms. Events that occur from the time the patient has taken the first dose of axitinib through 28 days after the last dose of axitinib will be recorded on "Adverse Event" CRFs. Any serious AE that is possibly related to axitinib occurring from the time of first dose or at any point after the reporting period must be promptly reported to TRACON.
16. **Axitinib Pharmacokinetic Trough Concentration:** One 5 mL blood sample to be collected at the time-points indicated in the Schedule of Assessments, prior to dosing with axitinib. The morning dose of axitinib should be taken after the PK draw. 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 manual for further collection and shipment information. Additional PK samples may also be collected at the time of unexpected clinical events.
17. **Protein Biomarkers:** One 10 mL purple top (K_2EDTA) tube will be collected at the time-points indicated in the schedule of assessments, prior to dosing with axitinib. The morning dose of axitinib should be taken after the Protein Biomarker draw. Samples will be stored at approximately -70°C to be analysed by a central laboratory. See separate laboratory manual for further collection and shipment information.
18. **Archival Tumor Tissue:** Archival specimens (formalin-fixed, paraffin-embedded) are required of the primary cancer and/or metastatic cancer specimen for each study participant, if they are available. It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 20 unstained slides are requested for immunohistochemical analysis (sections of 5 microns are preferred). Patients without available archival tumor tissue specimens are still eligible to participate in the study. See separate laboratory manual for further collection and shipment information.
19. **Cycle 3+ Treatment:** Patients who demonstrate a response of CR, PR or SD will be eligible for additional treatment until progression.
20. **Follow-up:** The follow-up visit should occur 28 days following the last dose of axitinib. The allowable visit window is +/- 7 days.
21. Allowable window for each visit within the cycle is +/- 2 days unless otherwise stated.

Table 10: Schedule of Assessments Phase 2: Arm B TRC105 + Axitinib (WEEKLY DOSING)

Protocol Activities	Screening	Cycle 1 and 2 [23]					Cycle 3+ [21] [23]				End of Study [3]	28 Day Follow-up [22]
	Day -28	Day 1 [1,2]	Day 4 (Cycle 1) [1]	Day 8 [1]	Day 15 [1]	Day 22 [1]	Day 1 [1]	Day 8 [1]	Day 15 [1]	Day 22 [1]		
Baseline Documentation												
Informed Consent [4]	X											
Medical/Oncology History [5]	X											
Physical Examination [6]	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 + Fe (C1)			X		X		X		X	
Coagulation [8]	X	X										
Blood Chemistry [8]	X + TSH	X + TSH			X		X + TSH				X + TSH	
Pregnancy Test [9]	Day -7	X					X					X
Urinalysis [10]	X	X					X				X	
Treatment w/ Study Drug												
TRC105 [11]		X C1 Split	X C1 Split	X	X	X	X	X	X	X		
Axitinib Dosing [12]		Day 1				Day 28	Day 1			Day 28		
Tumor Assessments												
CT or MRI Scans [13]	X Including Brain	EVERY 56 DAYS FROM DATE OF RANDOMIZATION									X	
Bone Scans [13]	X											
Other Clinical Assessments												
12-Lead ECG [14]	X	X					X				X	
Concomitant Medications/Treatments [15]	X	X	X		X		X		X		X	X
Baseline-Emergent Adverse Events [16]	X											
Adverse Events [16]		X	X		X		X		X		X	X
Special Laboratory Assessments												
Pre-Dose PK [17]		X					Even Cycles				X	X
Anti-Product Antibody Testing (Arm B) [18]		X					Even Cycles				X	X
Protein Biomarkers [19]		X					Even Cycles				X	
Archival Tumor Tissue [20]	X											

Schedule of Assessments Footnotes Arm B (TRC105 + Axitinib):

1. **Days of Treatment with TRC105:** All assessments should be performed prior to the TRC105 infusion and axitinib dosing unless otherwise indicated. Each cycle is 28 days in duration.
2. **Cycle 1 day 1:** Hematology (including Fe studies), blood chemistry (including TSH testing), coagulation, urinalysis, physical examination, ECG and pregnancy test not required if acceptable screening assessment is performed within 7 days prior to the start of treatment on cycle 1 day 1.
3. **End of Study:** Visit should generally occur within 7 days (+/- 1 day) of the last dose of TRC105 or axitinib. Assessments other than pharmacokinetics, immunogenicity and protein biomarkers do not need to be repeated if performed within the previous 2 weeks (previous 8 weeks for radiologic tumor assessments). Follow-up visits should occur 28 days following the last dose of TRC105 study drug as outlined in the Schedule of Assessments.
4. **Informed Consent:** Must be obtained prior to undergoing any study specific procedure and may occur prior to the 28-day screening period.
5. **Medical/Oncologic History and Demographics:** To include information on prior anticancer therapy.
6. **Physical Examination:** Examination of major body systems and ECOG performance status.
7. **Vital Signs:** Heart rate, temperature, blood pressure, respiratory rate, and weight. Assessment of vital signs during TRC105 Infusions: Vital signs are to be assessed pre-infusion (i.e., within 30 minutes of starting infusion), every 30 minutes during the infusion (+/- 15 minutes) and at the end of infusion (i.e., within 30 minutes after completing infusion). Vital signs should be monitored more frequently and/or beyond the completion of the infusion if medically indicated (e.g. if the patient experiences an infusion reaction that has not yet resolved).
8. **Hematology, Chemistry and Coagulation:** Testing to be performed locally (pre-dose). Thyroid stimulating hormone to be tested at screening, day 1 of each cycle and at the end of study visit. Iron studies to be performed at screening, cycle 1 day 1 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 8.1.1.1 for specific panel collection requirements.
9. **Pregnancy Test:** Testing to be performed locally. All female patients of childbearing potential must have a negative serum or urine pregnancy test within 7 days of cycle 1 day 1, day 1 of every cycle starting with cycle 2, and 28-days following last dose of TRC105 or axitinib, whichever occurs later.
10. **Urinalysis:** To be performed locally (pre-dose). 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 (cycle 1 day 1) will split into two doses whereby 3 mg/kg is administered on cycle 1 day 1 and 7 mg/kg 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 6.1.6 for specific TRC105 administration guidelines.
12. **Axitinib Dosing:** Oral axitinib will be dosed twice daily on days 1-28 of each 28 day cycle according to the axitinib package insert. Patients who tolerate the starting dose with no adverse reactions above grade 2 for four weeks will have the axitinib dose increased. See Section 6.2 for specific dosing guidelines.
13. **Imaging:** CT or MRI scans of chest, abdomen, and pelvis with contrast to be performed at screening, and on-study as outlined in the assessment table. 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 to assure absence of CNS metastases and on study as needed if metastases are suspected. Bone scans are to be performed at screening and throughout the study at the time of CT assessments if bone metastases are present and cannot be followed by CT. Known areas of disease should be consistently followed throughout the study. Assessments should be performed whenever disease progression is suspected. Allowable window for tumor imaging studies is +/- 7 days. Scans will be performed every 56 days from date of randomization.

14. **12-Lead ECG:** Single tracing 12-lead ECG will be performed at screening and at time points indicated in the Schedule of Assessments (pre-dose). For a QTc >500 ms, a repeat ECG for confirmation and evaluation of the ECG by a cardiologist is recommended. 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 up to 28 days following the last dose of TRC105 or axitinib, whichever occurs later. Required TRC105 premedications should be recorded on TRC105 premedications CRF.
16. **Baseline Emergent Adverse Events/Adverse Events:** Patients must be followed for safety from the day of informed consent until at least 28 days after the last dose of TRC105 or axitinib, whichever occurs later, or until all serious or study treatment related toxicities have resolved or are determined to be “chronic” or “stable”, whichever is later. Adverse events occurring prior to the initiation of the study treatment will be considered "Baseline-Emergent Adverse Events” and will be recorded on corresponding case report forms. Events that occur from the time the patient has taken the first dose of TRC105 study drug or axitinib through 28 days after the last dose of TRC105 study drug or axitinib will be recorded on “Adverse Event” CRFs. Any serious AE that is possibly related to TRC105 or axitinib occurring from the time of first dose or at any point after the reporting period must be promptly reported to TRACON.
17. **TRC105 and Axitinib Pharmacokinetic Trough Concentration:** Two (i.e., one for TRC105 and one for Axitinib) 5 mL blood samples to be collected at the time-points indicated in the Schedule of Assessments, **prior to dosing with axitinib and prior to starting the TRC105 infusion**. The morning dose of axitinib should be taken after the PK draw. This dose will still need to be taken 30 minutes before TRC105 dosing. 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.
18. **Anti-Product Antibody Testing:** 5 mL blood sample will be collected pre-dose to assess APA at the time-points indicated in the schedule of assessments and stored at approximately -70°C to be analysed by a central laboratory. Samples will be batch shipped as indicated in the laboratory manual to a third-party laboratory. See separate laboratory manual for further collection and shipment information. Additional APA samples may also be collected at the time of unexpected clinical events.
19. **Protein Biomarkers:** One 10 mL purple top (K_2EDTA) tube will be collected (pre-dose) 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 manual for further collection and shipment information.

20. **Archival Tumor Tissue:** Archival specimens (formalin-fixed, paraffin-embedded) are required of the primary cancer and/or metastatic cancer specimen for each study participant, if they are available. It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 20 unstained slides are requested for immunohistochemical analysis (sections of 5 microns are preferred). Patients without available archival tumor tissue specimens are still eligible to participate in the study. See separate laboratory guide for further collection and shipment information.
21. **Cycle 3+ Treatment:** Patients who demonstrate a response of CR, PR or SD will be eligible for additional treatment until progression.
22. **Follow-up:** The follow-up visit should occur 28 days following the last dose of TRC105 or axitinib whichever is later. The allowable visit window is +/- 7 days.
23. Allowable window for each visit within the cycle is +/- 2 days unless otherwise stated.

Table 11: Schedule of Assessments Phase 2: Arm B TRC105 + Axitinib (EVERY TWO WEEK DOSING) ***THIS SCHEDULE CANNOT BE FOLLOWED UNTIL NOTIFICATION FROM THE SPONSOR IS RECEIVED.

Protocol Activities	Screening	Cycle 1[23]					Cycle 2[23]			Cycle 3 and Odd Cycles ONLY[21,23]		Cycle 4 and Even Cycles ONLY[21,23]			End of Study [3]	28 Day Follow-up [22]
	Day - 28	Day 1[1,2]	Day 4[1]	Day 8[1]	Day 15 [1]	Day 22 [1]	Day 1 [1]	Day 15 [1]	Day 22 [1]	Day 1[1]	Day 15[1]	Day 1[1]	Day 15[1]	Day 22[1]		
Baseline Documentation																
Informed Consent[4]	X															
Medical/Oncology History[5]	X															
Physical Examination[6]	X	X					X			X		X			X	
Vital Signs[7]	X	X	X	X	X	X	X	X		X	X	X	X		X	
Laboratory Studies																
Hematology[8]	X + Fe	X (C1)			X		X	X		X	X	X	X		X	
Coagulation[8]	X	X					X									
Blood Chemistry[8]	X + TSH	X + TSH			X		X + TSH	X		X + TSH		X + TSH			X + TSH	
Pregnancy Test[9]	Day -7	X					X			X		X				X
Urinalysis[10]	X	X					X			X		X			X	
Treatment w/ Study Drug																
TRC105 Dosing[11]		X C1 Split	X C1 Split	X	X	X	X	X		X	X	X	X			
Axitinib[12]		28 Day Cycle					28 Day Cycle			28 Day Cycle		28 Day Cycle				
Tumor Assessments																
CT or MRI Scans[13]	X Including Brain	EVERY 56 DAYS FROM DATE OF RANDOMIZATION													X	
Bone Scans[13]	X															
Other Clinical Assessments																
12-Lead ECG[14]	X	X					X			X		X			X	
Concomitant Medications/Treatments[15]	X	X	X		X		X	X		X	X	X	X		X	
Baseline-Emergent Adverse Events[16]	X															
Adverse Events[16]		X	X		X		X	X		X	X	X	X		X	X
Special Laboratory Assessments																
Pre-Dose PK[17]		X					X					X			X	X
Anti-Product Antibody Testing(Arm B)[18]		X					X					X			X	X
Protein Biomarkers[19]		X					X					X			X	
Archival Tumor Tissue[20]	X															

Schedule of Assessments Footnotes Arm B (TRC105 + Axitinib) BIWEEKLY DOSING:

1. **Days of Treatment with TRC105:** All assessments should be performed prior to the TRC105 infusion and axitinib dosing unless otherwise indicated. Each cycle is 28 days in duration.
2. **Cycle 1 day 1:** Hematology (including Fe studies), blood chemistry (including TSH testing), coagulation, urinalysis, physical examination, ECG and pregnancy test not required if acceptable screening assessment is performed within 7 days prior to the start of treatment on cycle 1 day 1.
3. **End of Study:** Visit should generally occur within 7 days (+/- 1 day) of the last dose of TRC105 or axitinib. Assessments other than pharmacokinetics, immunogenicity and protein biomarkers do not need to be repeated if performed within the previous 2 weeks (previous 8 weeks for radiologic tumor assessments). Follow-up visits should occur 28 days following the last dose of TRC105 study drug as outlined in the Schedule of Assessments.
4. **Informed Consent:** Must be obtained prior to undergoing any study specific procedure and may occur prior to the 28-day screening period.
5. **Medical/Oncologic History and Demographics:** To include information on prior anticancer therapy.
6. **Physical Examination:** Examination of major body systems and ECOG performance status.
7. **Vital Signs:** Heart rate, temperature, blood pressure, respiratory rate, and weight. Assessment of vital signs during TRC105 Infusions: Vital signs are to be assessed pre-infusion (i.e., within 30 minutes of starting infusion), every 30 minutes during the infusion (+/- 15 minutes) and at the end of infusion (i.e., within 30 minutes after completing infusion). Vital signs should be monitored more frequently and/or beyond the completion of the infusion if medically indicated (e.g. if the patient experiences an infusion reaction that has not yet resolved).
8. **Hematology, Chemistry and Coagulation:** Testing to be performed locally (pre-dose). Thyroid stimulating hormone to be tested at screening, day 1 of each cycle and at the end of study visit. Iron studies to be performed at screening, cycle 1 day 1 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 8.1.1.1 for specific panel collection requirements.
9. **Pregnancy Test:** Testing to be performed locally. All female patients of childbearing potential must have a negative serum or urine pregnancy test within 7 days of cycle 1 day 1, day of every cycle starting with cycle 2, and 28-days following last dose of TRC105 or axitinib, whichever occurs later.
10. **Urinalysis:** To be performed locally (pre-dose). 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 is diluted in normal saline. TRC105 will be administered weekly during cycle 1. The first weekly TRC105 dose will be 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. Starting on cycle 2 day 1 and beyond, TRC105 will be administered every two weeks on days 1 and 15. See Section 6.1.6 for specific TRC105 administration guidelines.
12. **Axitinib Dosing:** Oral axitinib will be dosed twice daily on days 1-28 of each 28 day cycle according to the axitinib package insert. Patients who tolerate the starting dose with no adverse reactions above grade 2 for four weeks will have the axitinib dose increased. See Section 6.2 for specific dosing guidelines.
13. **Imaging:** CT or MRI scans of chest, abdomen, and pelvis with contrast to be performed at screening, and on-study as outlined in the assessment table. 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 to assure absence of CNS metastases and on study as needed if metastases are suspected. Bone scans are to be performed at screening and throughout the study at the time of CT assessments if bone metastases are present and cannot be followed by CT. Known areas of disease should be consistently followed throughout the study. Assessments should be performed whenever disease progression is suspected. Allowable window for tumor imaging studies is +/- 7 days. Scans will be performed every 56 days from date of randomization.

14. **12-Lead ECG:** Single tracing 12-lead ECG will be performed at screening and at time points indicated in the Schedule of Assessments (pre-dose). For a QTc >500 ms, a repeat ECG for confirmation and evaluation of the ECG by a cardiologist is recommended. 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 up to 28 days following the last dose of TRC105 or axitinib, whichever occurs later. Required TRC105 premedications should be recorded on TRC105 premedications CRF.
16. **Baseline Emergent Adverse Events/Adverse Events:** Patients must be followed for safety from the day of informed consent until at least 28 days after the last dose of TRC105 or axitinib, whichever occurs later, or until all serious or study treatment related toxicities have resolved or are determined to be “chronic” or “stable”, whichever is later. Adverse events occurring prior to the initiation of the study treatment will be considered "Baseline-Emergent Adverse Events” and will be recorded on corresponding case report forms. Events that occur from the time the patient has taken the first dose of TRC105 study drug or axitinib through 28 days after the last dose of TRC105 study drug or axitinib will be recorded on “Adverse Event” CRFs. Any serious AE that is possibly related to TRC105 or axitinib occurring from the time of first dose or at any point after the reporting period must be promptly reported to TRACON.
17. **TRC105 and Axitinib Pharmacokinetic Trough Concentration:** Two (i.e., one for TRC105 and one for Axitinib) 5 mL blood samples to be collected at the time-points indicated in the Schedule of Assessments, **prior to dosing with axitinib and prior to starting the TRC105 infusion**. The morning dose of axitinib should be taken after the PK draw. This dose will still need to be taken 30 minutes before TRC105 dosing. 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.
18. **Anti-Product Antibody Testing:** 5 mL blood sample will be collected pre-dose to assess APA at the time-points indicated in the schedule of assessments and stored at approximately -70°C to be analysed by a central laboratory. Samples will be batch shipped as indicated in the laboratory manual to a third-party laboratory. See separate laboratory manual for further collection and shipment information. Additional APA samples may also be collected at the time of unexpected clinical events.
19. **Protein Biomarkers:** One 10 mL purple top (K_2EDTA) tube will be collected (pre-dose) 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 manual for further collection and shipment information.

20. **Archival Tumor Tissue:** Archival specimens (formalin-fixed, paraffin-embedded) are required of the primary cancer and/or metastatic cancer specimen for each study participant, if they are available. It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 20 unstained slides are requested for immunohistochemical analysis (sections of 5 microns are preferred). Patients without available archival tumor tissue specimens are still eligible to participate in the study. See separate laboratory guide for further collection and shipment information.
21. **Cycle 3+ Treatment:** Patients who demonstrate a response of CR, PR or SD will be eligible for additional treatment until progression.
22. **Follow-up:** The follow-up visit should occur 28 days following the last dose of TRC105 or axitinib whichever is later. The allowable visit window is +/- 7 days.
23. Allowable window for each visit within the cycle is +/- 2 days unless otherwise stated.

5. SELECTION AND WITHDRAWAL OF PATIENTS

5.1. Patient Inclusion Criteria

5.1.1. Inclusion Criteria:

1. **PHASE 2 ONLY:** Histologically confirmed advanced or metastatic renal cell carcinoma with a clear cell component that has progressed by investigator assessment on treatment with one and only one multi-targeted tyrosine kinase inhibitor (TKI) other than axitinib that targets the VEGF receptor (VEGFR) (e.g., sunitinib, pazopanib, sorafenib, tivozanib, cabozantinib) **OR** bevacizumab. Patients who received VEGF inhibitor treatment for < one month due to documented intolerance in the absence of progression, and were started on a second VEGF inhibitor within one month of discontinuing the initial VEGF inhibitor are eligible. One prior immunotherapy (interleukin-2 or interferon-alpha or immune checkpoint inhibitor or tumor vaccine) and one prior mTOR inhibitor treatment are allowed. Prior adjuvant therapy is permitted in the absence of disease progression during treatment, but no further VEGF treatment is allowed if progression occurred on adjuvant VEGF inhibitor treatment.
2. **PHASE 1B COHORT 3 AND 4 ONLY**: Histologically confirmed advanced or metastatic renal cell carcinoma that has progressed by investigator assessment on treatment with at least **TWO** VEGF inhibitors (e.g., sunitinib, pazopanib, sorafenib, tivozanib, cabozantinib, bevacizumab). Prior immunotherapy (interleukin-2 or interferon-alpha or immune checkpoint inhibitor or tumor vaccine), or mTOR inhibitor treatment is allowed.
3. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission per investigators' clinical judgment.
4. Measurable disease by RECIST 1.1 criteria
5. Age of 18 years or older
6. ECOG performance status ≤ 1
7. Resolution of all acute adverse events resulting from prior cancer therapies to NCI CTCAE grade ≤ 1 or baseline (except alopecia)
8. Adequate organ function as defined by the following criteria:
   - AST and ALT ≤ 2.5 x ULN **OR** ≤ 5 x ULN in cases of liver metastases
   - Total serum bilirubin ≤ 1.5 times the upper limit of normal
   - Absolute neutrophil count (ANC) ≥ 1500/μL
   - Platelets ≥ 100,000/μL without transfusion support within the past 28 days
   - Hemoglobin ≥ 9.0 g/dL without transfusion support within the past 14 days (erythropoietin or darbepoetin permitted)

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

9. Willingness and ability to consent for self to participate in study
10. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures
11. Men who are sterile (including vasectomy confirmed by post vasectomy semen analysis) OR agree to use a condom with spermicide (refer to Section 2.3.6.1) and to not donate sperm during the study and for at least 180 days following last dose of TRC105 or axitinib.
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 two acceptable methods of birth control, one of which must be highly effective (refer to Section 2.3.6.1) during the study and for at least 180 days after stopping TRC105 or axitinib (refer to Section 2.3.6.1).

5.1.2. Exclusion Criteria:

1. **PHASE 2 ONLY:** Prior treatment with TRC105 or axitinib or any agent targeting the endoglin pathway (including a fusion protein that binds bone morphogenic protein)
2. **PHASE 1B COHORT 3 AND 4 ONLY**: Prior treatment with TRC105
3. Grade 3 or 4 toxicity related to prior VEGF inhibitor that did not resolve to grade 1
4. Current treatment on another therapeutic clinical trial
5. Receipt of systemic anticancer therapy, including investigational agents, within 28 days of starting study treatment. If anticancer therapy was given within 28 days of starting study treatment, patients may be included if 5 times the elimination half-life of the drug passed.
6. Prior radiation therapy within 28 days of starting the study treatment, except radiation therapy for bone metastases or radiosurgery is permitted up to 14 days of starting treatment
7. No major surgical procedure or significant traumatic injury within 6 weeks prior to study registration, and must have fully recovered from any such procedure; date of surgery (if applicable). Note: the following are not considered to be major procedures and are permitted up to 7 days before therapy initiation: Thoracentesis, paracentesis, port placement, laparoscopy, thoracoscopy, tube thoracostomy, bronchoscopy, endoscopic ultrasonographic procedures, mediastinoscopy, skin biopsies, incisional biopsies, imaging-guided biopsy for diagnostic purposes, and routine dental procedures
8. Uncontrolled chronic hypertension defined as systolic > 150 or diastolic > 90 despite optimal therapy (initiation or adjustment of BP medication prior to study entry is allowed provided that the average of 3 BP readings at a visit prior to enrollment is < 150/90 mm Hg)

9. History of brain involvement with cancer, spinal cord compression, or carcinomatous meningitis, or new evidence of brain or leptomeningeal disease. Patients with radiated or resected lesions are permitted, provided the lesions are fully treated and inactive, patients are asymptomatic, and no steroids have been administered for at least 28 days.
10. Angina, MI, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack, arterial embolism, pulmonary embolism, PTCA or CABG within the past 6 months. Deep venous thrombosis within 6 months unless the patient is anticoagulated without the use of warfarin for at least 2 weeks. In this situation, low molecular weight heparin is preferred.
11. Active bleeding or pathologic condition that carries a high risk of bleeding (e.g. hereditary hemorrhagic telangiectasia).
12. Thrombolytic use (except to maintain i.v. catheters) within 10 days prior to first day of study therapy
13. Known active viral or nonviral hepatitis or cirrhosis
14. History of hemorrhage or hemoptysis (> ½ teaspoon bright red blood) within 3 months of starting study treatment
15. History of peptic ulcer disease within 3 months of treatment, unless treated for the condition and complete resolution has been documented by esophagogastroduodenoscopy (EGD) within 28 days of starting study treatment
16. History of gastrointestinal perforation or fistula in the past 6 months, or while previously on antiangiogenic therapy, unless underlying risk has been resolved (e.g., through surgical resection or repair)
17. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness
18. Receipt of a strong CYP3A4/5 inducer within 12 days prior to cycle 1 day 1 or a strong CYP3A4/5 inhibitor within 7 days prior to cycle 1 day 1 (refer Table 18).
19. Other severe acute or chronic medical (including bone marrow suppressive diseases) or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for this study
20. Patients with known hypersensitivity to Chinese hamster ovary products or other recombinant human, chimeric, or humanized antibodies.
21. Significant ascites or pericardial or pleural effusion
22. Patients with hereditary problems of galactose intolerance, including Lapp lactase deficiency or glucose-galactose malabsorption

5.2. Patient Withdrawal Criteria

A patient should be withdrawn from study treatment if, in the opinion of the Investigator, it is medically necessary, or if it is the wish of the patient. If a patient does not return for a scheduled

visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome. Data to be collected at the end of study visit are described in the Schedule of Assessments (Table 7, Table 8, Table 9, Table 10, and Table 11). Patients will be followed for at least 28 days after the last dose of TRC105 study drug for adverse events. If the patient withdraws consent, no further evaluations should be performed, and no attempts should be made to collect additional data. Patients may be withdrawn for DLT, but DLT does not mandate withdrawal if the DLT resolves and can be treated (i.e., a first dose infusion reaction).

Patients will be withdrawn from treatment in the case of:

1. RECIST 1.1-defined disease progression. In cases where RECIST cannot be applied, progression should be based on unequivocal evidence of progressive disease sufficient to require a change in therapy.
2. A need for anticancer surgery, radiation, or for other anticancer therapy not specified in the protocol.
3. Lost to follow-up or noncompliant.
4. Any TRC105 dose delay > 2 days in cycle 1 (phase 1b only cohorts -1, 1, and 2 only)
5. Pregnancy. Pregnant patients should be followed for the duration of the pregnancy and the outcome of the pregnancy should be documented.
6. Arterial thrombosis of any grade (including cerebrovascular ischemia, cardiac ischemia/infarction, or peripheral or visceral arterial ischemia), grade 3 or 4 venous thrombosis (including pulmonary embolism), grade $\geq$ 2 intracranial hemorrhage, grade 3 or 4 non-CNS hemorrhage. Grade 2 non-CNS hemorrhage does not mandate withdrawal if the underlying condition is treatable. Grade 1 intracranial hemorrhage does not mandate withdrawal and may be treated with dose interruption if the patient is benefitting from treatment.
7. Missed study drug treatment for > 8 consecutive weeks (i.e., both TRC105 and axitinib dosing held if assigned to the combination arm or axitinib held if assigned to axitinib alone arm). However, patients assigned to the combination arm who cannot tolerate axitinib 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 axitinib alone.

6. TREATMENT OF PATIENTS

6.1. Description of TRC105 Study Drug

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

6.1.1. Composition of TRC105

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

6.1.2. TRC105 Dose Level

Each patient will be dosed with 6, 8, 0, 15, or 20 mg/kg. **The maximum weight that should be used for purpose of dose calculation is 85 kg for women and 100 kg for men.** Thus, the maximum dose that should be given to a woman at the 6 mg/kg dose level is 510 mg, at the 8 mg/kg dose is 680 mg, at the 10 mg/kg dose is 850 mg, at the 15 mg/kg dose is 1275 mg, and at the 20 mg/kg dose is 1700 mg and the maximum dose that should be given to a man at the 6 mg/kg dose level is 600 mg, at the 8 mg/kg dose is 800 mg, at the 10 mg/kg dose is 1000 mg, at the 15 mg/kg dose is 1500 mg, and at the 20 mg/kg dose is 2000 mg. 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. The calculated dose of TRC105 can be rounded up or down to the nearest 1.0 mg; in the case of an increment of 0.5 mg the dose should be rounded up.

Weekly Dosing (refer to Table 12):

The first weekly TRC105 dose (cycle 1 day 1) will be 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 (6, 8 or 10 mg/kg) is then given on cycle 1 day 8 and weekly thereafter and on days 1, 8, 15 and 22 of each subsequent 28 day cycle.

Every Two Week Dosing [refer to Table 13 (15 mg/kg) or Table 14 (20 mg/kg)]:

TRC105 can may be administered every two weeks starting with cycle 2 day 1 but **ONLY AFTER COHORT 3 &AND 4 IN THE PHASE 1B ARE COMPLETE AND THE& SPONSOR SENDS NOTIFICATION TO PROCEED WITH EVERY TWO WEEK DOSING**.

- Axitinib dosing will begin on cycle 1 day 1 and twice daily thereafter
- TRC105 will be administered weekly during cycle 1.
    - The first weekly TRC105 dose (i.e., 10 mg/kg) will be 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.

- Starting on cycle 2 day 1 and beyond, TRC105 may be administered every two weeks on days 1 and15

6.1.3. TRC105 Packaging and Labeling

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

Phosphate Buffered Saline Formulation (7 mg TRC105/mL)

- 210 mg TRC105/30 mL single-use vial

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

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

- 100 mg TRC105/4 mL single-use vial
- 200 mg TRC105/8 mL single-use vial
- 400 mg TRC105/16 mL single-use vial

6.1.4. TRC105 Storage and Shipping

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

6.1.5. TRC105 Preparation

TRC105 will be prepared in the pharmacy and diluted into normal saline using appropriate aseptic technique. TRC105 will be administered using an in-line 0.2 micron filter. No incompatibilities between TRC105 and polyvinyl chloride or polyolefin bags have been observed. Multiple vials will be required for a single dose. The following formulae should be used to calculate the volume of TRC105 to be added to normal saline:

- Patient weight (kg) × dose level (mg/kg) divided by TRC105 concentration (mg/mL) = volume of TRC105 (mL) to be administered.

The volume of TRC105 that is to be administered can be rounded up or down to the nearest 1.0 mL; in the case of an increment of 0.5 mL the volume should be rounded up. **The maximum weight that should be used for dose calculation in this study is 85 kg for women and 100 kg for men (note: there is not a weight restriction for enrollment purposes).** If the patient's weight changes by > 10% during the study, the dose of TRC105 will be recalculated. At that time a new baseline weight will be established such that subsequent weight changes by >10% from the new baseline weight would require further recalculation of the TRC105 dose. The calculated volume of TRC105 will be diluted with normal saline. Appropriate judgment should be exercised in withdrawing an adequate amount of saline necessary to permit injection of the appropriate volume of antibody into a normal saline bag in accordance with the dose needed. The final TRC105 concentration must be between 0.6 mg/mL and 10 mg/mL. The prepared TRC105 must be gently inverted several times in order to ensure a homogeneous solution. The diluted infusion solution of TRC105 should be used within 8 hours of preparation if stored at room temperature, or within 24 hours of dilution if stored at 2° to 8°C (36º to 46ºF). The expiration time should be labeled on the bag. If the diluted infusion solution of TRC105 cannot be infused within 8 hours of preparation (i.e.,: the prepared infusion is at room temperature for

more than 8 hours), a second bag will be prepared that contains the balance of the planned dose that was not already delivered. The prepared solution should not be frozen.

6.1.6. TRC105 Administration

Patients should be encouraged to drink abundant fluid [e.g., two eight ounce (237 mL) glasses of water or juice] prior to the first treatment. IV hydration prior to and during therapy is left to the discretion of the Investigator, but should be considered for patients that may be volume depleted.

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

- Acetaminophen at a dose of 500 mg to 1000 mg (e.g., 650 mg) p.o. x 1
- Famotidine 20 mg i.v. or p.o. (or similar H2 blocker) x 1. Famotidine (or similar H2 blocker) may be discontinued starting with Cycle 2 in the absence of infusion reactions with the prior dose.
- Cetirizine 10 mg i.v. or p.o. x 1 (or similar oral or intravenous antihistamine). Cetirizine (or similar oral or intravenous antihistimine) may be discontinued starting with Cycle 2 in the absence of infusion reactions with the prior dose.
- Methylprednisolone 100 mg i.v. will be given prior to the Cycle 1 Day 1 and Cycle 1 Day 4 infusions. **In addition, methylprednisolone will be given in the case of a delay of ≥ 10 days between any two scheduled weekly doses, a delay of ≥16 days between any two scheduled every other week doses, or if the patient develops an infusion reaction ≥ grade 2 during the immediate prior infusion**.

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

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

Three mg/kg of TRC105 will be administered on cycle 1 day 1 and administered over 4 hours (+/- 15 minutes). Do not increase the infusion rate above 25 mg/min during the Cycle 1 Day 1 dose. The remainder of the cycle 1 dose will be administered on cycle 1 day 4 and infused over a period of 2 hours (+/- 15 minutes). The full TRC105 dose will be administered on cycle 1 day 8 and infused over 1 hour (+/- 15 minutes). Patients must complete at least one 4 hour infusion without the development of any infusion reactions, in order to reduce the subsequent TRC105 infusion to 2 hours (+/- 15 minutes) and complete a 2 hour infusion without the development of any infusion reactions in order to reduce subsequent TRC105 infusions to 1 hour (+/- 15 minutes). Patients with infusion reactions of any kind should be managed appropriately (see Section 6.1.8) and are not permitted to reduce the duration of the next planned infusion. In the event a dose cannot be completed on a given day, the balance of the planned dose may be administered the following day at the rate of infusion planned for the prior day.

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

TRC105 WEEKLY DOSING: If a patient misses a weekly TRC105 dose and dosing is resumed ≥ 10 days after the last dose, full premedication, including methylprednisolone, should be reinstituted as per the initial infusion and first dose should be administered over two days as was done for the initial TRC105 dose.

TRC105 EVERY TWO WEEK DOSING: If a patient misses a TRC105 dose and dosing is resumed ≥ 16 days after the last dose, full premedication, including methylprednisolone, should be reinstituted as per the initial infusion and first dose should be administered over two days as was done for the initial TRC105 dose.

TRC105 Every Two Week Dosing:

Patients who received at least 1 cycle of weekly TRC105 may transition to TRC105 administered every two weeks.

The first administration of TRC105 given on an every two week schedule does not need to be split over two days unless there has been delay of ≥ 10 days since the **last weekly infusion**. In this case, TRC105 will be administered over two days with 3 mg/kg administered on day 1 and the reminder on day 4 with full premedication as outlined above.

Doses of TRC105 administrated every two weeks will be infused over a minimum of 60 minutes (+/- 15 minutes) for the 15 mg/kg dose and 90 minutes (+/- 15 minutes) for the 20 mg/kg dose. Full premedication will be given 2 hours to 30 minutes prior to the start of the initial two infusion (of TRC105 at either 15 mg/kg or 20 mg/kg) as described above. Premedication (except acetaminophen) may be discontinued in the absence of infusion reaction for subsequent doses (i.e., starting with Cycle 3 Day 1) of TRC105.

Table 12: TRC105 10 mg/kg Weekly Dosing Ideal Schema

	C1D1	**C1D4**	**C1D8**	**C1D15**	**C1D22**	**C2D1+**
TRC105 Dose (mg/kg)	3	7	10	10	10	10
Infusion Duration (hours)	4	2	1	1	1	1
Premedication						
Methylprednisolone (mg)	100	100	0	0	0	0
Famotidine (mg)	20	20	20	20	20	0
Cetirizine (mg)	10	10	10	10	10	0
Acetaminophen (mg)	500 - 1000	500 - 1000	500 - 1000	500 - 1000	500 - 1000	500 - 1000

Table 13: TRC105 15 mg/kg Every Two Weeks Dosing Ideal Schema

	C1D1	C1D4	C1D8	C1D15	C1D22	C2D1	C2D15	C3D1+
TRC105 Dose (mg/kg)	3	7	10	10	10	15	15	15
Infusion Duration (hours)	4	2	1	1	1	1	1	1
Premedication								
Methylprednisolone (mg)	100	100	0	0	0	100	100	0
Famotidine (mg)	20	20	20	20	20	20	20	0
Cetirizine (mg)	10	10	10	10	10	10	10	0
Acetaminophen (mg)	500 - 1000	500 - 1000	500 - 1000	500 - 1000	500 - 1000	500 - 1000	500 - 1000	500 - 1000

Table 14: TRC105 20 mg/kg Every Two Weeks Dosing Ideal Schema

	C1D1	C1D4	C1D8	C1D15	C1D22	C2D1	C2D15	C3D1+
TRC105 Dose (mg/kg)	3	7	10	10	10	20	20	20
Infusion Duration (hours)	4	2	1	1	1	1.5	1.5	1.5
Premedication								
Methylprednisolone (mg)	100	100	0	0	0	100	100	0
Famotidine (mg)	20	20	20	20	20	20	20	0
Cetirizine (mg)	10	10	10	10	10	10	10	0
Acetaminophen (mg)	500 - 1000	500 - 1000	500 - 1000	500 - 1000	500 - 1000	500 - 1000	500 - 1000	500 - 1000

6.1.7. TRC105 Dose Reduction/Dose Interruptions

TRC105 dose reductions and interruptions should be avoided in cycle 1. In cycle 2 and beyond, TRC105 dose reductions are allowed for grade 3 or 4 related adverse events that resolve to grade 1 or baseline (including anemia). Dose reductions for other toxicities are allowed at the discretion of the investigator. Treatment dose delays cannot exceed 8 weeks (i.e., both TRC105 and axitinib dosing cannot both be held at the same time for > 8 consecutive weeks if assigned to the combination arm or axitinib cannot be held for > 8 weeks if assigned to axitinib alone arm). However, patients assigned to the combination arm who cannot tolerate axitinib 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 axitinib alone per Section 5.2 of the protocol.

TRC105 and axitinib should be held for two weeks prior and for two weeks following surgical procedures. However, resumption of study treatment can be shorter (but no less than 7 days) or longer than two weeks based on clinical judgement of adequate wound healing and recovery from the procedure.

Table 15: Allowable TRC105 Dose Modifications

Toxicity Attributed to TRC105	**Dose Adjustment for Next Dose of TRC105**		
Dose Schedule/Level	10 mg/kg weekly	15 mg/kg every 2 weeks	20 mg/kg every 2 weeks
Grade 1 or 2	Maintain Dose Level	Maintain Dose Level	Maintain Dose Level
Grade 3 or 4			
• 1st appearance	8 mg/kg weekly	12 mg/kg every 2 weeks	16 mg/kg every 2 weeks
• 2nd appearance	6 mg/kg weekly	10 mg/kg every 2 weeks	12 mg/kg every 2 weeks
• 3rd appearance	4 mg/kg weekly	8 mg/kg every 2 weeks	8 mg/kg every 2 weeks
• 4th appearance	Discontinue treatment permanently	Discontinue treatment permanently*	Discontinue treatment permanently*
*After discussion with and agreement of the Sponsor, patients receiving TRC105 every two weeks have the option to return to weekly dosing at the lowest level (i.e., 4 mg/kg weekly), if 8 mg/kg every 2 weeks is not tolerable (i.e., 4th appearance of a Grade 3 or 4 toxicity attributable to TRC105 occurs) and the investigator believes that the patient is receiving benefit from the treatment.			

6.1.8. Management of TRC105 Infusion Reactions

If a patient experiences a grade 2 or higher adverse reaction during infusion, the infusion should be interrupted and the patient treated accordingly. Antipyretic, antihistamine, antiemetic, anti-inflammatory, or other symptomatic medications including epinephrine may be administered as indicated. For grade 2 and certain grade 3 infusion reactions, the infusion may be restarted (i.e., the same day) at half of the previous rate if and when the infusion reaction has resolved, and then increased per patient tolerance to a maximum of 25 mg/min. For grade 4 infusion reactions, the infusion should not be restarted and the patient should be discontinued from study treatment.

Infusion reactions will be recorded as AEs in the case report form. Interventions should be documented as concomitant medications or concomitant treatments as appropriate.

Table 16: Management of TRC105 Infusion Reactions

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

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

6.1.9. TRC105 Study Drug Accountability

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

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

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

6.1.10. TRC105 Study Drug Handling and Disposal

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

6.2. Description of Axitinib

See axitinib package insert in Section 20.3.

6.2.1. Composition of Axitinib

See axitinib package insert in Section 20.3.

6.2.2. Axitinib Dose Level

Each patient will be dosed initially with 5 mg of axitinib twice per day for each day of a 28 day cycle. Dose de-escalation is permitted in cycle one and thereafter per the package insert.

6.2.3. Axitinib Packaging and Labeling

See axitinib package insert in Section 20.3.

6.2.4. Axitinib Storage Handling and Disposal

See axitinib package insert in Section 20.3.

6.2.5. Axitinib Dosing

Axitinib should be taken with or without food twice daily approximately 12 hours apart. On TRC105 dosing days, the morning axitinib dose should be taken at least 30 minutes prior to TRC105 dosing. The recommended dose is 5 mg axitinib taken orally twice each day of a 28-day cycle. Axitinib should be dosed at approximately the same times each day. Tablets shall be swallowed whole with a glass of water.

If the patient vomits or misses a dose (i.e., more than 6 hours elapses from the time of the usual dose), an additional dose should not be taken. The next prescribed dose should be taken at the usual time. Patients should not take more than two doses of axitinib on the same day. See axitinib package insert in Section 20.3.

6.2.6. Axitinib Dose Modification

Patients who are intolerant of axitinib may continue TRC105 treatment alone on the study.

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

Dose reduction is allowed based on individual safety and tolerability. Following dose interruption, axitinib treatment may be reinitiated when the toxicity that prompted dose reduction has resolved to baseline or grade 1. See axitinib package insert in Section 20.3.

All patients will initially receive axitinib 5 mg twice daily; patients randomized to receive TRC105 will receive TRC105 at 3 mg/kg on day 1, 7 mg/kg on day 4, and 10 mg/kg on day 8 and weekly thereafter. Patients **in both arms** who tolerate axitinib for at least two consecutive weeks with no adverse reactions > Grade 1 considered clinically significant (according to the Common Toxicity Criteria for Adverse Events [CTCAE]), will, at the discretion of their treating physician, have the axitinib dose increased to 7 mg twice daily beginning on cycle 2 day 1, unless the patient's blood pressure is > 150/90 or the patient is receiving more than one antihypertensive medication. Subsequently, with the same criteria, patients who tolerate the axitinib dose of 7 mg twice daily for at least two consecutive weeks may have the axitinib dose increased to a maximum of 10 mg twice daily beginning with cycle 3 day 1. Dose reductions of axitinib and TRC105 are allowed per patient tolerance (including to doses of axitinib between 5 and 10 mg twice daily). Reasons for dose reduction and reasons for not increasing the axitinib dose will be documented on the CRF.

Over the course of treatment, management of some adverse drug reactions may require temporary interruption or permanent discontinuation and/or dose reduction of axitinib therapy (including hypertension and hypertensive crisis, arterial and venous thromboembolic events, hemorrhage, gastrointestinal perforation and fistula formation, thyroid dysfunction, reversible posterior leukoencephalopathy syndrome, wound healing complications, proteinuria, and liver enzyme elevations). If dose reduction from 10 mg twice daily is required the recommended dose is 7 mg twice daily. If dose reduction from 7 mg twice daily is required, the recommended dose is 5 mg twice daily. If dose reduction from 5 mg twice daily is required, the recommended dose is 3 mg twice daily. If additional dose reduction is required, the recommended dose is 2 mg twice daily.

In the case of persistent hypertension despite use of anti-hypertensive medications, reduce the axitinib dose. Discontinue axitinib if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of axitinib, and discontinuation should be considered if there is evidence of hypertensive crisis. If axitinib is interrupted, patients receiving antihypertensive medications should be monitored for hypotension.

Axitinib should be discontinued in patients who develop arterial thrombosis and the patient should be removed from study. Patients with grade 1 or 2 venous thromboembolism may dose reduce and continue treatment if it is the wish of the patient and physician and if the anticoagulation guidelines specified in Section 6.3 are satisfied.

Axitinib should be interrupted for any bleeding requires medical intervention, gastrointestinal perforation, fistula, reversible posterior leukoencephalopathy syndrome, or surgical procedure. Interruption prior to and following surgery should be for a minimum of 2 weeks.

Thyroid function should be monitored before initiation of, and periodically throughout, treatment with axitinib. Treat hypothyroidism and hyperthyroidism according to standard medical practice to maintain a euthyroid state.

The dose of axitinib should be temporarily interrupted and/or reduced for patients who develop grade 3 or 4 proteinuria or grade 3 or 4 transaminase or bilirubin elevations.

Patients assigned to the combination arm who cannot tolerate axitinib 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 TRC105 therapy may continue on study on TRC105 alone.

Table 17: Ideal Axitinib Dose Escalation Schedule

Axitinib Available Dose Levels	Cycle Day
5 mg BID	Cycle 1 Day 1 to Cycle 2 Day 1
7 mg BID	Cycle 2 Day 1 to Cycle 3 Day 1
10 mg BID	Cycle 3 Day 1+

6.2.7. Axitinib Drug Accountability

Patients will be asked to bring their axitinib bottle/blister packs to the clinic at the beginning of each cycle for proper drug accountability. Additional axitinib should be dispensed as needed. Upon patient discontinuation, unused axitinib tablets should be destroyed according to country-specific regulations/institution guidelines. Please see study specific pharmacy binder for detailed information regarding axitinib dispensing and accountability.

6.3. Concomitant Medications

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

Patients who receive NSAIDs on study for more than three consecutive days should also receive peptic ulcer disease (PUD) prophylaxis with an H2 or proton pump blocker.

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

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

Concomitant use of strong CYP3A4/5 inhibitors should be avoided (Table 18). Patients may not have received a strong CYP3A4/5 inducer within 12 days prior to registration nor a strong CYP3A4 inhibitor within 7 days prior to registration. Selection of an alternate concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. Grapefruit or grapefruit juice may also increase axitinib plasma concentrations and should be avoided. Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inhibitors, if a strong CYP3A4/5 inhibitor must be co-administered, a dose decrease of axitinib by approximately half is recommended, as this dose reduction is predicted to adjust the axitinib area under the plasma concentration versus time curve (AUC) to the range observed without inhibitors. The subsequent doses can be increased or decreased based on individual safety and

tolerability. If co-administration of the strong inhibitor is discontinued, the axitinib dose should be returned (after 3 – 5 half-lives of the inhibitor) to that used prior to initiation of the strong CYP3A4/5 inhibitor.

Co-administration of rifampin, a strong inducer of CYP3A4/5, reduced the plasma exposure of axitinib in healthy volunteers. Co-administration of axitinib with strong CYP3A4/5 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and St. John's wort) should be avoided. Selection of concomitant medication with no or minimal CYP3A4/5 induction potential is recommended. Moderate CYP3A4/5 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin) may also reduce the plasma exposure of axitinib and should be avoided if possible.

Table 18: Strong CYP3A4/5 Inducers and Inhibitors

Inducers:	**[a]Inhibitors:**	
dexamethasone	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/.

Patients with arterial thrombosis or grade 3 or 4 venous thrombosis should be removed from study. Patients with grade 1 or 2 venous thrombosis who require anticoagulation will have their TRC105 therapy interrupted. TRC105 therapy may resume once the following criteria are met:

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

6.4. Treatment Compliance

6.4.1. 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.

6.4.2. Axitinib Treatment Compliance

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

6.5. Patient Enrollment

Patients will be manually enrolled by TRACON Pharmaceuticals and assigned an eight digit patient number. This eight digit number will be used to identify patients throughout their participation in the trial. For the phase 2 portion of the study patients will also be assigned to Arm A (axitinib therapy alone) or Arm B (TRC105 + axitinib). A regulatory binder will be provided and will include detailed instructions for the manual enrollment process.

7. ASSESSMENT OF EFFICACY

7.1. Radiological Tumor Assessment

The primary efficacy assessment will be best overall response by RECIST 1.1 in Phase 1b and in phase 2 as defined in Section 7.1.2. The determination of antitumor efficacy will be based on objective tumor assessments made by Central Radiographic Review according to RECIST version 1.1 and Choi criteria [66]. However, Investigators will make treatment decisions using RECIST 1.1 based on their own review. 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.

Subjects 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. 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. Such a situation does not imply mandatorily a NE overall response.

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

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

Radiological tumor assessments will be performed at screening, as outlined in the Schedule of Assessments (Table 7, Table 8, Table 9, Table 10, and Table 11), and whenever disease progression is suspected. Another tumor assessment will be performed at the End of Study Visit if an assessment has not been performed within the prior 8 weeks. All patient files and radiological images must be available for CRF source verification.

7.1.1. Measurability of Tumor Lesions

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

- **Measurable:** Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with spiral CT scan. Lytic bone lesions, with an *identifiable soft tissue component*, evaluated by CT or MRI, *can be considered as measurable lesions* if the soft tissue component otherwise meets the definition of measurability previously described. Blastic bone lesions are non-measurable. Lesions in

previously irradiated areas (or areas treated with local therapy) should not be selected as target lesions, unless there has been demonstrated progression in the lesion. Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes) and ≥ 10 mm. Clinical lesions must be measured with calipers.

- **Non-Measurable:** All other lesions, including small lesions and bone lesions other than lytic bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusions, lymphangitis of the skin or lung, abdominal masses that are not confirmed and followed by imaging techniques, previously irradiated lesions (unless there has been demonstrated progression in the lesion), and disease documented by indirect evidence only (e.g. by laboratory tests such as alkaline phosphatase).

7.1.1.1. Recording Tumor Measurements

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

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

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

7.1.2. Definitions of Tumor Response

7.1.2.1. Target Lesions

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

7.1.2.2. Non-Target Lesions

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

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

7.1.3. Determination of Overall Response

7.1.3.1. Determination of Overall Response by RECIST 1.1

When both target and non-target lesions are present, individual assessments will be recorded separately. The overall assessment of response will involve all parameters as depicted in Table 19 below. Per RECIST 1.1, as the phase 1b portion is non-randomized and with response is a primary endpoint, confirmation of PR or CR is required. However, for the phase 2 portion, since the phase 2 portion **is** randomized, confirmation of response will not be required. Per RECIST 1.1, a modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

Table 19: Response Evaluation Criteria in Solid Tumors

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

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

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

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

NOTE: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "Need for additional anti-cancer therapy/surgery". Every effort should be made to document the objective progression even after discontinuation of treatment.

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

7.1.3.2. Determination of Overall Response by Choi Criteria

Central radiographic review will separately assess overall response using Choi criteria [66], as summarized in Table 14. The overall assessment of response will involve all parameters as depicted in Table 20 below.

Table 20: Choi Response Criteria

Response	Definition
CR	Disappearance of all lesions
	No new lesions
PR	A decrease in size ≥ 10% or a decrease in tumor attenuation (Houndsfield units) ≥ 15% on CT
	No new lesions
	No obvious progression of non-measurable disease
SD	Does not meet criteria for CR, PR or PD
	No symptomatic deterioration attributed to tumor progression
PD	An increase in tumor size ≥ 10% and does not meet criteria of PR by tumor attenuation on CT
	New lesions

7.1.4. Central Review of Disease Assessments

Central review of imaging studies and clinical information documenting disease status will be performed retrospectively 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 laboratory as each patient enrolls and progresses through the study.

Materials to be forwarded 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. Photographs of sites of disease assessed using clinical methods. Details concerning clinically assessed lesions will be collected on the CRFs and made available to the core laboratory.

Further information on materials to be forwarded for central review is provided in the Regulatory Binder.

8. ASSESSMENT OF SAFETY

8.1. Safety Parameters

Safety will be characterized in terms of the incidence, timing, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.0), seriousness, and relatedness of adverse events and laboratory abnormalities. In addition, physical examination, vital signs, and ECOG performance status will be serially monitored. Laboratory safety analyses will be based on the local laboratory data, and will include hematology, serum chemistry (including liver and kidney function), urinalysis, serum or urine pregnancy testing, and coagulation profile. Serum will also be assessed for immunogenicity to TRC105 (APA titers). In addition, ECGs will be recorded at baseline and day 1 of each cycle and as clinically indicated throughout the study.

8.1.1. Laboratory Safety Assessments

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

8.1.1.1. Hematology, Serum Chemistry, Coagulation, Pregnancy Test

Assessments will be performed at the time points indicated in the Schedule of Assessments (Table 7, Table 8, Table 9, Table 10, and Table 11) and analyzed at local laboratories. Investigators may have additional blood tests performed for the purpose of planning treatment administration, or for following adverse events as clinically indicated.

- Hematology: CBC with differential and platelet count. Iron studies (serum iron, ferritin and total iron binding capacity).
- Coagulation: International Normalized Ratio (INR) will be assessed
- Serum Chemistry: Total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, lipase, amylase, total protein, albumin, sodium, potassium, bicarbonate, chloride, calcium, phosphorus, blood urea nitrogen, creatinine, thyroid stimulating hormone and glucose
- Pregnancy test: Serum or urine pregnancy tests will be performed locally on all female patients of childbearing potential.

8.1.1.2. Urinalysis

Urinalysis (without microscopic analysis, unless indicated) will be performed at time points indicated in the Schedule of Assessments (see Table 7, Table 8, Table 9, Table 10 , and Table 11) and analyzed by local laboratories. Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated.

8.1.1.3. Physical Examination

A physical examination including, but not limited to, general appearance, head, eyes, ears, nose, throat, neck, heart, chest, abdomen, musculoskeletal, extremities, skin, lymph nodes, neurological genitourinary (as appropriate), and rectal (as appropriate) will be assessed at timepoints indicated within the Schedule of Assessments (see Table 7, Table 8, Table 9, Table 10 , and Table 11). The physical examination will include examination of known and suspected sites of disease.

8.1.1.4. Vital Signs

Heart rate, temperature, blood pressure, respiratory rate and weight will be assessed at timepoints indicated within the Schedule of Assessments (see Table 7, Table 8, Table 9, Table 10 , and Table 11). Heart rate, temperature, blood pressure, and respiratory rate will also be assessed during TRC105 infusions as described in Section 4.1.2.2 and the footnotes of the Schedule of Assessments.

8.1.1.5. Performance Status

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

8.1.1.6. ECG

A single 12-lead (with a 10–second rhythm strip) tracing will be used for all ECGs. It is preferable that the machine used has a capacity to calculate standard intervals automatically. ECG will be performed at the time-points indicated in the Schedule of Assessments (see Table 7, Table 8, Table 9, Table 10 , and Table 11) and as clinically indicated throughout the study

8.2. Adverse Events

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

8.2.1. Definition of Adverse Event

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

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

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

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

8.2.2. Serious Adverse Events

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

- Results in death
- Is life-threatening (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.
  - Cases of potential drug-induced liver injury as assessed by laboratory test values ("Hy's Law Cases") are also reportable as an SAE. If a Study subject develops abnormal values (3 x ULN) in aspartate transaminase (AST) or alanine transaminase

or both, concurrent with abnormal elevations (2 x ULN) in total bilirubin and no other known cause of liver injury, that event would be classified as a Hy's Law Case and an SAE.

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

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

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

8.2.2.1. Hospitalization

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

- Rehabilitation facility admission
- Hospice facility admission
- Respite care
- Skilled nursing facility admission
- Nursing home admission
- Emergency room visit
- Outpatient same day surgery/procedure
- Hospitalization or prolongation of hospitalization in the absence of precipitating clinical adverse events as follows:
    - Admission for treatment of preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition
    - Social admission
    - Administrative admission (e.g. for yearly physical exam)
    - Protocol-specified admission during a clinical trial

- Optional admission not associated with a precipitating clinical adverse event (e.g. for elective cosmetic surgery)
- Preplanned treatments or surgical procedures that are not related to an SAE
- Hospitalization for observation without an AE

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

8.3. Reporting Adverse Events

8.3.1. Eliciting Adverse Event Information

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

8.3.2. Adverse Event Reporting Period

Safety information for each patient will be collected from the date of informed consent. Adverse events occurring prior to the initiation of the study treatment will be considered "baseline-emergent adverse events" and will be recorded on corresponding case report forms and will not be retained for patients who fail screening. The adverse event reporting period for this trial begins when the patient has taken the first dose of axitinib or TRC105 study drug and ends 28 days after the last dose of axitinib or TRC105 study drug is administered.

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

8.3.3. Reporting Requirements

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

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

PRIMARY MEDICAL MONITOR

Ronald Shazer, MD, MBA
TRACON Pharmaceuticals Inc.
8910 University Center Lane, Suite 700
San Diego, California 92122
Email: rshazer@traconpharma.com
Cell Phone: 310.922.8039
Office Phone: 858.550.0780., Ext.230

SECONDARY MEDICAL MONITOR

Charles Theuer, MD, PhD
TRACON Pharmaceuticals Inc.
8910 University Center Lane, Suite 700
San Diego, California 92122
Email: ctheuer@traconpharma.com
Cell Phone: 858.344.9400
Office Phone: 858.550.0780, Ext. 233

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

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

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

Serious adverse events that are unexpected and associated with use of the study medication will be reported to the US Food and Drug Administration (FDA), Competent Authorities and Ethics Committees in other countries taking part in the study, as well as all participating clinical sites in all countries. Investigators should report to their local IEC/IRB as dictated by their board's policies and procedures. For events which are fatal or life-threatening, unexpected, and associated with use of the investigational product, a 7-Day Alert Report will be submitted to the regulatory authorities within 7 calendar days of receipt of the SAE information. For all other events that are serious, unexpected, and associated with use of the investigational product, a written report will be made no more than 15 calendar days from the date TRACON learns of the event. Participating clinical sites will be notified of these events in parallel.

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

8.3.4. Recording Adverse Events in the Case Report Forms

The Investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the trial patient. In addition, each trial patient will be questioned about adverse events. All adverse events that meet the criteria specified in Section 8.2.1 are to be recorded on patient source documents and on the CRFs. Adverse events should be reported using concise medical terminology on the CRFs.

8.3.5. Grading of Adverse Event Severity

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

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

Table 21: Adverse Event Grading

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

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

8.3.6. Relationship to TRC105 Study Drug/Axitinib

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

- Suspected Adverse Reaction to TRC105 (Arm B only): There is a reasonable possibility that TRC105 caused the adverse event (i.e., there is evidence to suggest a causal relationship between TRC105 and the adverse event).
- Suspected Adverse Reaction to axitinib (Arm A or B): There is a reasonable possibility that axitinib caused the adverse event (i.e., there is evidence to suggest a causal relationship between axitinib and the adverse event

- Not Related: There is no reasonable possibility that the adverse event is associated with TRC105 study drug or axitinib.

AE's maybe related to both drugs. AE's related to TRC105 study drug or Axitinib are considered Adverse Drug Reactions (ADR).

8.3.7. Expectedness

All TRC105 adverse events and adverse drug reactions are considered "unexpected" if it's not listed in the investigator brochure or not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

All axitinib adverse events and adverse drug reactions are considered "unexpected" if it's not listed in the package insert or not listed at the specificity or severity that has been observed. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with axitinib.

8.3.8. 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 TRC105 or axitinib, the Investigator must report the information to TRACON, or designee via the Pregnancy Notification Report Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery.

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

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.

8.3.9. Follow-up of Unresolved Adverse Events

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

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

8.4. Safety Monitoring

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

- Surveillance for SAEs according to regulatory guidelines
- Routine monitoring of non-serious adverse experiences as they are recorded in the case report forms and the source documents at study sites
- A formally chartered TRACON in-house Safety Review Team that includes, among other staff, two physicians
- Periodic teleconferences with the Principal Investigators to share experiences and ensure communication
- Toxicity information that may affect the treatment of patients on this study will be promptly communicated in writing to all participating clinical sites and institutions participating in this clinical trial.
- In addition a Data Monitoring Committee (DMC) will review the data from the trial. The DMC will periodically review the progress of the study and accumulating safety and efficacy data. Following each review, the DMC 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 TRACON Safety review Team will then determine whether to accept or modify the DMC recommendations and will communicate with study sites and regulators as appropriate. The DMC will be comprised of 3 voting members external to the Sponsor, including a clinician specializing in the treatment of renal cell cancer, a clinician with broader specialty in oncology clinical studies, and a biostatistician with expertise in the design, analysis, and interpretation of oncology clinical studies.

8.5. Steering Committee

An external steering committee comprised of renal cell cancer experts will assist with study design and will review study amendments as needed.

9. OTHER ASSESSMENTS

9.1. Other Laboratory Assessments

9.1.1. Pharmacokinetics (Phase 1b and Phase 2)

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

9.1.1.1. TRC105 Trough Concentration (Phase 1b and Phase 2 Arm B)

A 5 mL blood sample will be collected immediately prior to dosing with TRC105 on the days indicated within the Schedule of Assessments. Samples will be separated and stored at approximately -70 °C for shipment to third party laboratory. See separate laboratory guide for further collection and shipment information. For patients receiving axitinib and TRC105 in the study, population PK analysis will be performed for TRC105 in accordance with the FDA guidance on Population Pharmacokinetics (February 1999) and EMA Guideline on reporting the results of population pharmacokinetic analyses (June 2007). The serum concentration data set from this study will be pooled with data sets from additional TRC105 Phase 2 studies in other oncology populations. Population PK analyses will involve mixed effects modelling performed using appropriate software.

TRC105 Peak Concentration (Phase 1b)

A 5 mL blood sample will be collected within 10 minutes following each TRC105 infusion on the days indicated within the Schedule of Assessments. Samples will be separated and stored at approximately -70 °C for shipment to third party laboratory. See separate laboratory guide for further collection and shipment information.

9.1.1.2. Axitinib Trough Concentration (Phase 2)

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

9.1.2. TRC105 Immunogenicity

Samples will be sent to a third party laboratory for storage. See separate laboratory manual for specific collection, storage and shipping information.

Anti-Product Antibody (APA) concentrations will be measured using validated ELISA methods at the timepoints specified in the Schedule of Assessments in all patients. APA concentrations will be evaluated in the context of pharmacokinetic parameters and AE profiles. Samples will be separated and stored at approximately -70 °C for shipment to a third party laboratory. See separate laboratory guide for further collection and shipment information.

9.1.3. Protein Biomarkers

One 10 mL purple top (K_2EDTA) tube of blood will be collected on the days indicated within the Schedule of Assessments. Samples will be stored at approximately -70 °C and shipped to a third party laboratory for storage until the time of analysis. Duke University Medical Center will analyze plasma for several biomarkers including but not limited to VEGF, VEGF-R2, PIGF and sCD105 (Phase 1 Biomarker Laboratory, Duke University Medical Center, 309 MSRB, Research Dr., Durham, NC 27710). Please see the separate laboratory guide for further collection and shipment information.

9.1.4. Archival Tumor Specimens

Archival specimens (formalin-fixed, paraffin-embedded) of the primary cancer and/or metastatic cancer specimen for each study participant will be obtained, if they are available. It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 20 unstained slides are requested for immunohistochemical analysis (sections of ~ 5 microns are preferred). Samples will be stored at room temperature and shipped to third party laboratory for storage until the time of analysis. See separate laboratory guide for further collection and shipment information.

10. STATISTICS

10.1. Phase 1b

10.1.1. Statistical Design/Sample Size

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

The probability of escalation to the next higher dose for each underlying true DLT rate is shown in Table 22. For example, at a dose level with a true DLT rate of 5%, there is a greater than 95% probability of escalating. Conversely, for a dose level with a true DLT rate of 70%, the probability of escalating is < 5%.

Table 22: Probability of Escalation to the Next Dose for Each True Underlying DLT Rate at a Dose Level

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

Expanded Cohort 1:

The probability of failing to observe DLT in a sample size of 3 patients given various true underlying DLT rates is shown in Table 23. For example, with 3 patients, the probability of failing to observe DLT occurring at least 50% of the time is less than 15%.

Table 23: Probability of Failing to Observe True Underlying DLT Rate at a Dose Level

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

Following identification of the MTD using 3 or 6 patients, an additional 9 patients will be enrolled to further assess safety. If MTD was determined using 3 patients, then a total of 12 patients will be enrolled at the MTD, whereas, if the MTD was determined using 6 patients, then 15 patients will be enrolled at the MTD. The MTD will be exceeded if more than 33% of patients enrolled at the MTD experience DLT. In the case of 12 patients treated at the MTD, the chance of seeing no DLT, given a true underlying DLT rate of 30% is 1.4%. In the case that 15 patients are treated at the MTD, the chance of seeing one or fewer DLT, given a true underlying DLT rate of 30%, is 3%.

Expanded Cohort 2:

The probability of failing to observe toxicity in a sample size of 3 patients given various true underlying toxicity rates is shown in the Table16. Following identification of the MTD using 3 patients, at least 3additional patients will be enrolled to further assess safety.

10.2. Phase 2

10.2.1. Sample Size Justification

The study population for safety will include all patients receiving at least a portion of one dose of TRC105. The study population for efficacy will include all randomized patients (intention to treat). The primary endpoint is PFS and the primary analysis will compare the TRC105 and control groups using a one-sided, stratified (by performance status) log-rank test at the alpha=0.10 level of significance. The primary analyses of efficacy endpoints dependent on disease assessments (PFS, ORR and DR) will be performed in the intent-to-treat (ITT) population based on results of the central review of disease response and progression. Supportive analyses will be performed based on investigator assessments of disease response and progression. Pre-planned assessments of the primary endpoint will additionally be done based on number of prior therapies (one, two or three) and other known prognostic factors.

A hazard ratio of 0.67 is considered to be clinically relevant. Based on 1:1 randomization and the use of a one-sided log-rank test at the alpha=0.10 level of significance, 115 events are required in order to have 80% power to detect a hazard ratio of 0.67. The expected PFS of patients treated with axitinib who have progressed following first line treatment with a VEGFR TKI is 4.8 months. Based on a planned accrual period of 12 months, and a minimum follow-up period of 4.3 months, approximately 150 patients will be required.

An interim analysis for futility will be conducted by the DMC when 55 events have occurred. At the interim analysis, the conditional power based on the observed hazard ratio will be estimated. If the conditional power is less than 25%, the DMC may recommend to the sponsor that the study be terminated for futility. However, this interim analysis will not consider the possibility of early termination on the basis of superior efficacy.

10.3. Definition of Analyzed Study Populations

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

- For Phase 1b, the study population for safety includes all patients receiving at least a portion of 1 dose of TRC105.
- For Phase 1b, patients with treatment-related DLT and those without DLT who received less than the prescribed dose of TRC105 or axitinib due to documented toxicity in Cycle 1 will be considered evaluable for dose-escalation purposes. Only those patients who are deemed "ineligible" or who receive no therapy will be eliminated from the analysis. Ineligible patients who receive therapy will not be included in the assessment of efficacy endpoints, but their data will be included in the assessment of all adverse event reporting

- For Phase 1b, the study population for efficacy will include all safety population patients who have baseline and follow-up tumor measurements as required for assessment by RECIST 1.1.
- For Phase 2 the study population for safety includes all patients receiving at least a portion of 1 dose of TRC105.
- For Phase 2, the study population for efficacy will include all randomized patients (intention to treat).

10.4. 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 (APA), efficacy, pharmacokinetic parameters (phase 1b), protein biomarkers, and archival tumor tissue. Data will also be displayed graphically, where appropriate.

10.5. Analysis of Primary and Secondary Objectives

10.5.1. Phase 1b

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

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

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

10.5.2. Phase 2

The primary endpoint for efficacy will be PFS, defined as time from randomization to either first disease progression (per independent radiology review of images by RECIST) or death from any cause. PFS will be censored on the day following the date of the last tumor assessment documenting absence of progressive disease for patients who do not have objective tumor progression and are still on study at the time of analysis, are given antitumor treatment other than the study treatment, are removed from study follow-up prior to documentation of objective tumor progression, died of non-cancer causes including death due to an unknown cause in the absence of documented disease progression.

The PFS distributions in the two arms will be summarized using the Kaplan-Meier method. The distributions will be compared using a stratified (by performance status) log-rank test at the one-sided alpha=0.10 level of significance.

Additional exploratory analyses of PFS will be conducted in subgroups defined based on number of prior therapies (one, two or three). The same methods are for the primary analysis (Kaplan-Meier survival estimation, log rank tests) will be used. The effects of these covariates may also be assessed using Cox proportional hazards regression models.

The best response (CR, PR, SD or PD according to RECIST 1.1 and according to Choi criteria) for each patient with measurable disease who received at least one dose of study drug will be listed by cohort and response rate (CR or PR) between the two arms will be compared by Chi-square test or Fisher exact test. Stable disease will be defined as lack of tumor progression lasting for 2 cycles or longer. Additional analysis will be conducted based on duration of response, defined from the time to first response (CR or PR) to disease progression and will be compared between arms using Kaplan Meier methods. Other secondary analysis would include disease stability rate (DSR) defined as the percent of subjects in ITT population with CR, PR and SD at 12 weeks, and will be compared by Chi-square test or Fisher exact test.

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

The number and percentage of patients with the following types of treatment-emergent AEs will be summarized for each study arm: common and serious AEs, AEs related to study medication, AEs resulting in study discontinuation, and clinically significant laboratory abnormalities. Laboratory data will be summarized for baseline, treatment visits and change from baseline as appropriate for each arm. Non-treatment-emergent serious AEs will be described separately. Deaths will be reported with demographic information. Comparison of categorical values will be made by Chi-square or Fisher exact test and of continuous variables will be made by Student t test.

10.6. Analysis of Pharmacokinetics

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

10.7. Analysis of Protein Biomarkers

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

10.8. Analysis of Immunogenicity

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

10.9. Analysis of Archival Tumor Tissue

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

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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

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

12. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

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

13. ETHICS

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

Before this study starts, the trial protocol, protocol amendments, informed consent forms, and any other information for patients will be submitted to the FDA, EMA or other national health 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 relevant approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the Investigator must notify the IRB/IEC/health authorities and TRACON in writing within 5 business days after the implementation.

13.2. Ethical Conduct of the Study

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

13.3. Written Informed Consent

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

It is the responsibility of the Investigator to give each patient full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. This information must be provided to 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 subjects 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, ICHE6 requirements for impartial witnesses will apply.

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

13.4. Patient Compensation

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

14. DATA HANDLING AND RECORDKEEPING

14.1. Inspection of Records

CRF's are required and should be completed for each patient who receives treatment with TRC105. Screen failure CRF's will not be collected. Nevertheless, records of potential patients identified and screened shall be retained on site screening logs. The completed original CRFs are the sole property of TRACON and should not be made available in any form to third parties without written permission from TRACON (except for authorized representatives of the HRA and in accordance with HIPAA regulations).

It is the Investigator's responsibility to ensure completion and to review and approve all CRF data. The investigator will sign off on his/her data per patient. These signatures serve to attest that the investigator has reviewed and approved the information contained on the case report forms and that the information is complete, accurate, and true. At all times, the Investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

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

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

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

14.2. Retention of Records

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

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

clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor.

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

15. DEFINITION OF END TRIAL

15.1. End of Trial in all Participating Countries

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

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

15.2. TRACON Discontinuation Criteria

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

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

16. PUBLICATION OF TRIAL RESULTS

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

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

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

17. FINANCING AND INSURANCE

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

18. INVESTIGATOR PROTOCOL AGREEMENT: 105RC101

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

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

Investigator Name (PLEASE PRINT): _____

Signature: _____Date: _____

Please sign and return this agreement to:

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

Please keep a copy for your records.

19. REFERENCES

1. Carmeliet, P., *Angiogenesis in health and disease.* Nat Med, 2003. **9**(6): p. 653-60.
2. Folkman, J. and Y. Shing, *Angiogenesis.* J Biol Chem, 1992. **267**(16): p. 10931-4.
3. Hurwitz, H., et al., *Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.* N Engl J Med, 2004. **350**(23): p. 2335-42.
4. Sandler, A., et al., *Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.* N Engl J Med, 2006. **355**(24): p. 2542-50.
5. Miller, K.D., et al., *Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer.* J Clin Oncol, 2005. **23**(4): p. 792-9.
6. Friedman, H.S., et al., *Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma.* J Clin Oncol, 2009. **27**(28): p. 4733-40.
7. Escudier, B., et al., *Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival.* J Clin Oncol, 2010. **28**(13): p. 2144-50.
8. Escudier, B., et al., *Sorafenib in advanced clear-cell renal-cell carcinoma.* N Engl J Med, 2007. **356**(2): p. 125-34.
9. Llovet, J.M., et al., *Sorafenib in advanced hepatocellular carcinoma.* N Engl J Med, 2008. **359**(4): p. 378-90.
10. Motzer, R.J., et al., *Sunitinib versus interferon alfa in metastatic renal-cell carcinoma.* N Engl J Med, 2007. **356**(2): p. 115-24.
11. Rini, B.I., *Vascular endothelial growth factor-targeted therapy in metastatic renal cell carcinoma.* Cancer, 2009. **115**(10 Suppl): p. 2306-12.
12. *Sutent Package Insert*. Available from: http://www.pfizerpro.com/resources/minisites/oncology/sutent/pi/full-prescribing-information.pdf.
13. *Sutent Drug Approval Package*. 2006; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021938s000_021968s000_Stutent.cfm.
14. Escudier, B., J. Cosaert, and P. Pisa, *Bevacizumab: direct anti-VEGF therapy in renal cell carcinoma.* Expert Rev Anticancer Ther, 2008. **8**(10): p. 1545-57.
15. B. I. Rini, B.E., P. Tomczak, A. Kaprin, T. E. Hutson, C. Szczylik, J. C. Tarazi, B. Rosbrook, S. Kim, R. J. Motzer, *Axitinib versus sorafenib as second-line therapy for metastatic renal cell carcinoma (mRCC): Results of phase III AXIS trial.* J Clin Oncol, 2011. **29**(Suppl.): p. abst. #4503.
16. Motzer, R.J., et al., *Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial.* Lancet, 2008. **372**(9637): p. 449-56.

17. Hudes, G., et al., *Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma.* N Engl J Med, 2007. **356**(22): p. 2271-81.

18. N., F., *Pathways mediating VEGF-independent tumor angiogenesis.* . Cytokine Growth Factor Rev. , 2010. **21**(1): p. 21-26.

19. Bergers, G. and D. Hanahan, *Modes of resistance to anti-angiogenic therapy.* . Nat Rev Cancer, 2008. **8**(8): p. 592.

20. Kopetz S, H.P., Morris JS, Wolff RA, Eng C, Glover KY, Adinin R, Overman MJ, Valero V, Wen S, Lieu C, Yan S, Tran HT, Ellis LM, Abbruzzese JL, Heymach JV. , *Phase II trial of infusional fluorouracil, irinotecan, and bevacizumab for metastatic colorectal cancer: efficacy and circulating angiogenic biomarkers associated with therapeutic resistance.* . J Clin Oncol., 2010. **28**(3): p. 453-459.

21. You WK, S.B., Williamson CW, Falcon B, Hashizume H, Yao LC, Aftab DT, McDonald DM. , *VEGF and c-Met blockade amplify angiogenesis inhibition in pancreatic islet cancer.* Cancer Res., 2011. **71**(14): p. 4758-68.

22. Cunha SI, P.K., *ALK1 as an emerging target for antiangiogenic therapy of cancer.* . Blood Cells Mol Dis, 2011. **117**(26): p. 6999-7006.

23. Chen MF, W.W., Lin PY, Lee KD, Chen WC. , *Significance of the TGF-beta1/IL-6 axis in oral cancer.* . Clin Sci (Lond). 2012. **122**(10): p. 459-472.

24. Barbara Sennino, T.I.-O., Ying Wei, et al., *Suppression of Tumor Invasion and Metastasis by Concurrent Inhibition of c-Met and VEGF Signaling in Pancreatic Neuroendocrine Tumors.* Cancer Discovery AACR, 2012(doi:10.1158/2159-8290.CD-11-0240).

25. Haruta, Y. and B.K. Seon, *Distinct human leukemia-associated cell surface glycoprotein GP160 defined by monoclonal antibody SN6.* Proc Natl Acad Sci U S A, 1986. **83**(20): p. 7898-902.

26. Gougos, A. and M. Letarte, *Identification of a human endothelial cell antigen with monoclonal antibody 44G4 produced against a pre-B leukemic cell line.* J Immunol, 1988. **141**(6): p. 1925-33.

27. Seon, B.K., et al., *Long-lasting complete inhibition of human solid tumors in SCID mice by targeting endothelial cells of tumor vasculature with antihuman endoglin immunotoxin.* Clin Cancer Res, 1997. **3**(7): p. 1031-44.

28. Cheifetz, S., et al., *Endoglin is a component of the transforming growth factor-beta receptor system in human endothelial cells.* J Biol Chem, 1992. **267**(27): p. 19027-30.

29. Li, D.Y., et al., *Defective angiogenesis in mice lacking endoglin.* Science, 1999. **284**(5419): p. 1534-7.

30. Burrows, F.J., et al., *Up-regulation of endoglin on vascular endothelial cells in human solid tumors: implications for diagnosis and therapy.* Clin Cancer Res, 1995. **1**(12): p. 1623-34.

31. Seon, B.K., *Expression of endoglin (CD105) in tumor blood vessels.* Int J Cancer, 2002. **99**(2): p. 310-1; author reply 312.

32. Horsman, M.R. and D.W. Siemann, *Pathophysiologic effects of vascular-targeting agents and the implications for combination with conventional therapies.* Cancer Res, 2006. **66**(24): p. 11520-39.

33. Matsuno, F., et al., *Induction of lasting complete regression of preformed distinct solid tumors by targeting the tumor vasculature using two new anti-endoglin monoclonal antibodies.* Clin Cancer Res, 1999. **5**(2): p. 371-82.

34. Takahashi, N., et al., *Antiangiogenic therapy of established tumors in human skin/severe combined immunodeficiency mouse chimeras by anti-endoglin (CD105) monoclonal antibodies, and synergy between anti-endoglin antibody and cyclophosphamide.* Cancer Res, 2001. **61**(21): p. 7846-54.

35. Tsujie, M., et al., *Anti-tumor activity of an anti-endoglin monoclonal antibody is enhanced in immunocompetent mice.* Int J Cancer, 2008. **122**(10): p. 2266-73.

36. Uneda, S., H. Toi, and B.K. Seon, *Anti-endoglin monoclonal antibodies are effective for suppressing metastasis and the primary tumors by targeting tumor vasculature.* Int J Cancer, 2009. **125**: p. 1446.

37. Barbara, N.P., J.L. Wrana, and M. Letarte, *Endoglin is an accessory protein that interacts with the signaling receptor complex of multiple members of the transforming growth factor-beta superfamily.* J Biol Chem, 1999. **274**(2): p. 584-94.

38. She, X., et al., *Synergy between anti-endoglin (CD105) monoclonal antibodies and TGF-beta in suppression of growth of human endothelial cells.* Int J Cancer, 2004. **108**(2): p. 251-7.

39. Guo, B., et al., *CD105 inhibits transforming growth factor-beta-Smad3 signalling.* Anticancer Res, 2004. **24**(3a): p. 1337-45.

40. Warrington, K., et al., *Functional role of CD105 in TGF-beta1 signalling in murine and human endothelial cells.* Anticancer Res, 2005. **25**(3B): p. 1851-64.

41. Sanchez-Elsner, T., et al., *Endoglin expression is regulated by transcriptional cooperation between the hypoxia and transforming growth factor-beta pathways.* J Biol Chem, 2002. **277**(46): p. 43799-808.

42. van Laake, L.W., et al., *Endoglin has a crucial role in blood cell-mediated vascular repair.* Circulation, 2006. **114**(21): p. 2288-97.

43. Lenato, G.M. and G. Guanti, *Hereditary Haemorrhagic Telangiectasia (HHT): genetic and molecular aspects.* Curr Pharm Des, 2006. **12**(10): p. 1173-93.

44. Sabba, C., et al., *Life expectancy in patients with hereditary haemorrhagic telangiectasia.* Qjm, 2006. **99**(5): p. 327-34.

45. Rokhlin, O.W., et al., *Differential expression of endoglin on fetal and adult hematopoietic cells in human bone marrow.* J Immunol, 1995. **154**(9): p. 4456-65.

46. Kumar, S., et al., *Breast carcinoma: vascular density determined using CD105 antibody correlates with tumor prognosis.* Cancer Res, 1999. **59**(4): p. 856-61.

47. Vo, M.N., et al., *Elevated plasma endoglin (CD105) predicts decreased response and survival in a metastatic breast cancer trial of hormone therapy.* Breast Cancer Res Treat, 2008.

48. Tanaka, F., et al., *Evaluation of angiogenesis in non-small cell lung cancer: comparison between anti-CD34 antibody and anti-CD105 antibody.* Clin Cancer Res, 2001. **7**(11): p. 3410-5.

49. El-Gohary, Y.M., et al., *Endoglin (CD105) and vascular endothelial growth factor as prognostic markers in prostatic adenocarcinoma.* Am J Clin Pathol, 2007. **127**(4): p. 572-9.

50. Svatek, R.S., et al., *Preoperative plasma endoglin levels predict biochemical progression after radical prostatectomy.* Clin Cancer Res, 2008. **14**(11): p. 3362-6.

51. Li, C., et al., *Both high intratumoral microvessel density determined using CD105 antibody and elevated plasma levels of CD105 in colorectal cancer patients correlate with poor prognosis.* Br J Cancer, 2003. **88**(9): p. 1424-31.

52. Romani, A.A., et al., *The risk of developing metastatic disease in colorectal cancer is related to CD105-positive vessel count.* J Surg Oncol, 2006. **93**(6): p. 446-55.

53. Rubatt, J.M., et al., *Independent prognostic relevance of microvessel density in advanced epithelial ovarian cancer and associations between CD31, CD105, p53 status, and angiogenic marker expression: A Gynecologic Oncology Group study.* Gynecol Oncol, 2009. **112**(3): p. 469-74.

54. Taskiran, C., et al., *The prognostic value of endoglin (CD105) expression in ovarian carcinoma.* Int J Gynecol Cancer, 2006. **16**(5): p. 1789-93.

55. Ding, S., et al., *Comparative evaluation of microvessel density determined by CD34 or CD105 in benign and malignant gastric lesions.* Hum Pathol, 2006. **37**(7): p. 861-6.

56. Erdem, O., et al., *CD105 expression is an independent predictor of survival in patients with endometrial cancer.* Gynecol Oncol, 2006. **103**(3): p. 1007-11.

57. Yao, Y., et al., *Prognostic significance of microvessel density determined by an anti-CD105/endoglin monoclonal antibody in astrocytic tumors: comparison with an anti-CD31 monoclonal antibody.* Neuropathology, 2005. **25**(3): p. 201-6.

58. Yang, L.Y., et al., *Correlation between CD105 expression and postoperative recurrence and metastasis of hepatocellular carcinoma.* BMC Cancer, 2006. **6**: p. 110.

59. Saad, R.S., et al., *Endoglin (CD105) and vascular endothelial growth factor as prognostic markers in esophageal adenocarcinoma.* Hum Pathol, 2005. **36**(9): p. 955-61.

60. Kyzas, P.A., N.J. Agnantis, and D. Stefanou, *Endoglin (CD105) as a prognostic factor in head and neck squamous cell carcinoma.* Virchows Arch, 2006. **448**(6): p. 768-75.

61. Marioni, G., et al., *Endoglin expression is associated with poor oncologic outcome in oral and oropharyngeal carcinoma.* Acta Otolaryngol, 2006. **126**(6): p. 633-9.

62. Bockhorn, M., et al., *Differential vascular and transcriptional responses to anti-vascular endothelial growth factor antibody in orthotopic human pancreatic cancer xenografts.* Clin Cancer Res, 2003. **9**(11): p. 4221-6.

63. Davis, D.W., et al., *Regional effects of an antivascular endothelial growth factor receptor monoclonal antibody on receptor phosphorylation and apoptosis in human 253J B-V bladder cancer xenografts.* Cancer Res, 2004. **64**(13): p. 4601-10.

64. Shiozaki, K., et al., *Antiangiogenic chimeric anti-endoglin (CD105) antibody: pharmacokinetics and immunogenicity in nonhuman primates and effects of doxorubicin.* Cancer Immunol Immunother, 2006. **55**(2): p. 140-50.

65. David S. Mendelson, L.S.R., Francisco Robert, E. Gabriela Chiorean, Jonathan Wade Goldman, Ben K. Seon, Delia Alvarez, Bonne J. Adams, Charles P. Theuer, Bryan R. Leigh, Michael S. Gordon; , *A phase Ib dose-escalation study of TRC105 in combination with bevacizumab for advanced solid tumors.* Clin Cancer Res, 2014.

66. Choi, H.C., Chuslip; Faria, Silvana C.; Macapinlac, Homer A.; Burgess, Michael A.; and S.R.C. Patel, Lei L.; Podoloff, Donald A. and Benjamin, Robert S. , *Correlation of Computed Tomography and Positron Emission Tomography in Patients With Metastatic Gastrointestinal Stromal Tumor Treated at a Single Institution With Imatinib Mesylate: Proposal of New Computed Tomography Response Criteria.* Journal of Clinical Oncology, 2007. **25**(13).

20. APPENDICES

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

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

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

20.2. Appendix 2: ECOG Performance Status

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

20.3. Appendix 3: Axitinib Prescribing Information

http://labeling.pfizer.com/ShowLabeling.aspx?id=759