CLINICAL PROTOCOL

Title:	AN OPEN LABEL PHASE 1B/2 TRIAL OF TRC105 AND SORAFENIB IN PATIENTS WITH HEPATOCELLULAR CARCINOMA (HCC)
Protocol Number:	105HCC101
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Signature & Date:	Signed: _____ Print: C Theuer Date: 1 MAR 2018
Version Date:	Original Version: August 14, 2015 Amendment 1: September 15, 2015 Amendment 2: August 31, 2016 Amendment 3: February 09, 2017 Amendment 4: April 12, 2017 Amendment 5: February 15, 2018

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone number
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1. SYNOPSIS

Name of Sponsor/Company: TRACON Pharmaceuticals, Inc.	
Name of Investigational Product: TRC105	
Name of Active Ingredient: TRC105	
Title of Study: AN OPEN LABEL PHASE 1B/2 TRIAL OF TRC105 AND SORAFENIB IN PATIENTS WITH HEPATOCELLULAR CARCINOMA (HCC)	
Study center(s): This study will be performed at approximately 5 US centers (sites to be determined).	
Investigators: To be determined	
Studied period (years): Date first patient enrolled phase 1b portion: Nov 2016 Estimated Date phase 1b MTD obtained: January 2018 Estimated date first patient enrolled phase 2 portion: March 2018 Estimated date phase 2 endpoint obtained: May 2019 Estimated date last patient completed: May 2019	**Phase of development:** 1b/2
Rationale: Sorafenib is an oral multikinase inhibitor targeting several receptor tyrosine kinases, including the VEGF receptor (VEGFR), implicated in pathologic angiogenesis, tumor growth, and cancer progression. Sorafenib is approved for the treatment of unresectable hepatocellular carcinoma (HCC). TRC105 is an antibody to endoglin, an important angiogenic target on proliferating endothelial cells that is distinct from VEGFR. TRC105 inhibits angiogenesis, tumor growth and metastases and complements the activity of bevacizumab and multi-kinase inhibitors that target the VEGFR in preclinical models. Together, the use of TRC105 with sorafenib may result in more effective angiogenesis inhibition and improved clinical efficacy over that seen with sorafenib alone. A phase 1b/2 study of TRC105 with standard dose sorafenib was conducted by the NCI. Twenty patients were treated with sorafenib (400 mg BID) and 3, 6, 10 or 15mg/kg TRC105 every 2 weeks. The majority of patients had HCC with cirrhosis and compensated liver dysfunction (Childs Pugh A/B7) and an ECOG of 0/1. Overall, treatment was tolerable and the study proceeded as per protocol to the maximum planned dose level of TRC105 (15mg/kg every 2 weeks) in combination with 400 mg BID of sorafenib. Dose limiting transaminase elevation was encountered in a single patient at 10 mg/kg of TRC105 every 2 weeks and the cohort was expanded. One grade 5 cardiac event of myocardial infarction in a patient with preexisting coronary artery disease was observed in which the contribution of protocol treatment could not be excluded. The most common side-effect was hand-foot skin reaction attributed to sorafenib. Four of 10 patients (40%) treated at the top two dose levels of TRC105 (10 mg/kg every two weeks and 15 mg/kg every two weeks) had RECIST defined partial responses and the majority of patients had tumor reductions.	

An additional partial response was reported in one of the initial four patients treated in the Phase 2 portion of the study. Median time on study was 4 months and one patient remained on treatment for 22 months.

Given the results from the phase 1b portion of the NCI study, TRACON is conducting this multicenter phase 1b/2 study to assess the safety, tolerability and activity of TRC105 with standard dose sorafenib. This study includes an initial phase 1b dose escalation portion in order to assess the safety of TRC105 given at 10 mg/kg weekly for four weeks followed by 15 mg/kg every 2 weeks by i.v. infusion with daily sorafenib. A maximum of 21 additional patients will be treated in the phase 2 portion to assess the overall response rate to TRC105 and sorafenib. The recommended phase 2 dose of TRC105 is 10 mg/kg weekly in combination with 400 mg sorafenib twice daily. Ongoing patients in the Phase 1b portion of this study may, at the discretion of the investigator, be treated at the Phase 2 TRC105 dose of 10 mg/kg weekly.

Objectives:

Phase 1b:

Primary:

- To determine a recommended phase 2 dose for TRC105 by i.v. infusion when given with standard dose sorafenib in patients with hepatocellular carcinoma

Secondary:

- To determine the frequency and severity of adverse events as assessed by NCI CTCAE (Version 4.03)
- To characterize the pharmacokinetic profile of TRC105 and sorafenib when given together
- To evaluate TRC105 immunogenicity as assessed by Anti-Product Antibody (APA)
- To assess preliminary evidence of antitumor activity when TRC105 is added to sorafenib, by assessing overall response rate (ORR), progression-free survival (PFS) and overall survival (OS)
- To explore changes in circulating angiogenic biomarkers following treatment with TRC105 and sorafenib

Phase 2:

Primary:

- To estimate the ORR by RECIST 1.1 of patients with unresectable hepatocellular carcinoma given TRC105 and sorafenib

Secondary:

- To determine duration of response by RECIST 1.1
- To estimate PFS by RECIST 1.1, and determine overall survival (OS)
- To determine the frequency and severity of adverse events as assessed by NCI CTCAE (Version 4.03)
- To characterize the pharmacokinetic profile of TRC105 and sorafenib when given together

- To evaluate TRC105 immunogenicity as measured by APA
- To explore changes in circulating angiogenic biomarkers following treatment with TRC105 and sorafenib
- To prospectively assess IGF-1-modified Child-Pugh score [1] and outcomes in patients with HCC treated with sorafenib and TRC105

Methodology:

Phase 1b:

This is a multicenter, open-label, nonrandomized, phase 1b, dose-finding study of TRC105 in combination with standard dose sorafenib in patients with unresectable HCC. Escalating doses of i.v. TRC105 will be administered weekly or every two weeks, beginning with Dose Level 1 in combination with oral sorafenib given at 400 mg twice daily of each 28-day cycle. Sorafenib dose modifications are allowed starting in cycle 1, per the package insert and as outlined in section Section 7.8.6.

Dose Level[a]	Number of Evaluable Subjects	Sorafenib mg p.o., b.i.d. days 1-28	TRC105 mg/kg IV
-1	3-6	400	10 **(weekly C1),** 10 **(every 2 weeks C2+)**
1 (starting dose)	3-6	400	10 (**weekly** C1), 15 **(every 2 weeks C2+)**[b]

[a]Additional intermediate doses (below the MTD established during the trial) may be explored based upon clinical, PK, and/or biomarker data

[b]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.

Patients will be initially enrolled and treated at dose level 1. If <33% of patients experience a dose-limiting toxicity (DLT) during the 56-day evaluation period (cycle 1through the end of cycle 2), dose escalation will proceed following review of safety data with appropriate site staff including the principal investigators at all sites. At least 6 patients will be evaluated at the MTD (or highest dose administered if MTD is not reached) to confirm safety and tolerability. Additional patients may be enrolled at Dose Level 1 (as long as it does not exceed the MTD) to obtain additional safety and PK information.

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 TRC105 during the first 56 days (cycle 1 and 2). Patients who exit the study for reasons other than DLT prior to completion of the 56-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 sorafenib due to documented toxicity in Cycle 1 or 2 will be considered evaluable for dose escalation purposes. Upon agreement of the study investigators, a given TRC105 dose level may be reenrolled at 400 mg daily or 400 mg every other day of sorafenib 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 4
	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] • Grade 3 hypertension that can be controlled with oral medications and does not require treatment delay for > 7 days or dose reduction • Grade 3 rise in creatinine corrected to Grade 1 or less after 2 liters of intravenous fluids within 24 hours. • Grade 3 elevation in transaminases that is reversible following sorafenib dose reduction or interruption. • Grade 3 rash that decreases to ≤ Grade 2 after 1 week of symptomatic treatment. • Grade 3 hand-foot syndrome

[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 as outlined in Section 7.7.1.
[b]Patients with related grade 3 or 4 electrolyte abnormalities that persist for ≥ 48 hours will require a one-level dose reduction of TRC105 as outlined in Section 7.7.1.

Phase 2:

This is a multicenter, non-randomized, phase 2 study of TRC105 in combination with standard dose sorafenib. A maximum of 21 patients will be treated in the phase 2 portion of the study. Following completion of the Phase 1 portion of the study and discussions of Phase 1 safety and PK data with the study principal investigators, continuous weekly dosing with TRC105 at 10 mg/kg was selected as the recommended Phase 2 dose. Patients will receive TRC105 at 10 mg/kg weekly in combination with 400 mg sorafenib twice daily. Ongoing patients in the Phase 1b portion of this study may, at the discretion of the investigator, be treated at the Phase 2 TRC105 dose of 10 mg/kg weekly. Each cycle is 28 days in duration.

Number of patients (planned):

Approximately 6-12 patients with unresectable hepatocellular carcinoma will be enrolled in the phase 1b portion and a maximum of 21 patients will be enrolled in the phase 2 portion.

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

1. Patients must have confirmed hepatocellular carcinoma (HCC) by either histopathology or radiography. Diagnosis of HCC can be made without a biopsy if radiographic hallmarks of arterial hypervascularity and venous/late phase washout are present by either dynamic contrast-enhanced MRI or helical multidetector CT scan using contrast for a lesion ≥ 2 cm, or by both modalities for a lesion 1-2 cm. [2].
2. Patients must have disease that is not amenable to potentially curative resection or ablative techniques or that has recurred following ablative techniques. In addition, disease must not be amenable to transhepatic arterial chemoembolization (TACE) or must have progressed on TACE. Patients must not be candidates for liver transplantation.
3. Patient must have a Child-Pugh A or B (7 points) classification
4. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, or adequately treated Stage I or II cancer from which the patient is currently in complete remission per investigators' clinical judgment.
5. Measurable disease by RECIST 1.1 (Phase 2 only)
6. Age of 18 years or older
7. ECOG performance status ≤ 1
8. Resolution of all acute adverse events resulting from prior cancer therapies to NCI CTCAE grade ≤ 1 or baseline (except alopecia)
9. Adequate organ function as defined by the following criteria:
   - AST and ALT ≤ 5 x ULN
   - Absolute neutrophil count (ANC) ≥ 1500/μL
   - Platelets ≥ 60,000/μL without transfusion support within the past 28 days
   - Hemoglobin ≥ 9.0 g/dL without transfusion support within the past 14 days (erythropoietin or darbepoietin permitted)
   - Serum creatinine clearance > 30 mL/min by Cockcroft-Gault formula
10. Willingness and ability to consent to participate in study
11. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures
12. Men who are sterile (including vasectomy confirmed by post vasectomy semen analysis) OR agree to use at least two forms of a reliable and highly effective method of birth control (refer to Section 3.5.2.1) and to not donate sperm and for at least 180 days following last dose of TRC105 or sorafenib.
13. Woman of non-child bearing potential due to surgical sterilization (at least 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by medical history or menopause (i.e., no menstrual bleeding for more than 12 months in a women aged 45 years or more), OR woman of child bearing potential who test negative for pregnancy at time of enrollment based on serum pregnancy test and agree to use at least 2 forms of a reliable

and highly effective method of birth control during the study and for at least 180 days after stopping TRC105 or sorafenib (refer to Section 3.5.2.1).

Exclusion Criteria:

1. Prior anticancer systemic therapy
2. Current treatment on another therapeutic clinical trial
3. 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
4. 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, thorascopy, tube thoracostomy, bronchoscopy, endoscopic ultrasonographic procedures, mediastinoscopy, skin biopsies, incisional biopsies, imaging-guided biopsy for diagnostic purposes, and routine dental procedures
5. Proteinuria, as demonstrated by a 24-hour protein of ≥ 2000 mg. Urine protein will be screened by urine protein-creatinine ratio (UPC). For UPC ratio > 1.0, a 24-hour urine protein will need to be obtained and the level should be < 2000 mg for patient enrollment.
6. Uncontrolled chronic hypertension defined as systolic > 150 or diastolic > 90 on more than one measurement despite optimal therapy (initiation or adjustment of BP medication prior to study entry is allowed provided that the average of 3 BP readings prior to enrollment is < 150/90 mm Hg)
7. 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.
8. Angina, MI, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack, arterial embolism, pulmonary embolism, PTCA or CABG within the past 6 months.
9. Active bleeding or pathologic condition that carries a high risk of bleeding (e.g. hereditary hemorrhagic telangiectasia). No bleeding diathesis.
10. Thrombolytic use (except to maintain i.v. catheters) within 10 days prior to first day of study therapy
11. History of hemorrhage or hemoptysis (> ½ teaspoon bright red blood) within 3 months of starting study treatment
12. Need for anticoagulation
13. History of liver transplant
14. History of bleeding esophageal varices in previous 6 months, which have not been adequately managed with banding or sclerotherapy (i.e., following treatment, varices must be ≤ grade 1 with no stigmata of recent bleeding). Patients with cirrhosis must have had esophagogastric endoscopy within the past 6 months prior to study entry for the assessment of varices, and esophageal varices must be ≤ grade 1 with no stigmata of recent bleeding. Those with gastric

varices that are deemed as high risk by the endoscopist should be placed on appropriate medical therapy as advised by the gastroenterologist.

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. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness
17. Patients may not have received a strong CYP3A4 inducer within 12 days prior to registration (Table 19)
18. Patients with known hypersensitivity to Chinese hamster ovary products or other recombinant human, chimeric, or humanized antibodies.
19. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for this study
20. Ascites or pleural effusion requiring intervention or that required intervention within the last month and has recurred
21. Pericardial effusion (except trace effusion identified by echocardiogram)

TRC105 investigational product dose and mode of administration:

Phase 1b:

Dosing will begin at 10 mg/kg weekly in cycle 1 and 15 mg/kg every two weeks beginning with cycle 2(Dose Level 1); however, a -1 dose level has also been included of 10 mg/kg weekly in cycle 1 and 10 mg/kg every two weeks beginning with cycle 2 that will be enrolled if Dose Level 1 is found to exceed the MTD. Upon agreement of the study investigators, a given TRC105 dose level may be reenrolled at 400 mg daily or 400 mg every other day of sorafenib and/or the first dose of TRC105 may be delayed by one week (i.e., delayed to cycle 1 day 8). Following the appropriate premedication regimen, 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. Beginning with cycle 1 day 8 and for the rest of cycle 1, the full (e.g., 10 mg/kg) TRC105 dose will be administered i.v. weekly. Starting on cycle 2 day 1 and beyond, TRC105 will be administered at a dose of 15 mg/kg (Dose Level 1) every two weeks on days 1 and 15 of each 28-day cycle.

Phase 2:

Following completion of the Phase 1 portion of the study and discussions of Phase 1 safety and PK data with the study principal investigators, continuous weekly dosing with TRC105 at 10 mg/kg was selected as the recommended Phase 2 dose in combination with 400 mg sorafenib twice daily. Ongoing patients in the Phase 1b portion of this study may, at the discretion of the investigator, be treated at the Phase 2 TRC105 dose of 10 mg/kg weekly. Following the appropriate premedication regimen, TRC105 is to be administered intravenously.

Sorafenib dose and administration:

Sorafenib will be dosed at its approved dose of 400 mg p.o. b.i.d. daily. Sorafenib dose modifications are allowed starting in cycle 1 in accordance with the package insert and as outlined in Section 7.8.6.

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 only) unless discussed with sponsor.
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 sorafenib dosing held). Patients who cannot tolerate sorafenib and who demonstrate a response of complete response (CR), partial response (PR) or stable disease (SD) and are thought to benefit from continued single agent TRC105 therapy may continue on study on TRC105 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. In addition, recurring teleconferences will be held with Investigators at all clinical sites (Section 9.4).

Pharmacokinetics:

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

Immunogenicity:

Serum will be evaluated 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.

Efficacy:

RECIST 1.1 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 6 patients will be enrolled in the phase 1b portion.

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

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

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

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

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

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

The maximum tolerated dose (MTD) will have been exceeded if ≥ 33% of patients experience DLT at a given dose level.

Phase 2:

Efficacy Analyses

The primary endpoint of the phase 2 study is objective response (CR or PR) at any time during treatment. The sample size is determined using Simon's two-stage minimax design. This design will be used to test the null hypothesis that the true objective tumor response rate is < 5% versus the alternative hypothesis that the true response rate is > 20%.

One or more responses by RECIST 1.1 must be observed in the initial 12 patients enrolled to enroll the second stage, to a total of 21 patients. Three or more responses by RECIST of 21 patients will be considered sufficiently interesting to warrant further study in later trials.

Phase 2 Sample size justification:

With an alpha level of 0.1 and 80% power, a maximum of 21 treated patients will be required to evaluate the ORR. Twelve patients will be treated in stage 1. If < 1 objective response is observed in the first 12 patients, then the trial will be terminated, and the alternative hypothesis that the true ORR probability is > 20 % will be rejected. However, if one or more responses are observed in the first 12 patients, then the study will be expanded to enroll a total of 21 treated patients (9 additional patients to be treated in stage 2). At the end of the study, if > 3 objective responses are observed then the null hypothesis that the true response rate probability is < 5% will be rejected and further investigation of TRC105 and sorafenib in this population is warranted. Under this design, the expected sample size is 21. The probability of early termination under the null hypothesis is 50%.

The study will continue to enroll patients after the 12th patient has been enrolled unless no response is observed. If there is no patient achieving response at the time the 12th patient has been enrolled, the enrollment will be stopped temporarily. Once one patient is observed to have response, the enrollment will be resumed. However, if there is no patient achieving response after the first 12 patients have been fully evaluated, the study will be stopped for the futility.

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Table 2: Abbreviations and Specialist Terms

Abbreviation or specialist term	Explanation
ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
AE	Adverse Event
AFP	Alpha Fetoprotein
AIDS	Acquired Immunodeficiency Syndrome
ALKs	Activin receptor-Like Kinases
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
APA	Anti-Product Antibody
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AUC_{last}	Time of Last Measurable Concentration of Area Under the Curve
BALB/c mice	Mouse Strain
BMP	Bone Morphogenic Protein
BUN	Blood Urea Nitrogen
CABG	Coronary Artery Bypass Graft
CBC	Complete Blood Count
CEA	Carcinoembryonic Antigen
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

3. BACKGROUND

3.1. Hepatocellular Carcinoma

Worldwide, hepatocellular carcinoma (HCC) is the fifth most common malignancy with a median survival of 6-9 months [3], [4]. The approach to treating HCC has traditionally comprised of locoregional strategies; surgery (partial resection or transplantation) and interventional radiologic procedures, such as chemoembolization or ablative techniques remain the only treatments that are potentially curable. However, the publication of the landmark SHARP study established sorafenib as a standard consideration in unresectable disease and set the bar for future studies of systemic therapy [5].

3.1.1. Hepatocellular Carcinoma (HCC): sorafenib and angiogenesis

Sorafenib is an oral multi-kinase inhibitor of vascular endothelial growth factor (VEGF) receptor (VEGFR), the platelet-derived growth factor (PDGF) receptor, and Raf [5, 6], that improved overall survival in HCC in a phase III randomized, placebo-controlled study (10.7 months overall survival with sorafenib versus 7.9 months with placebo; HR 0.69; 95% CI, 0.55 to 0.87; P<0.001) which resulted in the adoption of sorafenib monotherapy as the standard of care for patients with HCC who are not eligible for, or have had disease progression after, surgical or locoregional therapies. A second major study conducted in Asia in predominantly Hepatitis B patients confirmed the treatment effect of sorafenib [6]. In that study overall survival was 6.5 months with sorafenib versus 4.2 months with placebo (p=0.014). The overall response rate in these studies was <2% by RECIST. Despite the survival improvement with sorafenib, patients either progress or do not respond at the outset. Resistance is not the result of receptor mutation, but rather appears to result from the development of escape pathways that mediate VEGF resistance. Endoglin (CD105) is a pathway implicated in resistance to VEGF inhibition.

3.2. CD105 and Angiogenesis

CD105 (endoglin) is a homodimeric cell membrane glycoprotein that was initially identified as a human leukemia-associated antigen [7] and later also found on endothelial cells [8, 9]. CD105 is a TGF-β coreceptor that is essential for angiogenesis [10, 11] and CD105 is strongly expressed on the proliferating vascular endothelium of solid tumors [9, 12], including HCC. All of these properties make CD105 an attractive target for the antiangiogenic therapy of cancer [13]. 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 [9, 14-17]. 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 [18] and bone morphogenic protein (BMP). 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) [19, 20]. CD105 has also been shown to protect hypoxic cells from apoptosis [21]. 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 [11].

CD105 is critical for normal human blood vessel development [22]. CD105 haplotype insufficiency causes a well-described syndrome known as hereditary hemorrhagic telangiectasia type 1 (HHT-1 or Osler-Weber-Rendu syndrome). HHT-1 is a rare autosomal dominant genetic disorder characterized by localized angiodysplasia involving the nasal, buccal, gastrointestinal mucosa and skin microvasculature. Angiodysplasia also occurs in vessels from internal organs including the lungs, liver and brain [23]. The genotype is manifested *in utero*, but the phenotype does not become apparent for many years following birth. Affected patients commonly present with epistaxis in the second decade of life. The phenotype of this disorder is characterized by vascular effects, emphasizing the dominant role of CD105 in vascular development [24]. Notably, HHT-1 is associated with superior overall cancer survival [Duarte].

CD105 is highly expressed on the proliferating endothelial cells of tumor vessels including lung, breast, colorectal, gastric, hepatocellular, endometrial, renal cell, head and neck, and ovarian cancers. In adults, CD105 expression is limited to endothelial cells, monocytes and proerythroblasts, a red blood cell precursor [25].

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 [26, 27], lung cancer [28], prostate cancer [29, 30], colorectal cancer [31, 32], ovarian cancer [33, 34], gastric cancer [35], endometrial cancer [36], astrocytic brain tumors [37], hepatocellular carcinoma [38], esophageal adenocarcinoma [39], and head and neck cancer [40, 41].

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 [42]. 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, allowing continued tumor growth despite VEGF inhibition [43]. Finally, inadequate expression of CD105, or conditional deletion in endothelium, resensitizes resistant tumors to VEGF inhibition [44].

3.3. TRC105 Background

TRC105 is a genetically engineered human/murine chimeric monoclonal antibody directed against human CD105 [45], a proliferation receptor found on the surface of normal and proliferating endothelial cells [9, 14, 20].

The antibody is an IgG1 kappa immunoglobulin containing murine variable region sequences and human constant region sequences [45]. 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 20 mM L-Histidine/L-Histidine Monohydrochloride, 240 mM Trehalose, 0.01% Polysorbate 20 Formulation (25 mg TRC105/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 [15]. Reactivity with tumor tissues is restricted to the tumor endothelium, as CD105 is not generally expressed on epithelial tumor cells [14]. TRC105 induces ADCC on proliferating HUVECs at low conentrations and induces apoptosis and growth inhibition at higher concentrations.

Studies at Duke University explored the *in vitro* effects of dual angiogenesis inhibition using bevacizumab and TRC105 in human umbilical vein endothelial cells (HUVEC) [46]. Combination therapy was found to be more potent in decreasing HUVEC proliferation, migration, and tubular network formation than bevacizumab or TRC105 treatment alone. 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 sorafenib, in mouse bearing cancer grafts [47]. For these reasons, CD105 blockade using TRC105 in combination with VEGF inhibition by sorafenib may provide greater clinical benefit than would be seen with either drug alone.

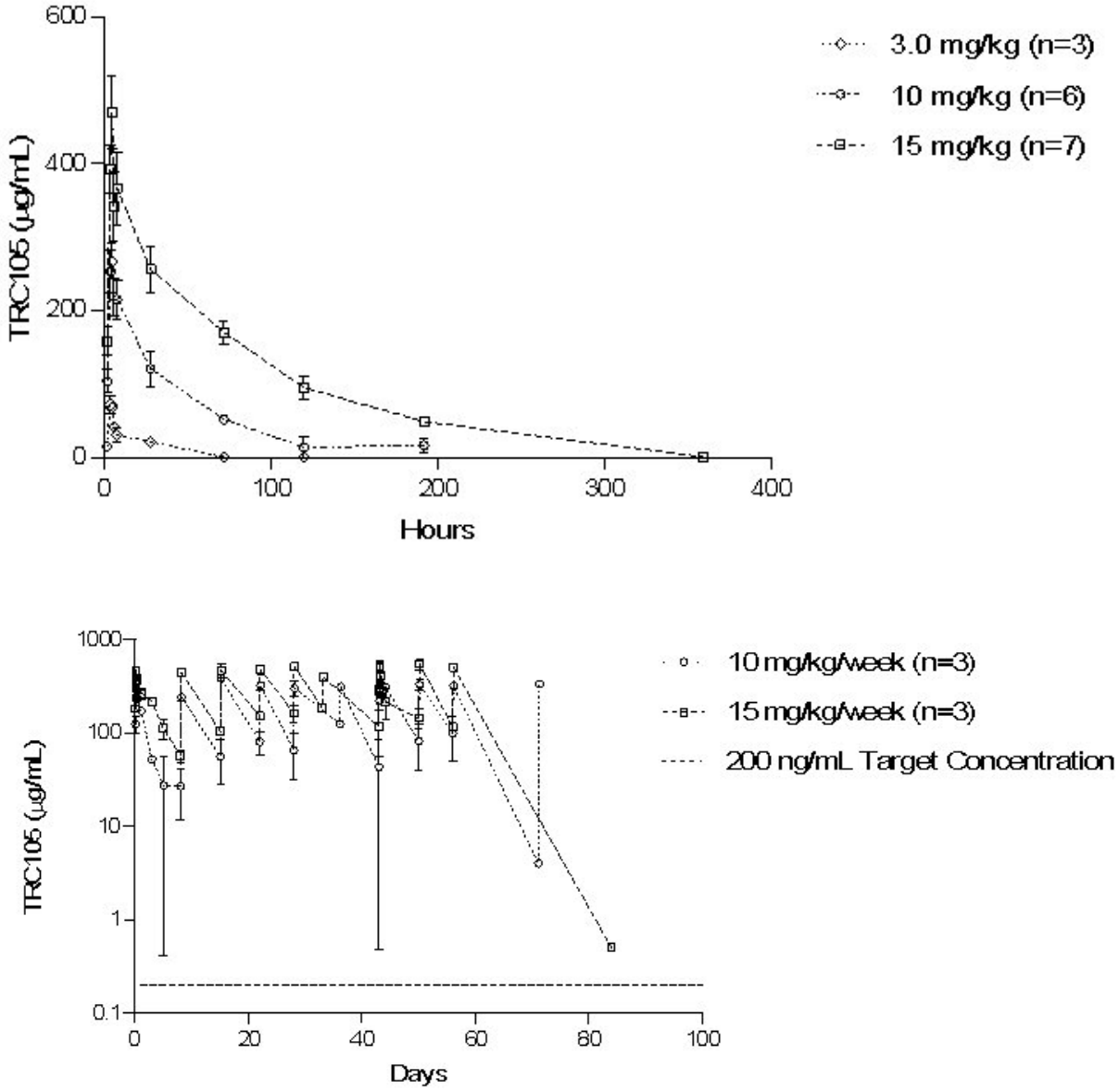
3.3.1. Phase 1 TRC105 Monotherapy Study Design for Solid Cancers

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.

3.3.1.1. 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



3.3.1.2. 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 this study.

3.3.1.3. 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 [25]. Anemia was reversible and manageable with dose reduction and standard supportive measures including erythropoietin and blood transfusion.

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

Infusion reactions, among the most common adverse events, were usually with the initial TRC105 dose and included one or more of the following signs or symptoms: rigors, bronchospasm, urticaria, hypertension, hypotension, tachycardia or bradycardia. A glucocorticoids-based premedication regimen and extended infusion time during the initial infusion mitigated the frequency and severity of first dose infusion reactions. At dose levels where continuous TRC105 serum levels were achieved (e.g., 10 mg/kg weekly and 15 mg/kg every two weeks), glucocorticoids were safely discontinued and the infusion duration reduced to 1 hour.

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

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

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

(unless healing was documented) and patients on ulcerogenic medications including non-steroidal anti-inflammatory drugs.

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

3.3.1.4. 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 7 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.

3.3.2. Phase 1b Study of TRC105 with Bevacizumab

3.3.2.1. Summary of Safety

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 at the recommended phase 2 doses of the two drugs of 10 mg/kg each. Two patients experienced grade 3 serious adverse suspected events as described below. Most adverse events were graded as 1 or 2 and Grade 4 and 5 suspected adverse events were not observed. Grade 3 suspected adverse reactions included anemia (the dose limiting toxicity of TRC105 established as a single agent; 9 patients), headache (4 patients; three of which occurred prior to adjusting the schedule of TRC105), fatigue (2 patients), brain abscess (1 patient), infusion reaction (in a patient dosed at 6 mg/kg), and decreased appetite (1 patient). Headache was the most common suspected adverse event and occurred in 31 patients (86.1%); three patients (7.9%) experienced migraine headaches (two of grade 1 and one of grade 2 severity). Headaches were treated with triptans and NSAIDs.

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

progression; grade 5 disease progression; grade 3 left foot cellulitis; grade 3 recurrent pneumothorax; grade 3 small bowel obstruction; grade 4 urosepsis.

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

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

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

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

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

Notably, hypertension and proteinuira, 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).

3.3.2.2. 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 measurable 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 (20% of those with measurable 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, two of whom continued to receive treatment under a continuation protocol for more than 1 year before coming off study.

3.4. Phase 1b Trial of TRC105 and Sorafenib and other VEGFR TKI

The NCI-sponsored Study 11-C-0102 was an open-label, non-randomized, dose-escalation, Phase 1b-2 study of TRC105 in combination with sorafenib 400 mg orally twice daily in patients with hepatocellular carcinoma (Childs Pugh A/B7 and ECOG performance status of 0 or 1). Standard eligibility criteria used in other TRC105 protocols were modified for the hepatocellular cancer population (including the inclusion of patients with thrombocytopenia), reflecting the frequent comorbidity of cirrhosis existent in this population. Twenty patients were enrolled in the Phase 1b stage, consisting of 3 patients at 3 mg/kg, 3 at 6 mg/kg, 6 at 10 mg/kg, and 8 at 15 mg/kg TRC105 every 2 weeks in combination with sorafenib (the MTD). Of the planned enrollment of up to 45 patients in the Phase 2 stage, 7 patients enrolled, at 15 mg/kg TRC105 every 2 weeks in combination with sorafenib. A total of 27 patients enrolled, this study is now complete. In general, the combination of TRC105 and sorafenib appears to be well tolerated with encouraging signs of activity in this study.

The only death in this study, myocardial infarction, was assessed as a suspected reaction to TRC105. This was a 60-year-old man with significant coronary artery disease was receiving TRC105 10 mg/kg every 2 weeks (last dose 10 days prior to the event) and sorafenib 400 mg p.o. daily (last dose 3 days prior to the event). During his second month of treatment he felt poorly and underwent cardiac catheterization, where he was found to “have a 90% heart blockage and expired of a myocardial infarction.” A total of 18 patients contributed a total of 25 SAEs in this study, of which 10 were assessed as suspected reactions to TRC105: Grade 5 Myocardial infarction; Grade 3 AST increased and Cerebrovascular accident; Grade 3 Hepatic failure; and Grade 2 Epistaxis, Flushing, Haemorrhage intracranial, Hypotension, Infusion-related reaction, and Pancreatitis.

A total of 7 patients were withdrawn from study due to 8 AEs, of which 2 were assessed as suspected reactions to TRC105: Grade 3 Hepatic failure and Grade 1 Epistaxis. Unrelated AEs that led to withdrawal were Grade 4 Sepsis; Grade 3 Blood bilirubin increased, Mucositis oral, and Rash maculo-papular; and Grade 1 Abdominal distension and Pain.

The majority of AEs were mild (Grade 1) or moderate (Grade 2) in severity. None of the 4 Grade 4 AEs were assessed as suspected reactions to TRC105. The only Grade 3 AEs assessed as suspected reactions to TRC105 were 1 event each of Grade 3 AST increased, Cerebrovascular accident, and Hepatic failure.

The most common AEs suspected to be reactions to TRC105 were Headache (63%); AST increased (59%); Blood bilirubin increased (55%); Anaemia (52%); Fatigue and Nausea (44%), Lymphocyte count decreased (41%); Hypoalbuminaemia and Blood alkaline phosphatase increased (37%); Infusion-related reaction (33%); and Platelet count decreased (26%). All of other related AEs occurred at an incidence ≤ 19%.

The most common AEs regardless of relatedness to TRC105 treatment were Hypophosphataemia (81%); Anaemia (78%); Hypoalbuminaemia (74%); AST increased and Pain (67%); Epistaxis, Headache, Lymphocyte count decreased, Blood bilirubin increased, Blood alkaline phosphatase increased, and Fatigue (each 63%); ALT increased (59%); Rash maculo-papular (52%); Hyponatraemia, Nausea, and Diarrhoea (each 48%); and Blood amylase increased and Activated partial thromboplastin time prolonged (each 44%). All other AEs occurred at an incidence ≤ 37%.

Five of 15 (33%) evaluable patients in Phase 1b treated at the top dose levels of 10 mg/kg or 15 mg/kg of TRC105 given every 2 weeks with sorafenib achieved partial responses by RECIST. Four additional patients had confirmed stable disease, 1 of whom was treated for 22 months. Median time on study was 4 months (range 2 to 22 months). The NCI concluded that TRC105 combined with sorafenib was well tolerated at the recommended doses of both drugs and demonstrated evidence of activity beyond the expected sorafenib response rate of 2-3% reported in its two pivotal Phase 3 studies.

3.5. Study Rationale

Given the novel mechanism of action and safety profile in early phase clinical studies, TRC105 is a logical therapy to use with sorafenib in HCC. This is a phase 2, open label study of TRC105 plus sorafenib including a lead-in phase 1b dose escalation study of sorafenib in combination with TRC105. The phase 1b portion is a standard "3+3" dose-escalation design of patients with unresectable HCC to assess the safety and tolerability of the recommended phase 2 dose (RPTD) and schedule of TRC105 given by i.v. infusion. The purpose of the dose escalation portion is to determine the maximum tolerated dose (MTD) of TRC105 with sorafenib and determine dose limiting toxicities.

The starting dose and schedule of TRC105 (10 mg/kg weekly in cycle 1, and 15 mg/kg every two weeks in cycle 2+) were selected based on safety, pharmacokinetics and early evidence of activity in a phase 1b/2 study of TRC105 in combination with sorafenib in patients with hepatocellular carcinoma (NCI Study 11-C-0102), and phase 1b studies of TRC105 with axitinib (105RC101) and pazopanib (105SAR101). NCI Study 11-C-0102 dosed TRC105 at 15 mg/kg every two weeks, starting on cycle 1 day1, with sorafenib. While the dose was tolerable when given with sorafenib, patients who did not achieve continuous TRC105 serum concentrations developed infusion reactions upon redosing or required chronic steroid premedication to prevent infusion reactions (i.e., patients without continuous TRC105 serum levels developed infusion

reactions upon repeat dosing when TRC105 bound *de novo* to its target on the tumor endothelium and engaged ADCC).

Weekly TRC105 dosing at 10 mg/kg is the recommended Phase 2 schedule, and has been administered to more than 350 cancer patients including patients enrolling in the Phase 3 pivotal study in angiosarcoma that is proceeding following Special Protocol Assessment by the FDA. However, TRC105 administration weekly for four weeks followed by every other week thereafter has also been studied to improve patient convenience. This TRC105 administration schedule was evaluated in combination with axitinib and pazopanib in separate Phase 1b studies. In each case, continuous TRC105 serum levels were achieved in all patients and recurrent infusion reactions were not observed when TRC105 was administered every other week. TRC105 was also tolerable when given at a dose of 10 mg/kg weekly for four doses in the phase 1 portion of this study without dose limiting toxicity. However, one patient developed a serious adverse event of Grade 3 infusion related reaction when dosed with 15 mg/kg every other week starting in cycle 2. PK analyses indicated that target TRC105 serum concentrations were achieved with weekly dosing but were below target concentrations, and were in some cases undetectable, following every other week dosing; this observation may reflect increased clearance of TRC105 in patients with HCC compared to other tumor types due to the vascular nature of the disease. Therefore, following recommendation of the principal investigators, weekly dosing at 10 mg/kg was chosen as the recommended Phase 2 dose for this study. Ongoing patients in the Phase 1b portion of this study may, at the discretion of the investigator, be treated at the Phase 2 TRC105 dose of 10 mg/kg weekly to achieve optimal target concentrations.

Secondary endpoints will be overall response rate (ORR) and progression free survival (PFS), safety, APA, TRC105 and sorafenib PK and correlative studies of plasma angiogenic biomarkers. Following completion of the phase 1b portion, the recommended phase 2 dose was determined by principal investigators to be 10 mg/kg TRC105 weekly in combination with 400 mg sorafenib twice daily. The phase 2 portion is a multicenter, open label, phase 2 study of TRC105 in combination with standard dose sorafenib in patients with unresectable HCC. The primary endpoint of the phase 2 portion is ORR. Secondary endpoints will evaluate PFS, safety, APA, TRC105 and sorafenib PK and correlative studies of plasma angiogenic biomarkers. Achievement of the primary and secondary endpoints of this Phase 1/2 trial will justify the initiation of a randomized Phase 3 trial of sorafenib +/- TRC105.

3.5.1. Population to be Studied

Patients with unresectable histologically confirmed hepatocellular carcinoma (HCC) will be enrolled in this trial.

3.5.2. Potential Risks and Benefits to Human Patients

3.5.2.1. Potential Risks

<u>TRC105</u>

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

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

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

Grade 3 anemia has occurred with TRC105 therapy at the recommended phase 2 dose. All patients treated with TRC105 should be monitored closely for anemia and treated appropriately, including the possibility of TRC105 dose interruption and/or reduction. The anemia related to TRC105 is hypoproductive in nature and is reversible with interruption of treatment, transfusion, erythropoietin, and other interventions as appropriate. Anemia may also be related to blood loss from epistaxis or gingival bleeding that result from mucocutaneous telangiectasia.

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

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

Sorafenib

The most common adverse reactions (≥ 20%), which were considered to be related to sorafenib, in patients with HCC or RCC are fatigue, weight loss, rash/desquamation, hand-foot skin reaction, alopecia, diarrhea, anorexia, nausea and abdominal pain.

Further details are available in the package insert.

Computed Tomography (CT) Scans

Patients will be exposed to a small amount of radiation as a result of the CT scans required in this study. This degree of exposure has not been associated with harmful health effects. In addition, the frequency of CT scans performed in this study is similar to the standard of care frequency. Patients with a medical contraindication to CT scans or known Iodinated contrast allergies may undergo MRI. There is minimal risk of MRI imaging in patients able to undergo

this type of exam including very rare reports of gadolinium-induce nephrogenic systemic fibrosis in patients with poor renal function

Venipuncture

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

Other Risks

This study treatment may involve risks to unborn children therefore patients should not become pregnant or father a baby while participating in this study. Patients should not nurse while on this study. Women of childbearing potential must have a negative pregnancy test before taking part in this study. Patients will be asked to practice an effective method of birth control during participation in this study and for 180 days after the last treatment. Women must be of non-child bearing potential due to surgical sterilization (at least 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by medical history or menopause; or must agree to use two methods of effective and highly reliable methods of contraception at the same time [i.e., tubal sterilization (tubes tied), partner's vasectomy, intra-uterine device (IUD), male latex condom with or without spermicide, diaphragm with spermicide, cervical cap with spermicide, vaginal sponge (contains spermicide)] during study treatment (including during temporary breaks from treatment), and for at least 180 days after stopping TRC105 or sorafenib. Men must agree to use two effective and highly reliable methods of contraception at the same time [i.e., vasectomy, male latex condom with or without spermicide, partner's tubal sterilization (tubes tied), partner's use of intra-uterine device (IUD), partner's use of diaphragm with spermicide, cervical cap with spermicide, vaginal sponge (contains spermicide)] during study treatment (including during temporary breaks from treatment), and for at least 180 days after stopping TRC105 or sorafenib. The long term risk of infertility is unknown. Ovarian failure has been observed with other antiangiogenic agents.

3.5.2.2. 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).

3.5.3. Conduct

The 105HCC101 clinical trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirements.

4. TRIAL OBJECTIVES AND PURPOSE

4.1. Purpose

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

4.1.1. Phase 1b Trial Objectives

4.1.1.1. Phase 1b Primary:

- To determine a recommended phase 2 dose for TRC105 by i.v. infusion when given with standard dose sorafenib in patients with hepatocellular carcinoma

4.1.1.2. Phase 1b Secondary

- To determine the frequency and severity of adverse events as assessed by NCI CTCAE (Version 4.03)
- To characterize the pharmacokinetic profile of TRC105 and sorafenib when given together
- To evaluate TRC105 immunogenicity as assessed by Anti-Product Antibody (APA)
- To assess preliminary evidence of antitumor activity when TRC105 is added to sorafenib, by assessing overall response rate (ORR), progression-free survival (PFS) and overall survival (OS)
- To explore changes in circulating angiogenic biomarkers following treatment with TRC105 and sorafenib

4.1.2. Phase 2 Trial Objectives

4.1.2.1. Phase 2 Primary

- To estimate the ORR by RECIST 1.1

4.1.2.2. Phase 2 Secondary:

- To determine duration of response by RECIST 1.1
- To estimate PFS by RECIST 1.1, and determine overall survival (OS)
- To determine the frequency and severity of adverse events as assessed by NCI CTCAE (Version 4.03)
- To characterize the pharmacokinetic profile of TRC105 and sorafenib when given together
- To evaluate TRC105 immunogenicity as measured by APA
- To explore changes in circulating angiogenic biomarkers following treatment with TRC105 and sorafenib

- To prospectively assess IGF-1-modified Child-Pugh score [1] and outcomes in patients with HCC treated with sorafenib and TRC105.

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design and Plan

5.1.1. 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 4.03.

5.1.1.1. Phase 1b Overview

This is a multicenter, open-label, nonrandomized, phase 1b, dose-finding study of TRC105 in combination with standard dose sorafenib in patients with unresectable HCC. Escalating doses of i.v. TRC105 will be administered weekly or every two weeks beginning with Dose Level 1 in combination with oral sorafenib given as 400 mg p.o. b.i.d. daily. Sorafenib dose modifications are allowed starting in cycle 1 as per the package insert and Section 7.8.6. Intermediate dose TRC105 (below the MTD established during the trial) may be explored based upon clinical, PK, and/or biomarker data.

TRC105 dosing will begin at 10 mg/kg weekly in cycle 1 and 15 mg/kg every two weeks beginning with cycle 2 (Dose Level 1) however a -1 Dose Level has also been included (10 mg/kg weekly in cycle 1 and 10 mg/kg every two weeks beginning with Cycle 2) and will be enrolled if Dose Level 1 exceeds the MTD. Upon agreement of the study investigators, a given TRC105 dose level may be reenrolled at 400 mg daily or 400 mg every other day of sorafenib and/or the first dose of TRC105 may be delayed by one week (i.e., delayed to cycle 1 day 8). Additional patients may be enrolled at Dose Level 1 or -1 (as long as it does not exceed the MTD) to obtain additional safety and PK information.

The first TRC105 dose will be split into two doses whereby 3 mg/kg is administered on cycle 1 day 1 and the balance (7 mg/kg) is administered on cycle 1 day 4. The entire dose of TRC105 (10 mg/kg) is then given weekly in cycle 1 and 10 mg/kg or 15 mg/kg every two weeks thereafter in cycle 2 and beyond (depending on Dose Level) in combination with oral sorafenib given as 400 mg p.o. b.i.d. Those who tolerate TRC105 without any infusion reactions may be eligible for reduced infusion durations and decreased premedication (see Section 7.7). Patients who demonstrate a complete response (CR), partial response (PR) or stable disease (SD) may continue on study until progression. Patients who cannot tolerate sorafenib therapy and are thought to benefit from continued TRC105 therapy may continue on study on TRC105 alone.

Patients who exit the study for reasons other than drug-related dose-limiting toxicity prior to completion of the DLT assessment period (first 56-days) will be replaced. Intrapatient dose escalation of TRC105 is not allowed.

Table 3: Dose Levels

Level[a]	Number of Evaluable Subjects	Sorafenib mg p.o., b.i.d. days 1-28	TRC105mg/kg IV
-1	3-6	400	10 (weekly C1), 10 (every 2 weeks C2+)[b]
1 (starting dose)	3-6	400	10 (weekly C1), 15 (every 2 weeks C2+)[b]

[a]Additional intermediate doses (below the MTD established during the trial) may be explored based upon clinical PK and/or biomarker data

[b]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.

Three patients will be initially enrolled and treated at Dose Level 1. If none of these 3 patients experiences a dose-limiting toxicity (DLT) during the 56-day evaluation period (cycle 1 through the end of cycle 2) a total of six patients will be treated at this dose level.

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 TRC105 during the first 56 days (cycle 1 and 2). Patients who exit the study for reasons other than DLT prior to completion of the 56-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 sorafenib due to documented toxicity in Cycle 1 or 2 will be considered evaluable for dose escalation purposes. Upon agreement of the study investigators, a given TRC105 dose level may be reenrolled at 400 mg daily or 400 mg every other day of sorafenib and/or the first dose of TRC105 may be delayed by one week (i.e., delayed to cycle 1 day 8).

Table 4: 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 4
	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]

Toxicity Category	Drug-Related Toxicity/Grade
	• Grade 3 hypertension that can be controlled with oral medications and does not require treatment delay for > 7 days or dose reduction • Grade 3 rise in creatinine, corrected to Grade 1 or less after 2 liters of intravenous fluids within 24 hours. • Grade 3 elevation in transaminases that is reversible following sorafenib dose reduction or interruption. • Grade 3 rash that decreases to ≤ Grade 2 after 1 week of symptomatic treatment. • Grade 3 hand-foot syndrome

[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 as outlined in Section 7.7.1.
[b]Patients with related grade 3 or 4 electrolyte abnormalities that persist for ≥ 48 hours will require a one-level dose-reduction of TRC105 as outlined in Section 7.7.1.

The recommended phase 2 dose for the combination determined by the study investigators, medical monitor, and TRACON after reviewing the toxicity and pharmacokinetic profile of the study combination is 10 mg/kg TRC105 weekly in combination with 400 mg sorafenib twice daily. Ongoing patients in the Phase 1b portion of this study may, at the discretion of the investigator, be treated at the Phase 2 TRC105 dose of 10 mg/kg weekly.

5.1.1.2. Phase 2 Overview

This is a multicenter, open label, phase 2 study of TRC105 in combination with standard dose sorafenib in patients with unresectable hepatocellular carcinoma. All patients will initially receive sorafenib 400 mg twice daily in combination with TRC105 at 3 mg/kg on day 1 and the remainder (7 mg/kg) on day 4, and weekly thereafter. Dose modifications of sorafenib and TRC105 are allowed per patient tolerance.

5.1.2. Trial Procedures

All on-study procedures are permitted within the time window indicated in the Schedule of Assessments (Table 5).

5.1.2.1. Screening

The following screening procedures must be performed within 28 days prior to the first day of study therapy. Qualifying hematology (including Fe studies), serum chemistry (including TSH testing), coagulation, physical examination, ECG, pregnancy and urinalysis collected within 7 days of cycle 1 day 1 do not need to be repeated. The following will be performed according to the Schedule of Assessments (Table 5).

- Patient signature on current Institutional Review Board (IRB) approved informed consent form. Prior to undergoing any study-specific procedure, patients must read and sign the current Institutional Review Board (IRB) approved informed consent form. Patients may sign consent prior to the 28 day screening period.

- Medical history, baseline signs and symptoms, prior cancer therapy, prior cancer surgery, prior radiation therapy, drug allergies, primary diagnosis and demographics.
- Physical examination including examination of all major body systems, ECOG performance status, and vital signs.
- Hematology (including serum iron, ferritin and total iron binding capacity), coagulation (PT or 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 and/or bone scans to be performed at screening if clinically indicated.
  - De-identified copies of MRI's, in DICOM format may be transferred to the Sponsor if requested
- Single tracing 12-Lead ECG (QT, PR and QRS intervals and heart rate will be captured).
- Assessment of concomitant medications and treatments from 28 days prior to the start of study treatment.
- Archival Tumor Tissue Specimens: Archival specimens (formalin-fixed, paraffin-embedded) of the primary cancer specimen and/or metastatic cancer specimen for each study participant, 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
- Patients with cirrhosis must have had esophagogastric endoscopy within the past 6 months prior to study entry for the assessment of varices. If the patient has not had this done they must be willing to undergo this procedure prior to study entry.

5.1.2.2. 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 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 (Table 5).

- 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 (PT or INR) and serum chemistry (including TSH) to be performed locally.
- Urinalysis to be performed locally. Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated.
- Blood sampling for TRC105 and sorafenib 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).
- 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)
- Blood sampling for tumor markers (i.e. AFP)
- 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 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 during study conduct. Scans will be performed on day 22 of even cycles (C2, C4, C6, etc.). Assessments should be performed whenever disease progression is suspected. Allowable window for tumor imaging studies is +/- 7 days.
    - De-identified copies of CTs or MRI's, in DICOM format, may be transferred to the Sponsor if requested
- Administration of TRC105. TRC105 diluted in normal saline will be administered as a 1 to 4 hour infusion (+/- 15 minutes) following premedication (see Section 7.7) according to the schedule of assessments (Table 5).
    - **(Dose Level -1):** 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 (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, day 15 and day 22. The full 10 mg/kg dose will then be administered beginning on cycle 2 day 1 and every two weeks thereafter for the remainder of the trial period. **Note this dose level will only be enrolled if the TRC105 MTD is exceeded in Dose Level 1**.

- **Dose Level 1:** The first 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 (7 mg/kg) is administered on cycle 1 day 4 (7 mg/kg). The entire weekly dose of TRC105 (10 mg/kg) is then given on cycle 1 day 8, day 15 and day 22. The full 15 mg/kg dose will then be administered beginning on cycle 2 day 1 and every two weeks thereafter for the remainder of the trial period
- **Phase 2 Dosing:** The first 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 (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, day 15 and day 22 and weekly thereafter for the remainder of the trial period (see Section 7.7)

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

- Sorafenib dosing. The oral dose of sorafenib is 400 mg twice daily of each 28 day cycle. Sorafenib tablets should be taken without food (at least 1 hour before or 2 hours after a meal). Patients are to swallow the tablets whole with approximately 250 ml (8 oz) of water, each morning and evening (i.e., approximately 12 hours apart). Sorafenib dose reductions are allowed starting on cycle 1 based on patient tolerability as per the package insert and Section 7.8.6.
- Assessment of adverse events.
- Assessment of concomitant medications and concomitant treatments.

5.1.3. End of Study Assessments

Assessments other than TRC105 pharmacokinetics, immunogenicity, and protein biomarkers only need to be completed if they were not completed during the previous 2 weeks on study (during the last 8 weeks on study for radiologic tumor assessments unless progression is suspected). The following will be performed according to the Schedule of Assessments (Table 5).

- Physical examination including examination of all major body systems, ECOG performance status, and vital signs.
- Single tracing 12-Lead ECG (QT, PR and QRS intervals and heart rate will be captured).
- Hematology and serum chemistry (including TSH) to be performed locally.

- Urinalysis to be performed locally. Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated.
- Blood sampling for TRC105 and sorafenib pharmacokinetics to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection times, procedures, processing, storage and shipment).
- Blood sampling for immunogenicity (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)
- Blood sampling for tumor markers (i.e. AFP)
- 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.
  - De-identified copies of CTs or MRI's, in DICOM format, may be transferred to the Sponsor if requested
- Assessment of adverse events.
- Assessment of concomitant medications and concomitant treatments.

5.1.4. Post Treatment Follow-up

The following will be performed according to the Schedule of Assessments (Table 5). 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 adverse events that occur beyond the adverse event reporting period.
- Serum or urine pregnancy test for all females of childbearing potential to be performed locally.
- Blood sampling for TRC105 and sorafenib pharmacokinetics to be analyzed by a third party laboratory (see laboratory manual for specific instructions regarding collection times, procedures, processing, storage and shipment).
- Blood sampling for immunogenicity (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.

Table 5: Schedule of Assessments (Phase 1b)

Protocol Activities	Screening	Cycle 1 **(10 mg/kg Weekly)** [23]					Cycle 2 + **(10 mg/kg or 15 mg/kg every two weeks)** [23]		End of Study [3]	28 Day Follow-up [23]	Long Term Follow Up (bimonthly)
	Day -28	Day 1 [1] [2]	Day 4 [1]	Day 8 [1]	Day 15 [1]	Day 22 [1]	Day 1 [1]	Day 15 [1]			
Baseline Documentation											
Informed Consent [4]	X										
Medical/Oncology History [5]	X										
Baseline Signs and Symptoms	X										
Physical Examination [6]	X	X					X		X		
Vital Signs [7]	X	X	X	X	X	X	X	X	X		
Laboratory Studies											
Hematology [8]	X+Fe	X+Fe			X		X	X	X		
Coagulation [8]	X	X							X		
Blood Chemistry [8]	X+TSH	X+TSH			X		X+TSH	X	X + TSH		
Pregnancy Test [9]	Day -7						X			X	
Urinalysis [10]	X	X					X		X		
Treatment w/ Study Drug											
TRC105 Dosing [11]		X Split	X Split	X	X	X	X	X			
Sorafenib [12]		Daily (28 days)					Daily (28 days)				
Tumor Assessments											
CT or MRI Scans [13]	X							X Day 22*	X		
Other Clinical Assessments											
12-Lead ECG [14]	X								X		
Concomitant Medications/Treatments [15]	X	X	X	X	X	X	X	X	X	X	
Adverse Events [16]		X	X	X	X	X	X	X	X	X	
Overall Survival [17]											X
Special Laboratory Assessments				X					X		
Pre Dose PK [18]		X		X	X	X	X (Even Cycles)	X (C2 Only)	X	X	
Anti-product antibodies [19]		X		X	X	X	X (Even Cycles)	X (C2 Only)	X	X	
Protein Biomarkers [20]		X					X (Even Cycles)		X		
Tumor Markers [21]		X					X		X		
Archival Tumor Tissue [21]	X										

Schedule of Assessments Footnotes

1. Days of Treatment with TRC105: All assessments should be performed prior to the TRC105 infusion unless otherwise indicated. Each cycle is 28 days in duration.
2. **Cycle 1 day 1**: Hematology (including iron studies), blood chemistry (including TSH testing), urinalysis, physical examination, ECG and pregnancy test not required if acceptable screening assessment is performed within 7 days prior to the start of treatment on cycle 1 day 1.
3. **End of Study**: The end of study visit should generally occur within 14 days (+/- 1 day) of the last dose of TRC105. 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 and Oncologic** History, Demographics and Baseline Signs and Symptoms: All information related to prior anticancer treatment should be recorded. Significant medical history and baseline signs and symptoms should be captured from the date of informed consent.
6. **Physical Examination**: Examination of major body systems and ECOG performance status.
7. **Vital Signs**: Heart rate, temperature, blood pressure, respiratory rate, weight. Assessment of vital signs during TRC105 Infusions: Vital signs are to be assessed pre-infusion (i.e., within 30 minutes of starting the infusion) every 30 minutes during the infusion (+/- 15 minutes) and at the end of the infusion (i.e. within 30 minutes after completing the infusion). Vital signs should be monitored more frequently and/or beyond the completion of the infusion if medically indicated (e.g. if the patient experiences an infusion reaction that has not yet resolved).
8. **Hematology, Chemistry & Coagulation**: Testing to be performed locally. Thyroid stimulating hormone to be tested at screening, day 1 of each cycle and at the end of study visit. Cycle 1 day 1 assessments only need to be performed if screening assessments were performed more than 7 days prior to cycle 1 day 1. Iron studies (FE) to be performed according to the schedule of assessments and as clinically indicated during the study. Thyroid stimulating hormone (TSH) to be performed according to the schedule of assessments and as clinically indicated during the study. Lab assessments may be performed within 3 days prior to TRC105 dosing. In addition to the assessments scheduled for the clinical trial, patients should undergo assessment as appropriate to ensure safe treatment. See Section 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. Cycle 1 day 1 urinalysis only needs to be performed if screening urinalysis was performed more than 7 days prior to cycle 1 day 1. Microscopic analysis and/or urine protein creatinine ratio or 24-hour urine protein collection should be performed as clinically indicated.
11. **TRC105 Administration**: Intravenous TRC105 diluted in normal saline will be administered every 7 days during Cycle 1. The first weekly TRC105 dose will be given on cycle 1 day 1and split into two doses whereby 3 mg/kg is administered on cycle 1 day 1 and the balance is administered on cycle 1 day 4. The entire dose of TRC105 (10 mg/kg) is then given on cycle 1 day 8, cycle 1 day 15 and cycle 1 day 22. Starting on cycle 2 day 1 and beyond, TRC105 will be administered every two weeks on days 1 and 15. See Section 7.7 for specific TRC105 administration guidelines.

12. **Sorafenib Dosing:** Oral sorafenib will be dosed twice daily on days 1-28 of each 28 day cycle according to the sorafenib package insert. See Section 7.8 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. A brain MRI or CT with contrast and bone scans to be performed at screening and on study if metastases are suspected. 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 study is +/- 7 days. Scans will be performed every 2 cycles (day 22 of cycle 2, 4, 6, 8, 10, etc.). De-identified copies of CT/MRI's, in DICOM format, may be transferred to the Sponsor if requested. Patients are eligible for treatment until progression.
14. **12-Lead ECG**: Single tracing 12-lead ECG will be performed at screening and at the time-points indicated in the Schedule of Assessments (pre-dose). If the patient develops an arrhythmia, the ECG should be repeated on day 1 of each subsequent cycle. For a QTc >500 ms, 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. **Adverse Events**: Patients must be followed for adverse events from the first day of treatment with sorafenib or TRC105 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. Baseline signs and symptoms will be recorded on corresponding case report forms. 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. **Overall Survival:** Phone call to patient every two months to determine overall survival.
18. **TRC105 and Sorafenib Pharmacokinetics Pre-Dose (Trough) Concentration:** One 5 mL blood sample and one 4 mL sample to be collected at the time-points indicated in the Schedule of Assessments, prior to dosing with sorafenib and 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.
19. **Anti-product antibodies**: 5 mL blood sample will be collected to assess anti-product antibodies at the time-points indicated in the schedule of assessments and stored at approximately -70°C to be analysed by a central laboratory. Samples will be batch shipped as indicated in the laboratory manual to a third-party laboratory. See separate laboratory guide for further collection and shipment information. Additional anti-product antibody samples may also be collected at the time of unexpected clinical events.
20. **Protein Biomarkers**: One 10 mL purple top (K3EDTA) tube will be collected at the time-points indicated in the schedule of assessments and stored at approximately -70°C to be analysed by a central laboratory. See separate laboratory guide for further collection and shipment information.

21. Tumor Marker: Blood sampling for tumor markers (i.e. AFP) will be collected and analyszed locally as indicated in the schedule of assessments.

22. Archival Tumor Tissue: Archival specimens (formalin-fixed, paraffin-embedded) are required of the primary cancer and/or metastatic cancer specimen for each study participant. It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 20 unstained slides are requested for immunohistochemical analysis (sections of 5 microns are preferred). See separate laboratory guide for further collection and shipment information.

23. 28-Day Follow-up: The follow-up visit should occur 28 days following the last dose of TRC105. The allowable visit window is +/- 7 days.

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

Table 6: Schedule of Assessments (Phase 2)

Protocol Activities	Screening	Cycle 1 **(10 mg/kg Weekly)** [23]					Cycle 2 + **(10 mg/kg Weekly)** [23]				End of Study [3]	28 Day Follow-up [23]	Long Term Follow Up (bimonthly)
	Day -28	Day 1 [1] [2]	Day 4 [1]	Day 8 [1]	Day 15 [1]	Day 22 [1]	Day 1 [1]	Day 8 [1]	Day 15 [1]	Day 22 [1]			
Baseline Documentation													
Informed Consent [4]	X												
Medical/Oncology History [5]	X												
Baseline Signs and Symptoms	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			X		X		X		X		
Coagulation [8]	X	X					X				X		
Blood Chemistry [8]	X+TSH	X+TSH			X		X+TSH		X		X + TSH		
Pregnancy Test [9]	Day -7											X	
Urinalysis [10]	X	X					X				X		
Treatment w/ Study Drug													
TRC105 Dosing [11]		X Split	X Split	X	X	X	X	X	X	X			
Sorafenib [12]		Daily (28 days)					Daily (28 days)						
Tumor Assessments													
CT or MRI Scans [13]	X									X	X		
Other Clinical Assessments													
12-Lead ECG [14]	X										X		
Concomitant Medications/Treatments [15]	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events [16]		X	X	X	X	X	X	X	X	X	X	X	
Overall Survival [17]													X
Special Laboratory Assessments				X					X		X		
Pre Dose PK [18]		X		X	X	X	X (Even Cycles)		X (C2 Only)		X	X	
Anti-product antibodies [19]		X		X	X	X	X (Even Cycles)		X (C2 Only)		X	X	
Protein Biomarkers [20]		X					X (Even Cycles)				X		
Tumor Markers [21]		X					X				X		
Archival Tumor Tissue [21]	X												

Schedule of Assessments Footnotes

1. Days of Treatment with TRC105: All assessments should be performed prior to the TRC105 infusion unless otherwise indicated. Each cycle is 28 days in duration.
2. **Cycle 1 day 1**: Hematology (including iron studies), blood chemistry (including TSH testing), urinalysis, physical examination, ECG and pregnancy test not required if acceptable screening assessment is performed within 7 days prior to the start of treatment on cycle 1 day 1.
3. **End of Study**: The end of study visit should generally occur within 14 days (+/- 1 day) of the last dose of TRC105. 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 and Oncologic** History, Demographics and Baseline Signs and Symptoms: All information related to prior anticancer treatment should be recorded. Significant medical history and baseline signs and symptoms should be captured from the date of informed consent.
6. **Physical Examination**: Examination of major body systems and ECOG performance status.
7. **Vital Signs**: Heart rate, temperature, blood pressure, respiratory rate, weight. Assessment of vital signs during TRC105 Infusions: Vital signs are to be assessed pre-infusion (i.e., within 30 minutes of starting the infusion) every 30 minutes during the infusion (+/- 15 minutes) and at the end of the infusion (i.e. within 30 minutes after completing the infusion). Vital signs should be monitored more frequently and/or beyond the completion of the infusion if medically indicated (e.g. if the patient experiences an infusion reaction that has not yet resolved).
8. **Hematology, Chemistry & Coagulation**: Testing to be performed locally. Thyroid stimulating hormone to be tested at screening, day 1 of each cycle and at the end of study visit. Cycle 1 day 1 assessments only need to be performed if screening assessments were performed more than 7 days prior to cycle 1 day 1. Iron studies (FE) to be performed according to the schedule of assessments and as clinically indicated during the study. Thyroid stimulating hormone (TSH) to be performed according to the schedule of assessments and as clinically indicated during the study. Lab assessments may be performed within 3 days prior to TRC105 dosing. In addition to the assessments scheduled for the clinical trial, patients should undergo assessment as appropriate to ensure safe treatment. See Section 8.1.1.1 for specific panel collection requirements.
9. **Pregnancy Tes**t: 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. Cycle 1 day 1 urinalysis only needs to be performed if screening urinalysis was performed more than 7 days prior to cycle 1 day 1. Microscopic analysis and/or urine protein creatinine ratio or 24-hour urine protein collection should be performed as clinically indicated.
11. **TRC105 Administration**: Intravenous TRC105 diluted in normal saline will be administered every 7 days. The first weekly TRC105 dose will be given on cycle 1 day 1and split into two doses whereby 3 mg/kg is administered on cycle 1 day 1 and the balance is administered on cycle 1 day 4. The entire dose of TRC105 (10 mg/kg) is then given on cycle 1 day 8, cycle 1 day 15, cycle 1 day 22 and weekly thereafter. See Section 7.7 for specific TRC105 administration guidelines.
12. **Sorafenib Dosing:** Oral sorafenib will be dosed twice daily on days 1-28 of each 28 day cycle according to the sorafenib package insert. See Section 7.8 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. A brain MRI or CT with contrast and bone scans to be performed at screening and on study if metastases are suspected. 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 study is +/- 7 days. Scans will be performed every 2 cycles (day 22 of cycle 2, 4, 6, 8, 10, etc.). De-identified copies of CT/MRI's, in DICOM format, may be transferred to the Sponsor if requested. Patients are eligible for treatment until progression.
14. **12-Lead ECG**: Single tracing 12-lead ECG will be performed at screening and at the time-points indicated in the Schedule of Assessments (pre-dose). If the patient develops an arrhythmia, the ECG should be repeated on day 1 of each subsequent cycle. For a QTc >500 ms, 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. **Adverse Events**: Patients must be followed for adverse events from the first day of treatment with sorafenib or TRC105 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. Baseline signs and symptoms will be recorded on corresponding case report forms. 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. **Overall Survival:** Phone call to patient every two months to determine overall survival.
18. **TRC105 and Sorafenib Pharmacokinetics Pre-Dose (Trough) Concentration:** One 5 mL blood sample and one 4 mL sample to be collected at the time-points indicated in the Schedule of Assessments, prior to dosing with sorafenib and 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.
19. **Anti-product antibodies**: 5 mL blood sample will be collected to assess anti-product antibodies at the time-points indicated in the schedule of assessments and stored at approximately -70°C to be analysed by a central laboratory. Samples will be batch shipped as indicated in the laboratory manual to a third-party laboratory. See separate laboratory guide for further collection and shipment information. Additional anti-product antibody samples may also be collected at the time of unexpected clinical events.
20. **Protein Biomarkers**: One 10 mL purple top (K3EDTA) tube will be collected at the time-points indicated in the schedule of assessments and stored at approximately -70°C to be analysed by a central laboratory. See separate laboratory guide for further collection and shipment information.
21. **Tumor Marker:** Blood sampling for tumor markers (i.e. AFP) will be collected and analyszed locally as indicated in the schedule of assessments.

22. Archival Tumor Tissue: Archival specimens (formalin-fixed, paraffin-embedded) are required of the primary cancer and/or metastatic cancer specimen for each study participant. It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 20 unstained slides are requested for immunohistochemical analysis (sections of 5 microns are preferred). See separate laboratory guide for further collection and shipment information.

23. 28-Day Follow-up: The follow-up visit should occur 28 days following the last dose of TRC105. The allowable visit window is +/- 7 days.

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

6. SELECTION AND WITHDRAWAL OF PATIENTS

6.1. Patient Inclusion Criteria

6.1.1. Inclusion Criteria:

1. Patients must have confirmed hepatocellular carcinoma (HCC) by either histopathology or radiography. Diagnosis of HCC can be made without a biopsy if radiographic hallmarks of arterial hypervascularity and venous/late phase washout are present by either dynamic contrast-enhanced MRI or helical multidetector CT scan using contrast for a lesion ≥ 2 cm, or by both modalities for a lesion 1-2 cm. [2].
2. Patients must have disease that is not amenable to potentially curative resection or ablative techniques or that has recurred following ablative techniques. In addition, disease must not be amenable to transhepatic arterial chemoembolization (TACE) or must have progressed TACE. Patients must not be candidates for liver transplantation.
3. Patient must have a Child-Pugh A or B (7 points) classification
4. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, or adequately treated Stage I or II cancer from which the patient is currently in complete remission per investigators' clinical judgment.
5. Measurable disease by RECIST 1.1 (Phase 2 only)
6. Age of 18 years or older
7. ECOG performance status ≤ 1
8. Resolution of all acute adverse events resulting from prior cancer therapies to NCI CTCAE grade ≤ 1 or baseline (except alopecia)
9. Adequate organ function as defined by the following criteria:
    - AST and ALT ≤ 5 x ULN
    - Absolute neutrophil count (ANC) ≥ 1500/μL
    - Platelets ≥ 60,000/μL without transfusion support within the past 28 days
    - Hemoglobin ≥ 9.0 g/dL without transfusion support within the past 14 days (erythropoietin or darbepoietin permitted)
    - Serum creatinine clearance > 30 mL/min by Cockcroft-Gault formula
10. Willingness and ability to consent to participate in study
11. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
12. Men who are sterile (including vasectomy confirmed by post vasectomy semen analysis) OR agree to use at least two forms of a reliable and highly effective method of birth

control (refer to Section 3.5.2.1) and to not donate sperm and for at least 180 days following last dose of TRC105 or sorafenib.

13. Woman of non-child bearing potential due to surgical sterilization (at least 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by medical history or menopause (i.e., no menstrual bleeding for more than 12 months in a women aged 45 years or more), OR woman of child bearing potential who test negative for pregnancy at time of enrollment based on serum pregnancy test and agree to use at least 2 forms of a reliable and highly effective method of birth control during the study and for at least 180 days after stopping TRC105 or sorafenib (refer to Section 3.5.2.1)

6.1.2. Exclusion Criteria:

1. Prior anticancer systemic therapy
2. Current treatment on another therapeutic clinical trial
3. 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
4. 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, thorascopy, tube thoracostomy, bronchoscopy, endoscopic ultrasonographic procedures, mediastinoscopy, skin biopsies, incisional biopsies, imaging-guided biopsy for diagnostic purposes, and routine dental procedures
5. Proteinuria, as demonstrated by a 24-hour protein of ≥ 2000 mg. Urine protein will be screened by urine protein-creatinine ratio (UPC). For UPC ratio > 1.0, a 24-hour urine protein will need to be obtained and the level should be < 2000 mg for patient enrollment.
6. Uncontrolled chronic hypertension defined as systolic > 150 or diastolic > 90 on more than one measurement despite optimal therapy (initiation or adjustment of BP medication prior to study entry is allowed provided that the average of 3 BP readings prior to enrollment is < 150/90 mm Hg)
7. 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.
8. Angina, MI, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack, arterial embolism, pulmonary embolism, PTCA or CABG within the past 6 months.
9. Active bleeding or pathologic condition that carries a high risk of bleeding (e.g. hereditary hemorrhagic telangiectasia). No bleeding diathesis.

10. Thrombolytic use (except to maintain i.v. catheters) within 10 days prior to first day of study therapy
11. History of hemorrhage or hemoptysis (> ½ teaspoon bright red blood) within 3 months of starting study treatment
12. Need for anticoagulation
13. History of liver transplant
14. History of bleeding esophageal varices in previous 6 months, which have not been adequately managed with banding or sclerotherapy (i.e., following treatment, varices must be ≤ grade 1 with no stigmata of recent bleeding). Patients with cirrhosis must have had esophagogastric endoscopy within the past 6 months prior to study entry for the assessment of varices, and esophageal varices must be ≤ grade 1 with no stigmata of recent bleeding. Those with gastric varices that are deemed as high risk by the endoscopist should be placed on appropriate medical therapy as advised by the gastroenterologist.
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. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness
17. Patients may not have received a strong CYP3A4 inducer within 12 days prior to registration (Table 19)
18. Patients with known hypersensitivity to Chinese hamster ovary products or other recombinant human, chimeric, or humanized antibodies.
19. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for this study
20. Ascites or pleural effusion requiring intervention or that required intervention within the last month and has recurred
21. Pericardial effusion (except trace effusion identified by echocardiogram)

6.2. 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 5). 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) unless discussed with sponsor.
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 > 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 sorafenib dosing held concurrently). Patients who cannot tolerate sorafenib and who demonstrate a response of complete response (CR), partial response (PR) or stable disease (SD) and are thought to benefit from continued single agent TRC105 therapy may continue on study on TRC105 alone.

7. TREATMENT OF PATIENTS

7.1. 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.

7.2. Composition of TRC105

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

7.3. TRC105 Dose Level

7.3.1. Phase 1b

Each patient will be dosed with 10 mg/kg weekly during cycle 1 then, 10 mg/kg (Dose Level -1) or 15 mg/kg (Dose Level 1) every two weeks thereafter of each 28 day cycle beginning with cycle 2 in the phase 1b portion and 10 mg/kg weekly in Phase 2. 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 10 mg/kg dose is 850 mg and at the 15 mg/kg dose is 1275 mg. The maximum dose that should be given to a man at the 10 mg/kg dose is 1000 mg and the 15 mg/kg dose is 1,500 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. The first 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 (i.e., 7 mg/kg), in both Phase 1b and 2. Patients enrolled into the Phase 1b Dose Level -1 or Dose Level 1 will receive the entire dose of TRC105 (i.e. 10 or 15 mg/kg respectively) starting on cycle 2 day 1 and every two weeks thereafter of each subsequent 28 day cycle.

As outlined in Section 3.5 10 mg/kg of TRC105 weekly is the recommended phase 2 dose. Ongoing patients in the Phase 1b portion of this study may, at the discretion of the investigator, be treated at the Phase 2 TRC105 dose of 10 mg/kg weekly.

7.3.2. Phase 2

Patients enrolled in the Phase 2 portion of the trial will receive 10 mg/kg weekly (see Section 3.5 for dose selection rational).

7.4. TRC105 Packaging and Labeling

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

200 mg TRC105/8 mL single-use vial

400 mg TRC105/16 mL single-use vial

7.5. TRC105 Storage and Shipping

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

7.6. TRC105 Preparation

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

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

The volume of TRC105 that is to be administered can be rounded up or down to the nearest 1.0 mL; in the case of an increment of 0.5 mL the volume should be rounded up. **The maximum weight that should be used for dose calculation in this study is 85 kg 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.

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

7.7. TRC105 Administration

Patients should be encouraged to drink abundant fluid (e.g., two eight-ounce glasses of water or juice) prior to the first treatment. 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 and completed 2 hours to 30 minutes prior to the start of each infusion as described below:

Phase 1b Dose Levels -1, 1 (10 mg/kg weekly C1, and 10 or 15 mg/kg every 2 weeks C2+) and Phase 2 (10 mg/kg weekly)

- Acetaminophen 650 mg p.o. x 1
- Famotidine 20 mg i.v. or p.o. (or similar H2 blocker) x 1. Famotidine or similar H2 bloacker may be discontinued begining with cycle 2 in the absence of an infusion reaftion with the previous dose
- Cetirizine 10 mg i.v. or p.o. x 1 (or similar oral or intravenous antihistamine). Ceterizine or similar antihistamine may be discontinued begining with cycle 2 in the absence of an infusion reaftion with the previous 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 $\geq$ 10 days between any weekly doses or $\geq$ 17 days between any two TRC105 doses or if the patient develops an infusion reaction $\geq$ grade 2 during the immediate prior infusion.
- Anti-emetic treatment, while not required, may be given prior to the initial dose and subsequent doses to reduce the frequency of nausea and vomiting that may be observed during TRC105 infusions.

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 (e.g., 7 mg/kg) and infused over a period of 2 hours (+/- 15 minutes). The full cycle 1 dose (i.e., 10 mg/kg) will be administered on cycle 1 day 8 and infused over 1 hour (+/- 15 minutes) and every week thereafter for the remainder of cycle 1 (and cycle 2 in the phase 2 portion). The full every two week TRC105 dose for patients in phase 1b Dose Level -1 and 1 (10 mg/kg or 15 mg/kg) and weekly dosing for patients in phase 2 will be administered on cycle 2 day 1 and infused over 1

hour (+/- 15 minutes) in the absence of infusion reaction with the prior dose 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). Starting on cycle 2 day 1, TRC105 will be administered at 10 mg/kg or 15 mg/kg over 1 hour (+/- 15 minutes). Patients with infusion reactions of any kind should be managed appropriately (see Section 7.7.2) 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 minimum infusion duration for Dose Level 1 is 1 hour (60 minutes +/- 15 minutes).

Table 7: Ideal TRC105 Dosing Schema for Phase 1b Dose Levels -1 and 1 (10 mg/kg weekly C1, 10 or 15 mg/kg every 2 weeks C2+)

	C1D1	C1D4	C1D8	C1D15	C1D22	C2D1	C2D15	C3D1+
TRC105 Dose level -1: 10mg/kg weekly C1 and 15 mg/kg every 2 weeks C2+	3	7	10	10	10	10	10	10
Infusion Duration (hours)	4	2	1	1	1	1	1	1
TRC105 Dose level 1: 10mg/kg weekly C1 and 15 mg/kg every 2 weeks C2+	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	0	0	0
Famotidine (mg)	20	20	20	20	20	0	0	0
Cetirizine (mg)	10	10	10	10	10	0	0	0
Acetaminophen (mg)	500 - 1000	500 - 1000	500 - 1000	500 - 1000	500 - 1000	500 - 1000	500 - 1000	500 - 1000

Table 8: Ideal TRC105 Dosing Schema for Phase 2 (10 mg/kg weekly C1+)

	C1D1	C1D4	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22
TRC105 Dose level -1: 10mg/kg weekly	3	7	10	10	10	10	10	10	10

Infusion Duration (hours)	4	2	1	1	1	1	1	1	1
Methylprednisolone (mg)	100	100	0	0	0	0	0	0	0
Famotidine (mg)	20	20	20	20	20	0	0	0	0
Cetirizine (mg)	10	10	10	10	10	0	0	0	0
Acetaminophen (mg)	500 - 1000	500 - 1000	500 - 1000	500 - 1000	500 - 1000	500 - 1000	500- 1000	500 - 1000	500- 1000

7.7.1. TRC105 Dose Reduction/Dose Delays

TRC105 dose reductions and interruptions should be avoided in cycle 1 and 2. In cycle 3 and beyond, TRC105 dose reductions are allowed for grade 3 or 4 related adverse events that resolve to ≤ grade 2 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 sorafenib dosing cannot both be held at the same time for > 8 consecutive weeks). However, patients who cannot tolerate sorafenib 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 alone per Section 6.2 of the protocol.

Table 9: Allowable TRC105 Dose Modifications

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

[a]After discussion with and agreement of the Sponsor, patients receiving TRC105 every two weeks have the option to return to weekly dosing 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.

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.
- The patient has a platelet count > 60,000.
- 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).

TRC105 and sorafenib 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. For **minor procedures** (e.g., port placement), TRC105 (and sorafenib) should be held for at least 1 week prior and for at least 1 week after (or until adequate healing).

TRC105 DOSING DELAY: If a patient misses a scheduled weekly TRC105 dose and dosing is resumed ≥ 10 days after the last dose or if a patient misses a scheduled every-2-week dose and dosing is resumed ≥ 17 days after the last dose, premedication (including methylprednisolone) and TRC105 are to be administered as described in Table 10. **Split dosing is not required.** However, it is recommended that if the patient experienced a severe headache with a previous infusion, the first TRC105 dose upon resumption should be administered over two days as was done for the initial dose, see Table 11.

Table 10: TRC105 dosing after Dose Delay (with no split dosing)

	CxDy	**CxDy**	**CxDy**	**CxDy**	**CxDy+**
TRC105 Dose (mg/kg)	10 or 15	10 or 15	10 or 15	10 or 15	10 or 15
Infusion Duration (hours)	4	2	1	1	1
Premedication					
Methylprednisolone (mg)	100	0	0	0	0
Famotidine (mg)	20	20	20	20	0
Cetirizine (mg)	10	10	10	10	0
Acetaminophen (mg)	650	650	650	650	650

Note that acetaminophen should NOT be discontinued.

Table 11: TRC105 Dosing after Dose Delay (with split dosing)

	Day 1 resuming TRC105	3 days later	Weekly or every 2 weeks from Day 1	Weekly or every 2 weeks	CxDy+
TRC105 Dose (mg/kg)	3	7 or 12	10 or 15	10 or 15	10 or 15
Infusion Duration (hours)	4	2	1	1	1
Premedication					
Methylprednisolone (mg)	100	100	0	0	0
Famotidine (mg)	20	20	20	20	0
Cetirizine (mg)	10	10	10	10	0
Acetaminophen (mg)	650	650	650	650	650

Note that acetaminophen should NOT be discontinued.

The schedule of assessment should be followed with regards to visits, labs, and any other required assessments even if TRC105 dosing is held.

7.7.2. Management of TRC105 Infusion Reactions

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

Table 12: Management of TRC105 Infusion Reactions

Infusion Reaction Severity	Recommended Management
Grade 1 (mild)	1. No intervention 2. Continue infusion unless symptoms worsen

Infusion Reaction Severity	Recommended Management
Grade 2 (moderate)	1. Interrupt infusion 2. Treat with symptomatic medications[a] 3. Resume infusion at half the previous rate when infusion-related symptoms improve to grade 1 or less.
Grade 3 (severe)	1. Interrupt infusion 2. Treat with symptomatic medications[a] 3. Monitor patient until infusion-related symptoms resolve, including hospitalization if necessary 4. Discontinue TRC105 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. Permanently discontinue TRC105

[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).

7.7.3. TRC105 Study Drug Accountability

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

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

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

7.7.4. TRC105 Study Drug Handling and Disposal

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

7.8. Description of Sorafenib

See sorafenib package insert.

7.8.1. Composition of Sorafenib

See sorafenib package insert.

7.8.2. Sorafenib Dose Level

Each patient will be dosed initially with 400 mg of sorafenib twice per day for each day of a 28 day cycle. Dose de-escalation is permitted per the package insert starting in cycle 1.

7.8.3. Sorafenib Packaging and Labeling

See sorafenib package insert.

7.8.4. Sorafenib Storage Handling and Disposal

See sorafenib package insert.

7.8.5. Sorafenib Dosing

The oral dose of sorafenib is 400 mg (2 tablets) twice daily of each 28 day cycle (for a total of 4 tablets each day). Sorafenib tablets should be taken without food (at least 1 hour before or 2 hours after a meal). Patients are to swallow the tablets whole with approximately 250 ml (8 oz) of water, each morning and evening (i.e., approximately 12 hours apart).

7.8.6. Sorafenib Dose Modification

Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of sorafenib therapy. Dose reduction is allowed based on individual safety and tolerability starting in cycle 1 as outlined below and in accordance with sorafenib package insert.

Doses will be delayed or reduced for clinically significant hematologic and non-hematologic toxicities that are related to sorafenib according to the guidelines that follow.

Dose modifications will follow predefined dose levels in Table 13. Dose adjustments for hematologic toxicity are based on blood counts obtained in preparation for the day of treatment.

Table 13: Sorafenib Dose Modification Levels

Dose	Sorafenib

Starting Dose	400 mg twice daily
-1	400 mg once daily
-2	400 mg every other day

Table 14: Dose Modification for Hematologic Toxicities

Recommended Dose Modification for Hematologic Toxicities				
Toxicity	**ANC/AGC (x 109/L)**	**Hemoglobin (g/dL)**	**Platelets (x 109/L)**	**Sorafenib**
Grade 1	≥ 1.5	< LLN – 10.0	≥ 75	Treat on time No change
Grade 2	≥ 1.0 to < 1.5	< 10.0 – 8.0	≥ 50 to < 75	Treat on time No change
Grade 3	≥ 0.5 to < 1.0	< 8.0 – 6.5	≥ 25 to < 50	Treat on time Reduce by one dose level
Grade 4	< 0.5	Life-threatening consequence; urgent intervention indicated	<25	Delay sorafenib until toxicity resolves to Grade 2 or less then Reduce by two dose levels
Febrile Neutropenia				Sorafenib held until toxicity has resolved to Grade 2 or less; when sorafenib is restarted, reduce by one dose level

ANC - absolute neutrophil count; AGC - absolute granulocyte count

[a]If no recovery after 28 day delay, treatment should be permanently discontinued unless treating physician determines subject is deriving clinical benefit.

Table 15: Dose Modification for Non-hematologic Toxicities

Recommended dose modification for non-hematologic toxicity (excluding hypertension and hand foot skin reaction, diarrhea and fatigue)		
Grade	**Dose Interruption**	**Dose Modification**
Grade 0-2	Treat on time	No Change
Grade 3	Interrupt until ≤Grade 2	Reduce one dose level
Grade 4	OFF protocol therapy	OFF protocol therapy

[a]If no recovery after 28 day delay, treatment will be discontinued unless subject is deriving clinical benefit.

Prevention/management strategies for diarrhea and fatigue

Diarrhea and fatigue are common side effects of sorafenib. The same dose-modification algorithm used for skin toxicities can be used to address these toxicities. However, the preventive/management strategies for diarrhea and fatigue should be consistent with local standards (e.g., anti-diarrheals and optimized hydration status for diarrhea).

Table 16: Dose Modifications for Hand-Foot-Skin Reaction

Recommended dose modification for hand foot skin reaction		
Toxicity Grade		**Suggested dose modification**
Grade 1	Any occurrence	Maintain dose level and consider topical therapy for symptomatic relief
Grade 2	1st occurrence	Maintain dose level and consider topical therapy for symptomatic relief If no improvement within 7 days, see below
	No improvement within 7 days or 2nd occurrence	Interrupt until resolved to Grade 0-1 When resuming treatment, reduce dose by one dose level
	3rd occurrence	Interrupt until resolved to Grade 0-1 When resuming treatment, reduce dose by two dose levels
	4th occurrence	Discontinue treatment permanently
Grade 3	1st occurrence	Interrupt until resolved to Grade 0-1 When resuming treatment, reduce dose by one dose level
	2nd occurrence	Interrupt until resolved to Grade 0-1 When resuming treatment, reduce dose by two dose levels
	3rd occurrence	Discontinue treatment permanently

At first occurrence of HFSR, independent of grade, prompt institution of supportive measures such as topical emollients, low potency steroids, or urea-containing creams should be administered.

Table 17: Recommended Prevention/Management Strategies for Skin Toxicities Consistent With HFSR

Toxicity Grade	Practical Prevention / Management Strategies for HFSR
Grade 0 (Preventive strategies)	• Maintain frequent contact with trial physician to ensure early diagnosis of HFSR. • Practical prevention strategies o Pedicure[a] for subjects with pre-existing hyperkeratosis. o Subjects should avoid hot water, and clothing or activities that can cause friction on the skin. o Moisturizing cream should be applied sparingly. • Padded gloves and open shoes with padded soles should be worn to relieve pressure points.
Grade 1 Any occurrence	• Continue preventive strategies and in addition: o Soak hands in cool water. o Apply petroleum jelly to moist skin. • In the case of hyperkeratotic lesions, exfoliate the hands or feet and apply moisturizing cream immediately afterwards.
Grade 2 Any occurrence or Grade 3 Any occurrence	• Continue supportive/management measures and add analgesic(s) for pain.

[a]Pedicure should be done by a podiatrist.

Treatment-emergent hypertension

Hypertension is a known and potentially serious adverse event associated with sorafenib treatment. Subjects will check blood pressure at home, on a weekly basis through the first 4 weeks of therapy. Thereafter, blood pressure will be monitored at each clinic visit. Subjects with pre-existing hypertension will monitor blood pressure at home daily basis.

Blood pressure measurements that are out of the normal range must be reported by the treating physician. Blood pressure measurements considered out of the normal range are diastolic pressure > 90 mm Hg and/or systolic pressure > 140 mm Hg, or a 20 mm Hg increase in diastolic pressure if the previous measurement was within normal limits.

The dose-modification schedule to be followed in the event of treatment-emergent hypertension is outlined below. The choice of anti-hypertensive medication to be used in cases of treatment-emergent hypertension will be at the investigator's discretion and based on site-specific treatment guidelines as applicable. All anti-hypertensive medications used for the management of treatment-emergent hypertension should be recorded in the subject's records and pertinent CRFs.

Once a dose-reduction modification has been made for treatment-emergent hypertension, NO dose re-escalation will be allowed.

Table 18: Management of Treatment-Emergent Hypertension

Grade of Event (NCI-CTCAE v4.0)	Management/ Next Dose
Grade 1	Consider increasing blood pressure monitoring. Continue sorafenib dosing as scheduled.
Grade 2 asymptomatic and diastolic pressure 90-99 mm Hg	Begin anti-hypertensive therapy. Continue sorafenib dosing as scheduled.
Grade 2 (symptomatic/persistent) OR Grade 2 symptomatic increase by > 20 mm Hg (diastolic) or to > 140/90 mm Hg if previously within normal limits OR Grade 3	Sorafenib should be held[a] until symptoms resolve and diastolic blood pressure < 90 mm Hg; also treat subject with anti-hypertensives and when sorafenib is restarted, reduce by 1 dose level[b] If diastolic blood pressure is not controlled (< 90 mm Hg) on anti-hypertensive therapy, reduce another dose level[b]
Grade 4	Discontinue sorafenib

[a]Subjects requiring a delay of > 28 days should discontinue sorafenib unless, in the opinion of the treating physician, the subject may benefit from continued treatment.
[b]Subjects requiring dose reductions beyond 400 mg once daily, every other day, should discontinue sorafenib.

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

Patients who cannot tolerate sorafenib 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.

7.8.7. Sorafenib Drug Accountability

Patients will be asked to bring their sorafenib prescription bottle to the clinic at the beginning of each cycle for proper drug accountability and destruction in accordance with institution guidelines. A new prescription will be dispensed at the beginning of each new cycle.

7.9. 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.

The concomitant use of strong CYP3A4/5 inducers is strongly discouraged and should be avoided (Table 19) as they may decrease sorafenib plasma concentrations. Patients may not have received a strong CYP3A4 inducer within 12 days prior to registration (see eligibility.

Table 19: Strong CYP3A4 Inducers and Inhibitors[a]

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/

Furthermore, patients taking narrow therapeutic index medications, (e.g. quinidine or digoxin) should be monitored proactively.

Sorafenib has the ability to inhibit a variety of liver metabolic enzymes in vitro. The clinical impact of this inhibition in humans taking drugs metabolized by these enzymes is unknown. Therefore, all patients enrolled onto this trial who are taking concomitant medications that are known to be metabolized by the liver should be closely observed for side effects of these concomitant medications.

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 > 60,000.
- 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).

7.10. Treatment Compliance

7.10.1. TRC105 Treatment Compliance

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

7.10.2. Sorafenib Treatment Compliance

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

7.11. Patient Enrollment

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

8. ASSESSMENT OF EFFICACY

8.1. Radiological Tumor Assessment

The primary efficacy assessment for phase 1b is best overall response and progression free survival (defined as time from screening to either first disease progression or death from any cause, patients alive at the time of analysis will be censored at the date of last disease assessment) by RECIST 1.1. The primary efficacy assessment for phase 2 will be best overall response, including duration of response by RECIST 1.1 in as defined in Section 8.1.2. The determination of antitumor efficacy will be based on objective tumor assessments made by the Investigator according to RECIST version 1.1 [48]. Investigators will make treatment decisions based on these assessments. All lesions will be classified as target or non-target lesions at the Screening visit. Each lesion designation will be maintained through the course of the study.

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

Whenever possible, clinical evaluation of superficial lesions should not be used as the sole form of measurement. However, when necessary, color photograph with metric caliper 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 5), 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. De-identified copies of MRI's, in DICOM format, may be transferred to the Sponsor if requested

8.1.1. 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).

8.1.1.1. Recording Tumor Measurements

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

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

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present", "complete response", "non-CR/non-PD" or "progressive disease".

8.1.2. Definitions of Tumor Response

8.1.2.1. Target Lesions

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

8.1.2.2. Non-Target Lesions

- **Complete response (CR)** is defined as the disappearance of all non-target lesions.
- **non-CR/non-PD** is defined as a persistence of $\geq$ 1 non-target lesions.

- **Progressive disease (PD)** is defined as unequivocal progression of existing non-target lesions, or the appearance of ≥ 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.

8.1.2.3. Determination of Overall Response

8.1.2.4. Determination of Overall Response by the RECIST Criteria

When both target and non-target lesions are present, individual assessments will be recorded separately. The overall assessment of response will involve all parameters as depicted in Table 20 below. Per RECIST 1.1, as this is a non-randomized trial with response is a primary endpoint, confirmation of PR or CR is required. Per RECIST 1.1, a modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

Table 20: Response Evaluation Criteria in Solid Tumors

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

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

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.

9. ASSESSMENT OF SAFETY

9.1. 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 4.03), 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, ECG will be performed at the time-points indicated in the Schedule of Assessments (Table 5) and as clinically indicated throughout the study.

9.1.1. 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.).

9.1.1.1. Hematology, Serum Chemistry, Coagulation, Pregnancy Test

Assessments will be performed at the time points indicated in the Schedule of Assessments (Table 5) 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. Patients must be surgically sterile (i.e., hysterectomy) or be postmenopausal, or must agree to use two methods of effective and highly reliable contraception at the same time [i.e., tubal sterilization (tubes tied), partner's vasectomy, intra-uterine device (IUD), male latex condom with or without spermicide, diaphragm with spermicide, cervical cap with spermicide, vaginal sponge (contains spermicide)] during study treatment (including during temporary breaks from treatment), and for at least 180 days after stopping TRC105.

9.1.1.2. Urinalysis

Urinalysis (without microscopic analysis, unless indicated) will be performed at time points indicated in the Schedule of Assessments (Table 5) and analyzed by local laboratories. Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated.

9.1.1.3. Physical Examination

A physical examination including, but not limited to, general appearance, head, eyes, ears, nose, throat, neck, heart, chest, abdomen, musculoskeletal, extremities, skin, lymph nodes, neurological genitourinary (as appropriate), and rectal (as appropriate) will be assessed at time points indicated within the Schedule of Assessments (Table 5). The physical examination will include examination of known and suspected sites of disease.

9.1.1.4. Vital Signs

Heart rate, temperature, blood pressure, respiratory rate and weight will be assessed at time points indicated within the Schedule of Assessments (Table 5). Heart rate, temperature, blood pressure, and respiratory rate will also be assessed during TRC105 infusions as described in Section 5.1.2.2 and the footnotes of the Table 5.

9.1.1.5. Performance Status

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

9.1.1.6. ECG

A single 12-lead (with a 10–second rhythm strip) tracing will be used for all ECGs. It is preferable that the machine used has a capacity to calculate standard intervals automatically. ECG will be performed at the time-points indicated in the Schedule of Assessments (Table 5) and as clinically indicated throughout the study

9.2. Adverse Events

All observed or volunteered AEs regardless of suspected causal relationship to study drug will be reported as described below. Medications administered and all other actions taken to treat the event, the outcome, and any recurrence upon re-challenge will be captured.

9.2.1. Definition of Adverse Event

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

- Clinically significant symptoms and signs including:
    - Signs and symptoms resulting from drug overdose, abuse, misuse, withdrawal, sensitivity, dependency, interaction or toxicity.

- All possibly related and unrelated illnesses, including the worsening of a preexisting illness.
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (hip fracture from a fall secondary to dizziness), the medical condition (dizziness) and the outcome of the accident (hip fracture from a fall) should be reported as 2 separate 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 AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.):
  - Test result that is associated with accompanying symptoms
  - Test result that requires additional diagnostic testing or medical/surgical intervention
  - Test result that leads to a change in study drug dosing outside of protocol-stipulated dose adjustments or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy
  - Test result that is considered to be an AE by the Investigator or TRACON

9.2.2. Serious Adverse Events

An AE that meets one or more of the following criteria/outcomes is classified as 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 human rights act 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 SAE with NCI CTC grade 5.

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

9.2.2.1. Hospitalization

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

- 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 procedure).

9.3. Reporting Adverse Events

9.3.1. Eliciting Adverse Event Information

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

9.3.2. Adverse Event Reporting Period

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

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

9.3.3. Reporting Requirements

Each AE is to be classified by the Investigator as SERIOUS or NONSERIOUS (Section 9.2.2 for SAE definition). This classification of the event determines the reporting procedures to be followed. If an SAE occurs, reporting will follow local and international regulations, as appropriate.

The Investigator must notify the Sponsor of any AE that meets one of the criteria for an SAE immediately upon learning of the event. Any subsequent revisions that are made to information pertaining to SAEs (e.g., change in seriousness criteria, relationship to study drug, etc.) should be communicated to TRACON immediately. This notification should be made to:

Primary Medical Monitor

Charles Theuer, MD, PhD

TRACON Pharmaceuticals, Inc.

4350 La Jolla Village Drive, Suite 800

San Diego, California 92122

Office Phone: 1.858.550.0780 x233

Cell Phone: 1.858.344.9400

Email: ctheuer@traconpharma.com

Secondary Medical Monitor

James Freddo, MD

TRACON Pharmaceuticals, Inc.

4350 La Jolla Village Drive, Suite 800

San Diego, California 92122

Cell Phone: 1.858.472.2330

Email: jfreddo@traconpharma.com

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 AE 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.

SAEs that are unexpected and associated with use of the study medication will be reported to the US Food and Drug Administration (FDA) and all participating clinical sites by TRACON via MedWatch or CIOMS forms. For AEs that are fatal or life-threatening, unexpected, and associated with use of the investigational product, a 7-Day Alert Report will be submitted to the FDA within 7 calendar days of receipt of the SAE information. For all other AEs 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 AEs, including SAEs, are to be reported on the AE CRFs.

9.3.4. Recording Adverse Events in the Case Report Forms

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

9.3.5. Grading of Adverse Event Severity

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

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

Table 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 AE. A severe AE is not necessarily a serious AE. 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.

9.3.6. Relationship to TRC105 Study Drug/Sorafenib

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

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

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

9.3.7. Expectedness

All TRC105 AEs 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 AEs 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 sorafenib AEs 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 AEs 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 sorafenib.

9.3.8. Exposure *in Utero*

An exposure *in utero* (EIU) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (e.g., environmental exposure) the investigational product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational product (maternal exposure)
- A male has been exposed, either due to treatment or environmental, to the investigational product prior to or around the time of conception and/or is exposed during the partner's pregnancy (paternal exposure)

A pregnant patient will be withdrawn from the study. If any trial patient becomes or is found to be pregnant during the study or within 28 days of discontinuing the investigational medication/product, the Investigator must report the information to TRACON, or designee via the Pregnancy Notification Report Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery.

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

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

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

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

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

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

9.3.9. Follow-up of Unresolved Adverse Events

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

All serious and those non-serious AEs assessed by the Investigator as possibly related to the investigational medication/product should continue to be followed even after the patient's participation in the trial is over. Such events should be followed until they resolve or until the Investigator assesses them as chronic or stable; every effort should be made to make this determination by the 28 day follow-up visit.

9.4. 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 AEs 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.

10. OTHER ASSESSMENTS

10.1. Other Laboratory Assessments

10.1.1. Pharmacokinetics

Samples will be sent to Fisher BioServices (Franklin, MA 02038). See separate laboratory manual for specific collection, storage and shipping information.

10.1.1.1. TRC105 Trough Concentration

A 5 mL blood sample will be collected prior to dosing with TRC105 on the days indicated within the Schedule of Assessments (Table 5). 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. 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.

10.1.1.2. Sorafenib Trough Concentration

A 4 mL blood sample will be collected prior to dosing with sorafenib on the days indicated within the Schedule of Assessments (Table 5). 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.

10.1.2. TRC105 Immunogenicity

Samples will be sent to Fisher BioServices (Franklin, MA 02038) 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 time points specified in the Schedule of Assessments (Table 5) 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 Fisher BioServices. See separate laboratory guide for further collection and shipment information.

10.1.3. Protein Biomarkers

One 10 mL purple top (K_2EDTA) tube of blood will be collected on the days indicated within the Schedule of Assessments (Table 5). Samples will be stored at approximately -70 °C and shipped to Fisher BioServices Inc. (10 Forge Park, Franklin, MA 02038) for storage until the time of analysis. Duke University Medical Center will analyze plasma for several biomarkers including but not limited to VEGF, 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.

10.1.4. 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 Fisher BioServices Inc. (10 Forge Park, Franklin, MA 02038) for storage until the time of analysis. See separate laboratory guide for further collection and shipment information.

11. STATISTICS

11.1. Phase 1b

11.1.1. Phase 1b 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 6 patients will be treated in the phase 1b portion of the 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%.

The maximum tolerated dose (MTD) will have been exceeded if ≥ 33% of patients experience DLT at a given dose level in which at least 6 patients have been evaluated.

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

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

11.1.1.1. Phase 1b Definition of Analyzed Study Populations

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

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

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

Only those patients who are deemed ineligible or who receive no therapy (i.e. no TRC105 or sorafenib) 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.

11.2. Phase 2

11.2.1. Phase 2 Statistical Design/Sample Size

Efficacy Analysis

The primary endpoint of the phase 2 study is objective response (CR or PR) at any time during treatment. The sample size is determined using Simon's two-stage minimax design. This design will be used to test the null hypothesis that the true objective tumor response rate is < 5% versus the alternative hypothesis that the true response rate is > 20%.

One or more responses by RECIST 1.1 must be observed in the initial 12 patients enrolled to enroll the second stage, to a total of 21 patients. Three or more responses by RECIST of 21 patients will be considered sufficiently interesting to warrant further study in later trials.

Sample size justification

With an alpha level of 0.1 and 80% power, a maximum of 21 treated patients will be required to evaluate the ORR. Twelve patients will be treated in stage 1. If < 1 objective response is observed in the first 12 patients, then the trial will be terminated, and the alternative hypothesis that the true ORR probability is $\geq$ 20 % will be rejected. However, if one or more responses are observed in the first 12 patients, then the study will be expanded to enroll a total of 21 treated patients (9 additional patients to be treated in stage 2). At the end of the study, if $\geq$ 3 objective responses are observed then the null hypothesis that the true response rate probability is $\leq$ 5% will be rejected and further investigation of TRC105 and sorafenib in this population is warranted. Under this design, the expected sample size is 21. The probability of early termination under the null hypothesis is 50%.

The study will continue to enroll patients when the 12th patient has been enrolled unless no response is observed. If there is no patient achieving response at the time the 12th patient has been enrolled, the enrollment will be stopped temporarily. Once one patient is observed to have response, the enrollment will be resumed. However, if there is no patient achieving response after the first 12 patients have been fully evaluated, the study will be stopped for the futility.

11.2.1.1. Phase 2 Definition of Analyzed Study Populations

The following study populations will be considered when reporting study results for the phase 2 portion:

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

- The study population for efficacy will include all safety population patients who have baseline and follow-up tumor measurements as required for assessment by RECIST 1.1.

Only those patients who are deemed ineligible or who receive no therapy (i.e., no TRC105 or sorafenib) 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.

11.3. 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 protein biomarkers, and archival tumor tissue. Data will also be displayed graphically, where appropriate. Overall survival and progression-free survival will be presented as Kaplan-Meier plots and estimates of the median time until death or the earlier of documented progression or death, respectively.

11.4. Analysis of Primary and Secondary Objectives

11.4.1. 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.

11.4.2. Phase 2

The primary endpoint of the phase 2 study is objective response (CR or PR) at any time during treatment. The sample size is determined using Simon's two-stage minimax design. This design will be used to test the null hypothesis that the true objective tumor response rate is < 5% versus the alternative hypothesis that the true response rate is > 20%.

One or more responses by RECIST 1.1 must be observed in the initial 12 patients enrolled to enroll the second stage, to a total of 21 patients. Three or more responses by RECIST of 21 patients will be considered sufficiently interesting to warrant further study in later trials.

11.5. Analysis of Pharmacokinetics

Serum TRC105 and plasma sorafenib 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.

11.6. Analysis of Protein Biomarkers

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

11.7. 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 (Table 5). APA concentrations will be evaluated in the context of pharmacokinetic parameters and AE profiles.

11.8. 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.

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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

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

13. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

14. ETHICS

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

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

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

14.2. Ethical Conduct of the Study

The trial will be performed in accordance with the protocol, applicable local regulatory requirements and laws, and the International Conference on 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).

14.3. Written Informed Consent

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

It is the responsibility of the Investigator to give each patient full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. This information must be provided to the patient prior to undertaking any trial-related procedure. Patients must be informed about their right to withdraw from the trial at any time. Furthermore, it is the responsibility of the Investigator to ensure all 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.

14.4. Patient Compensation

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

15. DATA HANDLING AND RECORDKEEPING

15.1. Inspection of Records

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.

15.2. Retention of Records

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

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

16. DEFINITION OF END OF TRIAL

16.1. End of Trial in all Participating Countries

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

16.2. End of Trial in a Member State

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

16.3. TRACON Discontinuation Criteria

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

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

17. PUBLICATION OF TRIAL RESULTS

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

18. FINANCING AND INSURANCE

Financing and Insurance are discussed in the Clinical Trial Agreement.

19. INVESTIGATOR PROTOCOL AGREEMENT: 105HCC101

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
4350 La Jolla Village Drive, Suite 800
San Diego, CA 92122

Please keep a copy for your records.

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21. APPENDICES

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

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

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

21.2. Appendix 2: ECOG Performance Status

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

21.3. Appendix 3: Sorafenib Prescribing Information

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021923s008s009lbl.pdf