PROTOCOL SUBMISSION FORM **Amendment Form**	PROTOCOL NO. 10C0062-N	PRINCIPAL INVESTIGATOR (NIH Employee Name, Inst/Br, Telephone and e-mail): William Dahut NCI MOB 301.435.8183 dahutw@mail.nih.gov

PROTOCOL TITLE: A Phase I/II Study of TRC105 in Metastatic Castrate Resistant Prostate Cancer (CRPC)

ABBREVIATED TITLE: PhI/II TRC105 in Prostate Ca Reference Number: 321760

Amendment Version Date: 06/19/2012 Amendment Letter: N

The Following revisions were incorporated into this protocol and approved by:

☒ Expedited Review (risk/ benefit ratio not changed)
☐ Full Board Review (meeting date)

Amendment includes changes required by:

☒ N/A
☐ NCI IRB (CCR)
☐ CTEP
☐ Other
☐ Other Sponsor
☐ FDA
☐ Special Studies IRB (DCEG)

If Other, list:

Amendment required Scientific Review?

☐ Yes ☒ No

ADMINISTRATIVE CHANGES

☐ Protocol Title/ Abbreviated Title
☐ New Principal Investigator
☒ NIH Personnel Change
☐ Non-NIH Personnel Change
☐ Converting to multi-institutional trial

DEC clearance required? ☒ Yes ☐ No

Date submitted to IC DEC: 06/26/2012 Date cleared by IC DEC: 07/16/2012

PROTOCOL CONTENT CHANGES

☐ Precis
☐ Study Objectives
☐ Background and Rationale
☐ Eligibility Assessment and Enrollment
☐ Implementation of Study Design
☐ Supportive Care
☐ Accrual Ceiling Changed to: N/A
☐ Data Collection/Evaluation
☐ Human Subject Protections
☐ Data Reporting
☐ Ionizing Radiation Use
☐ Pharmaceutical Information
☐ Appendices
☐ Transfer of Materials/Data (DCEG Only)

Does the amendment impact the risk/benefit assessment?

☐ Yes ☒ No

INFORMED CONSENT DOCUMENTATION

☐ Text Revisions to Consent(s)
☐ Investigator Contact Information on Consent(s)
☒ No Changes to Consent Form

SIGNATURE

William Dahut - applied signature on 07/18/2012 3:28 PM EDT
New and Old Principal Investigators - electronic signature and date

APPROVALS

Giuseppe Giaccone - applied signature on 07/20/2012 3:57 PM EDT
Branch Chief - electronic signature and date

Not Applicable
Branch Scientific Review Committee Chair - electronic signature and date

Kevin Camphausen - applied signature on 07/25/2012 8:43 AM EDT
Clinical Director- electronic signature and date

Michael Hamilton - applied signature on 07/25/2012 7:49 AM EDT
Chair, IRB Review - electronic signature and date

Dawn Roy 8/2/12 AM N

IRB Meeting Date:

Protocol Number: 10-C-0062

TITLE: A Phase I/II Study of TRC105 in Metastatic Castrate Resistant Prostate Cancer (CRPC)

Abbreviated Title: Ph I/II TRC105 in Prostate Ca

Coordinating Center: Medical Oncology Branch
National Cancer Institute

Principal Investigator: William L. Dahut, MD
Medical Oncology Branch
National Cancer Institute
Building 10, Room 3-2571
10 Center Drive
Bethesda, MD 20892
301-496-4251
FAX: 301-496-9020
dahutw@mail.nih.gov

Lead Associate Investigator: Fatima Karzai, MD
Medical Oncology Branch
National Cancer Institute
Building 10, Room 12N226
9000 Rockville Pike
Bethesda, MD 20892
301-496-4916
karzaifh@mail.nih.gov

Statistician: Seth Steinberg, PhD
Biostatistics and Data Management Section
National Cancer Institute
6116 Executive Blvd, Room 702
Bethesda, MD 20892
301-496-9502
Fax: 301-402-1259
steinbes@mail.nih.gov

Sponsor: William L Dahut, MD, MOB/NCI
IND 107424

Tracon Pharmaceuticals, Inc. Supplied Agent: TRC105

Drug Manufacturer: Tracon Pharmaceuticals, Inc

Protocol Version Date: **June 19, 2012- Amendment N**

Associate Investigators:

Andrea Apolo, M.D., MOB/CCR/NCI
William D. Figg, PharmD, MOB/CCR/NCI
James Gulley, MD, Ph.D., LTIB/CCR/NCI
Philip M. Arlen, MD, LTIB/CCR/NCI
Ravi Madan, MD, LTIB/CCR/NCI
Howard Parnes, MD, DCP/PUCR/NCI
John Wright, MD, CTEP, NCI
Jane Trepel, PhD, MOB, CCR, NCI
Douglas K. Price, PhD CTB/CCR/NCI
Peter Choyke, MD, CCR, MIP, NIH

David Kohler, Pharm. D., PD/CCR/NIH
Anna Couvillon, NP MOB/CCR/NCI
Melony Beatson, RN, MOB/CCR/NCI
Nancy Harold, RN, MOB/CCR/NCI

Research Contact:

Melony Beatson, RN MOB/CCR/NCI

SCHEMA (All times are approximated)

Phase I

TRC105 will be administered intravenously every two weeks on days 1 and 15 of each 28 day cycle in Cohorts 1, 2, 3, 5, and 6 and every week on days 1, 8, 15, and 22 of each 28 day cycle in cohort 4. In the phase I portion, doses will be escalated in six separate cohorts (see below). No intra-patient dose escalation will be allowed. The maximum administered dose will be 20 mg/kg.

Table 1: Phase I Cohorts

Cohort	Phase I Dose	Planned Number of Patients
1	1 mg/kg every 2 weeks	3-6
2	3 mg/kg every 2 weeks	3-6
3	10 mg/kg every 2 weeks	3-6
4	10 mg/kg weekly	Up to six patients
5	15 mg/kg every 2 weeks	3-6
6	20 mg/kg every 2 weeks	3-6

Phase II

TRC105 will be administered as an intravenous infusion at the 20 mg/kg every two weeks (the phase I MTD defined from the phase I portion) every 2 weeks (days 1 and 15) of each 28 (+/- 2 days) day cycle.

Phase I and II

Screening evaluation prior to C1D1:

1. History and physical exam with vital signs (within 1 week prior to dosing)
2. Laboratory evaluation (within 16 days)
3. Scans (within 4 weeks prior to dosing):
    a. Technetium-99 bone scintigraphy
    b. CT scan of chest, abdomen and pelvis
4. PSA (within 7 days prior to dosing)
5. Electrocardiogram (within 16 days)

Cycle 1 Day 1:

1. Pharmacodynamic and pharmacokinetic studies to be drawn pre-dose
2. Thirty minutes to 2 hours prior to the start of each TRC105 infusion, all patients will receive the following medications:
    a. Acetaminophen 650 mg PO x 1

   b. Dexamethasone 20 mg IV x 1. This dose may be tapered or discontinued if no infusion reaction occurs. (See Section 4.3)
   c. Famotidine 20 mg i.v. (or similar H2 blocker) x 1
   d. Cetirizine 10 mg iv or po x1 (or similar oral or intravenous antihistamine)
   e. TRC105 IV over 4 hours
3. Pharmacokinetic samples will be drawn following TRC105 infusion
4. Laboratory evaluation (CBC and following panels will be monitored every two weeks prior to each dose of TRC105 for as long as patient is being treated)
   a. CBC with differential and platelets will need to be repeated on cycle 1, day 1 unless results are ≤ 7 days from the start of treatment
   b. An acute care panel, hepatic panel, mineral panel, uric acid and total protein will need to be repeated on cycle 1, day 1 unless results are ≤ 7 days from the start of treatment
   c. INR if patient is on an anticoagulant

Cycle 1 Day 2:

1. Pharmacokinetic sample will be drawn (phase I)

Cycle 1 Day 3:

1. Pharmacokinetic sample will be drawn (phase I)

Cycle 1 Day 15:

1. Laboratory evaluation (CBC/differential, acute care panel, hepatic panel, mineral panel, uric acid and total protein, INR if patient is on an anticoagulant)
2. TRC105
3. Pharmacodynamic and pharmacokinetic studies will be drawn pre-dose on C1D15
4. Post-dose pharmacokinetic sample(s) will be drawn

Cycle 1 Day 16:

1. Pharmacokinetic sample will be drawn (phase I)

Cycle 1 Day 17:

1. Pharmacokinetic sample will be drawn (phase I)

Cycle 2 Day 1:

1. Laboratory evaluation (CBC/differential, acute care panel, hepatic panel, mineral panel, uric acid and total protein., INR if patient is on an anticoagulant)
2. TRC105
3. Pharmacokinetic sample pre-dose and post-infusion

Cycle 2 Day 15:

1. Laboratory evaluation (CBC/differential, acute care panel, hepatic panel, mineral panel, uric acid and total protein, INR if patient is on an anticoagulant)
2. TRC105
3. Pharmacodynamic studies will be drawn pre-dose on C2D15

4. Pharmacokinetic sample pre-dose and post-infusion

Cycle 3 Day 1 and Cycle 3 Day 15:

1. Pharmacokinetic sample pre-dose and post-infusion

Prior to the start of every other cycle

1. UPC to be performed prior to the start of every other cycle

Re-staging bone scans and CT scan of chest, abdomen, and pelvis will be required every two months for the first four months of the study (following cycles two and four), and then after every 3 cycles of treatment. If screening CT scan is negative for soft tissue disease, repeat CT imaging will not be required.

Off study evaluation is to be performed within 30 days of withdrawal from study therapy.

PRECIS

Background:

- Inhibition of angiogenesis has demonstrable antitumor efficacy against castrate-resistant prostate cancer (CRPC). TRC105 is a human/murine chimeric IgG1 kappa monoclonal antibody that binds to human CD105 (endoglin), thus inhibiting angiogenesis and tumor growth. Data from an ongoing phase I clinical trial suggests that TRC105 is well tolerated with evidence of clinical efficacy in patients with metastatic CRPC.

Primary Objectives:

- Define the maximum tolerable dose (MTD) of TRC105 given every one to two weeks.
- Determine if single-agent TRC105, when administered at 20 mg/kg IV every two weeks (the phase I MTD) to patients with CRPC, is associated with a 6-month progression-free survival probability of 30%

Secondary Objectives:

- Define the dose-limiting toxicities and toxicity profile of TRC105 given every one to two weeks
- Evaluate time to disease progression, overall response rate and overall survival.
- Describe the prostate specific antigen (PSA) response rate to therapy with TRC105
- Characterize the pharmacokinetics of TRC105
- Demonstrate a biologic effect of TRC105 in the patient and, when possible, on the tumor via laboratory evaluation of the molecular markers of angiogenesis before and after drug administration respectively

Eligibility:

- Progressive, castrate-resistant, metastatic adenocarcinoma of the prostate
- ECOG ≤ 2

Design:

- An initial single-arm, phase I dose escalation study open to all patients with progressive metastatic CRPC. The study will evaluate patients in six cohorts of escalating dose levels. A maximum of 30 patients will be needed to complete the phase I evaluation.
- Following completion of the phase I study will be a two-stage, phase II study that will be conducted separately in the following two arms:
    1. Chemotherapy-naïve for metastatic disease (no prior antiangiogenic therapy)
    2. Post-docetaxel disease progression
- In each arm, the primary objective will be to determine if a 6 month progression free survival probability of 30.0% can be identified.
- Initially, 12 patients will be enrolled in each stratum and evaluated for progression. If 2 or more are progression-free at 6 months, then enrollment will continue until a full 35 patients have been enrolled in that stratum. Enrollment may continue to the other stratum if one stratum has ended accrual.

TABLE OF CONTENTS

Tables

Figures

1 OBJECTIVES

1.1 PRIMARY

Phase I

- Define the maximum tolerable dose (MTD) of TRC105 given as an intravenous infusion every one to two weeks of each 28 day cycle that will be administered in the phase II portion of the study

Phase II

- Determine if single-agent TRC105, when administered at 20 mg/kg every 2 weeks, the MTD from phase I, to patients with castrate-resistant prostate cancer, is associated with a 6-month progression-free survival probability of 30% in two separate strata of patients:
    - Those who are chemotherapy naïve for metastatic disease and have not received prior antiangiogenic therapy, and
    - Those with evidence of disease progression despite prior docetaxel.

1.2 SECONDARY

- Define the dose-limiting toxicities and toxicity profile associated with administration of TRC105 as an intravenous infusion given every one to two weeks
- Evaluate time to disease progression, overall response rate and overall survival. Determination of progression will be based on clinical and radiographic criteria without the use of PSA, in accordance with recommendations from the Prostate Cancer Clinical Trials Working Group-2 [53]. Objective response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
- Describe the prostate specific antigen (PSA) response rate to therapy with TRC105
- Characterize the pharmacokinetics of TRC105 and determine if any pharmacodynamic relationships exist between plasma concentrations of TRC105 and clinical activity or toxicity
- Demonstrate a biologic effect of TRC105 in the patient via measurement of plasma levels of angiogenic factors pre- and post TRC105 administration. Angiogenic biomarkers to be evaluated include, soluble CD105 (sCD105), vascular endothelial growth factor (VEGF), placenta-derived growth factor (PlGF), basic fibroblast growth factor (bFGF), soluble VEGF receptor 1 (sVEGFR1), circulating endothelial progenitor cells (CEP) and mature circulating endothelial cells (CEC) and circulating tumor cells (CTC).

2 BACKGROUND

2.1 CASTRATE RESISTANT PROSTATE CANCER

Prostatic adenocarcinoma is the leading non-cutaneous malignancy in American men, and the second leading cause of cancer related deaths in this population [2]. In 2009, it is estimated that just over 192,000 men will be diagnosed with prostate cancer and more than 27,000 will die as a result of metastatic disease [3]. With the onset of biochemical (PSA) or radiographic disease

recurrence following definitive local therapy, androgen deprivation therapy (ADT) is the first-line approach with the goal of achieving a castrate level of testosterone (< 50 ng/mL) [4, 5, 6]. Disease progression to a castration-resistant phenotype occurs in virtually all patients after a median of 18-36 months on ADT [7, 8]. Currently, there is no curative therapy for metastatic castrate-resistant prostate cancer (CRPC).

2.2 RATIONALE

While there is no curative therapy for metastatic CRPC, two large randomized trials have established docetaxel with prednisone as the only cytotoxic therapy that improves overall survival in men with CRPC [8, 9], with a modest 2.9 month improvement in median overall survival compared to mitoxantrone with prednisone [10]. There remains a need to identify novel agents to be administered prior to docetaxel that would delay disease progression with less toxicity compared to traditional chemotherapy. Currently, there is no prospective data that defines the optimal timing of chemotherapy initiation in CRPC [11], and recent trials investigating experimental therapies have included chemotherapy-naïve, progressive metastatic castrate-resistant prostate cancer [12]. Furthermore, clinical responses induced by docetaxel are not durable and eventual progression of disease is inevitable [7], highlighting the need to continue to seek out agents that would be efficacious in the docetaxel-refractory setting.

Angiogenesis is the fundamental process by which new blood vessels are formed. In 1971, Folkman proposed that tumor growth and metastasis are angiogenesis-dependent [13] and hence, blocking angiogenesis could be a strategy to arrest tumor growth [13,14,15]. It is now widely accepted that angiogenesis is required for the survival and growth of solid cancers (16, 17). It is generally believed that solid cancers grow in two phases, an avascular phase and a vascular phase (16). During the initial avascular phase, tumors exist as small aggregates of malignant cells supported by simple diffusion of oxygen and nutrients. The progressive growth of solid cancers beyond clinically occult sizes requires the continuous formation of new blood vessels, a process known as tumor angiogenesis. Tumor growth and metastasis are dependent upon angiogenesis. Subsequently, there have been numerous published papers that demonstrate an association between increasing microvessel density count, as a surrogate measure of angiogenesis, and metastasis in a range of solid tumors, including breast, lung, bladder and prostate cancer [18 - 22]. Increased microvessel density has also been correlated with poorer prognosis for several solid malignancies, including prostate cancer [22].

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

Inhibition of angiogenesis, either as a stand-alone approach or in combination with chemotherapy, has demonstrable antitumor efficacy against castrate-resistant prostate cancer and there are several anti-angiogenic agents that are now in clinical trials in this population of

patients. The vast majority of anti-angiogenic agents being utilized in the clinical setting are based on strategies that either interfere with pro-angiogenic ligands or block signaling of pro-angiogenic receptor tyrosine kinases. Thalidomide (α-*N*-[phthalimido]glutarimide) has been shown to inhibit basic fibroblast growth factor (bFGF) – induced angiogenesis in vitro [23, 24] and decrease levels of bFGF in vivo in prostate cancer patients [25]. An open-label phase II study of thalidomide in CRPC showed a total of 28% of the patients having a greater than 40% decline in PSA [25]. In a subsequent phase II trial of thalidomide plus docetaxel versus docetaxel alone in metastatic CRPC [26], the combination arm showed improvements in PSA response, median progression-free survival and median overall survival [26, 27]. At the NCI, a phase II trial using combination therapy with bevacizumab (a humanized monoclonal antibody against all major isoforms of VEGF-A), thalidomide, docetaxel and prednisone in patients with metastatic CRPC has resulted in a 90% biochemical response rate, overall response rate in measurable disease of 64% and a median overall survival rate of 28.4 months [28]. When considered in the context of historical data showing a median overall survival of 19.2 months with docetaxel and prednisone alone in patients with CRPC [10], this data suggests that the addition angiogenesis-targeted agents would be beneficial in this patient population. While these studies validate the potential for an anti-angiogenic approach to CRPC, they also indicate the need to investigate alternative ways to target the tumor vasculature. Of particular interest are agents that target unique mechanisms for tumor angiogenesis, have a better risk-benefit profile, have activity in tumors resistant to existing therapies, and could even be combined with anti-VEGF therapy to enhance efficacy and limit the development of resistance.

One such alternative anti-angiogenic approach is the direct targeting of the proliferating endothelial cell, a major component of the tumor vasculature, through modification of CD105 signaling in response to transforming growth factor-ß (TGF-ß), induction of endothelial cell apoptosis, and antibody-mediated cellular cytotoxicity (ADCC) aimed against CD105.

2.3 CD105

CD105 (endoglin) is a 180 kDa homodimeric transmembrane protein that is selectively and highly expressed on the surface of proliferating vascular endothelial cells [29, 30, 31]. The CD105 pathway is essential for angiogenesis during fetal development and cell-surface expression of this molecule is required for the formation of new blood vessels [32]. This is evidenced by CD105 null mice that die in utero as a result of impaired angiogenesis in the yolk sac [32].

CD105 acts as an accessory protein that interacts with the signaling receptor complex of the TGF- ß superfamily, thus modulating the effects of TGF- ß [33]. CD105 expression protects endothelial cells from the growth-inhibitory effects of TGF-β signaling [34]. When engaged by the TGF- ß/TGF-ßRII complex, CD105 preferentially activates Alk-1 which in turn phosphorylates Smad proteins 1, 5 and 8. This ultimately leads to stimulatory effects on endothelial cell proliferation, migration and transcription of pro-angiogenic genes [34, 35, 36]. CD105 expression is induced by hypoxia through HIF-1α and protects hypoxic endothelial cells from apoptosis [37]. Additionally, CD105 also regulates components of the extracellular matrix to facilitate endothelial cell migration and promote formation of neo-vessels [35].

Immunohistochemistry has shown that CD105 is strongly expressed in blood vessels of multiple tumor tissues, including prostate cancer [38, 39]. Increased intratumoral microvessel density (MVD), as assessed by anti-CD105 antibodies, correlates with Gleason score, tumor stage,

metastasis, tumor cell proliferation index and shorter survival in prostate cancer [38, 39]. CD105 is able to be detected in the urine and serum of patients with prostate cancer with higher levels of urinary CD105 present in biopsy-proven prostate cancer compared with biopsy-negative patients [40]. Anti-VEGF therapy up-regulates CD105 expression [41], indicating that a therapeutic strategy which targets CD105 may complement VEGF-inhibition.

Mutations in CD105 or its downstream signaling mediator leading to 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 vascular dysplasias, frequent episodes of epistaxis, mucocutaneous telangiectasias and arteriovenous malformations of the lung, brain, liver and gastrointestinal tract [30]. The genotype is manifested *in utero*, but the phenotype does not become apparent for many years following birth. Affected patients most commonly present with epistaxis in the second decade of life. The phenotype of this disorder is limited to vascular effects, indicating the specific role of CD105 in the vasculature. Most patients affected with HHT-1 experience epistaxis by the age of 10 to 20 years, while telangiectasias of the skin and mucosa first appear by the age of 20 to 40 years. Visceral arteriovenous malformations are less common sequelae but may result in significant morbidity, including pulmonary shunting and intracranial hemorrhage.

CD105 is also expressed on pre-B leukemia cells, a subset of normal pre-B cells in fetal bone marrow, on erythroid precursors and stromal cells of fetal and adult bone marrow (42, 43, 44), syncytiotrophoblasts (45) and hematopoietic stem cells (46); however it is not expressed on normal peripheral blood lymphocytes or monocytes (47). In adults, CD105 expression can be measured on activated monocytes and endothelial cells, and expression levels on endothelial cells exceed those on activated monocytes by approximately 10-fold (48, 49).

2.4 TRC105

All data cited in this section (unless otherwise noted) has been obtained from Tracon Pharmaceuticals, Inc and is found in the Tracon Pharma Investigator's Brochure, Project TRC105 Oncology, version 2.0: May 11, 2009. Edition 2.0.

TRC105 is a human/murine chimeric anti-CD105 IgG1 kappa monoclonal antibody consisting of human Cκ and Cγ1 constant regions with murine Vκ and V_H regions. TRC105 is composed of two light chains of 213 amino acids and two heavy chains of 448 amino acids and has an approximate molecular weight of 148 kDa. This monoclonal antibody binds with high avidity to human CD105 (endoglin), thus inhibiting angiogenesis and tumor growth.

2.4.1 Nonclinical Pharmacology, Efficacy and Toxicology

Pharmacology studies include *in vitro* and *in vivo* studies performed with the murine parent antibody (SN6j) and TRC105. These antibodies share identical variable regions. SN6j, the murine parent monoclonal antibody of TRC105, was generated by immunizing mice with an isolated CD105 preparation from human leukemia cells (50).

Pharmacology studies were conducted in murine and human models. Collectively, the studies demonstrate that TRC105 (or SN6j) binds with higher avidity to human than murine endothelial cells, and reacts more strongly with proliferating than quiescent endothelial cells. Studies also indicate that these anti-CD105 antibodies are able to mediate TGF-β dependent growth inhibition, induce apoptosis of human umbilical vein endothelial cells (HUVECs), mediate

antibody dependent cell-mediated cytotoxicity (ADCC) of HUVECs, saturate CD105 binding at concentrations ≥ 250 μg/mL, and inhibit the growth of human tumor xenografts.

TRC105 binds to purified human CD105 with high avidity by surface Plasmon resonance assay (5 - 35 pM). As expected, binding studies indicate that both SN6j and TRC105 bind with nearly identical avidity to human endothelial cells that express CD105 as determined by Scatchard analysis.

In Vitro Pharmacology of SN6j

Using Scatchard plot analyses performed by incubating fixed combinations of radiolabeled and native antibody with KM-3 cells, the avidity of SN6j was calculated by regression analysis to be 2.85×10^{9} liter/mole (or 3.51×10^{-10} mole/liter).

TGF-β Dependent Growth Inhibition of HUVECs

SN6j was studied for its ability to inhibit the growth of HUVECs *in vitro* in the presence of TGF-β. HUVEC cells were cultured at 37 °C overnight prior to the addition of SN6j and TGF-β. Cells were then exposed to antibody or TGF-β for 72 hours, during which time the media containing antibody and/or growth factors was replaced every 24 hours. Cell growth was then quantified by assaying tritiated thymidine incorporation for 20 hours. The concentration of SN6j needed to inhibit HUVEC growth by 50% was 90 μg/mL in the absence of TGF-β. However, the concentration of SN6j needed to inhibit HUVEC growth by 50% was much lower when cells were incubated with antibody in the presence of TGF-β. These data indicate that anti-endoglin antibody potently inhibits HUVEC growth in the presence of TGF-β. At physiologic concentrations of TGF-β (>100 pg/mL), the amount of SN6j needed to inhibit HUVEC cell growth was <10 μg/mL.

Induction of Apoptosis of Proliferating HUVECs

SN6j was studied for its ability to induce apoptosis of proliferating HUVECs *in vitro*. HUVEC cells were seeded and then incubated at 37 °C with SN6j (50 or 100 μg/mL) or 100 μg of MOPC, an IgG1-kappa isotype-matched control antibody. Following incubation, cells were washed and then lysed. The cytoplasmic and nuclear fractions were separated by centrifugation and nucleosomes contained in the cytoplasmic fraction were then detected via their histone components. Apoptosis was determined by assaying the fragmented nucleosome content of cytoplasmic fractions using a commercial ELISA (Roche Diagnostics). The degree of apoptosis induced by SN6j on proliferating HUVECs from multiple donors was 9.1% at 50 μg/mL and 25.6% at 100 μg/mL concentrations, relative to the value induced by camptothecin. Apoptosis of SN6j (100 μg/mL) treated HUVECs was 4.58 times as large as that of MOPC control IgG (100 μg/mL) treated HUVECs, while apoptosis of SN6j (50 μg/mL) treated HUVECs was 2.28 times as large as that of MOPC control IgG (100 μg/mL) treated HUVECs.

In a separate experiment using HUVECs from a single donor, the degree of apoptosis induced by SN6j was 31.5% at 50 μg/mL and 43.7% at 100 μg/mL concentrations, relative to the value induced by camptothecin. Apoptosis of SN6j (100 μg/mL) treated HUVECs was 2.53 times as large as that of MOPC control IgG (100 μg/mL) treated HUVECs, while apoptosis of SN6j (50 μg/mL) treated HUVECs was 2.10 times as large as that of MOPC control IgG (100 μg/mL) treated HUVECs. Overall, SN6j induced significant levels of apoptosis (although lower than those induced by camptothecin) on HUVECs at concentrations of ≥ 50 μg/mL.

In Vitro Pharmacology of TRC105

The constant regions of SN6j were humanized to yield TRC105 for full-scale development and evaluation in clinical studies. TRC105 (c-SN6j) is a chimeric IgG1 kappa antibody made by grafting the constant regions of human IgG1 heavy chain and kappa light chain onto the murine variable regions of monoclonal antibody SN6j that binds human CD105. Using Scatchard plot analyses performed by incubating fixed combinations of radiolabeled and native antibody with KM-3 cells, the avidity of TRC105 (c-SN6j) was calculated by regression analysis to be 2.98 x 10^9 liter/mole (or 3.36 x 10^{-10} mole/liter).

Avidity to Human CD105

A study of binding of TRC105 with human CD105 using a surface plasmon resonance assay indicated that avidity and affinity of TRC105 for human CD105 were approximately 5 x 10^{-12} and 35 x 10^{-12} mole/liter, respectively.

Binding Potency to Human CD105

An ELISA assay was performed using plates coated with human CD105. TRC105 was found to half saturate human CD105 at concentrations of approximately 34-50 ng/mL and to fully saturate human CD105 at concentrations of ≥ 250 ng/mL. TRC105 concentrations of ≥ 250 ng/mL are expected to saturate CD105 expressed on human endothelial cells and fully engage effector functions.

Avidity of TRC105 to HUVECs *In Vitro*

A binding assay was performed to determine the avidity of TRC105 to cultured HUVECs. TRC105 was found to half saturate non-confluent (or proliferating) HUVECs at 2.3 ng/mL and to half saturate confluent (or non-proliferating) HUVECs at 22 ng/mL. Saturation was achieved at approximately 250 ng/mL in both cases.

TRC105 Induction of ADCC of Proliferating HUVECs *In Vitro*

TRC105 was investigated for its ability to mediate antibody-dependent cell-mediated cytotoxicity (ADCC) *in vitro*. In the presence of effector cells from three different donors, concentrations of ≥ 1 μg/mL of TRC105 lysed significant proportions of proliferating HUVECs, indicating that TRC105 exhibits ADCC activity *in vitro*. Lower concentrations of TRC105 were evaluated for ADCC using HUVEC cells and peripheral blood mononuclear cells that were activated with interleukin-2 (see graph below). TRC105 concentrations of < 1 ng/mL lysed significant proportions of proliferating HUVECs in the presence of interleukin-2 activated NK cells at an effector to target ratio of 10:1. TRC105 did not engage complement-mediated cytotoxicity (CDC) on proliferating HUVECs in vitro.

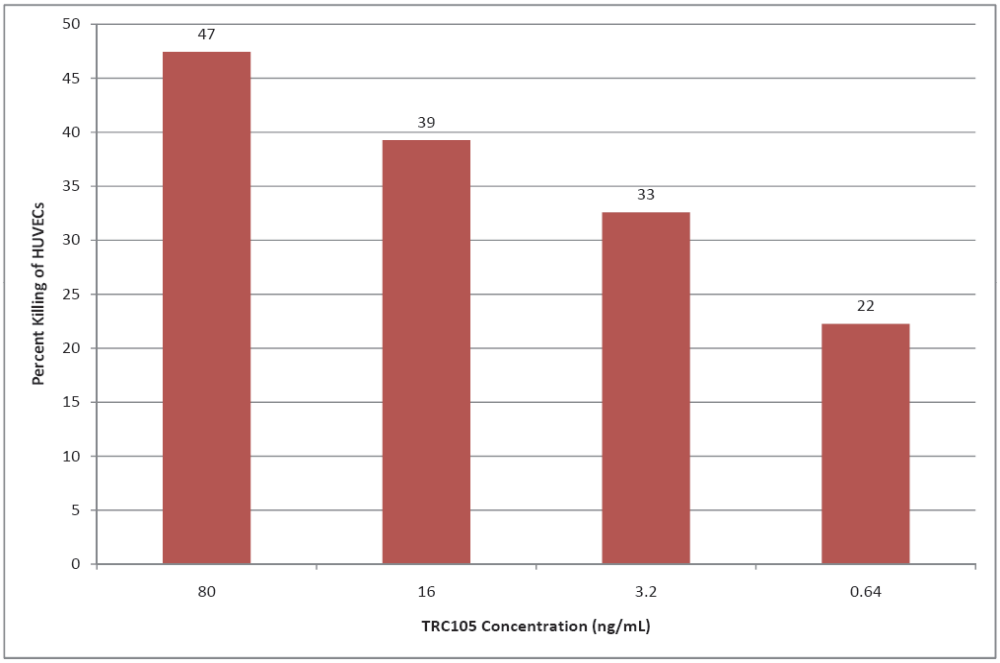

Figure 1

In vitro analysis has shown that anti-CD105 antibodies are internalized following binding to CD105. SN6j and isotype-matched control IgG were individually labeled with FITC and then incubated with SVEC4-10 murine endothelial cells for four hours at room temperature. SN6j reacted with viable SVEC4-10 murine endothelial cells and was internalized into the cells as shown by strong FITC-SN6j staining within the intracellular portion of cells. In contrast, only weak background staining was seen with the cells treated with FITC-labeled isotype-matched control IgG. Internalization of bound TRC105 is expected to limit the ability of the antibody to engage effector functions at low CD105 surface densities, such as those on quiescent endothelium.

In Vivo Nonclinical Toxicology Studies of TRC105

TRC105 Toxicology

TRC105 was administered by intravenous infusion over 30 minutes weekly for 5 doses to cynomolgus monkeys, at doses of 3 mg/kg, 10 mg/kg and 30 mg/kg. Three monkeys of each gender were treated at the two lower doses and six animals of each gender were treated at the high dose (30 mg/kg). Animals tolerated TRC105 at all doses tested. There was no clinical, clinical pathologic or histopathologic evidence of toxicity. The no observed event level was determined to be 30 mg/kg given by 30 minute intravenous infusion weekly for five doses.

A GLP repeat-dose toxicology study was undertaken in cynomolgus monkeys to determine the onset, reversibility, persistence, or delayed occurrence of toxic effects after five weekly doses of TRC105, followed by a four-week recovery period. Single-dose pharmacokinetic characterization of TRC105 was performed after Day 1 and multiple-dose pharmacokinetic

characterization of TRC105 was performed after Day 29. In addition, the immunogenicity of TRC105 was determined. Doses were administered by a 30 minute infusion on days 1, 8, 15, 22 and 29 into 36 adult monkeys. There were three males and three females per dose at 3 and 10 mg/kg/dose and six males and six females at control (vehicle) and 30 mg/kg/dose. All animals were dosed on days 1, 8, 15, 22 and 29 via a 30 minute intravenous infusion. Three animals per sex per group in Groups 1 through 4 were euthanized on Day 30, and three animals per sex per group in Groups 1 and 4 were euthanized on Day 57. Toxicity was assessed by monitoring mortality, clinical condition, body weight, food consumption, ophthalmic examination results, electrocardiography (including heart rate), blood pressure, body temperature, respiratory rate, clinical pathology (hematology, coagulation, serum chemistry, urinalysis and fecal occult blood). All received a comprehensive necropsy; selected organs were weighed and tissues were evaluated microscopically. Survival, clinical condition, body weight, food consumption, ophthalmology examinations, physiologic parameters (electrocardiograms, blood pressure, body temperature, heart rate and respiratory rate), hematology and coagulation, clinical chemistry, urinalysis, fecal occult blood evaluations, organ weights, and macroscopic and microscopic findings were unaffected by TRC105 administration. Accordingly, the no observed effect level (NOEL) for intravenous TRC105 under the conditions of this study was 30 mg/kg. Tissue binding assays were conducted on selected tissues from the control and high-dose groups. Animals dosed with TRC105 demonstrated binding to endothelial cells consistent with internalization of bound antibody. While this staining pattern is consistent with CD105 distribution, internalized antibody may also reflect binding to Fc receptors known to be expressed by endothelial cells. Roswell Park Cancer Institute sponsored a non-GLP study in which cynomolgus monkeys were dosed twice weekly for three weeks with 1.0 mg/kg, 3.0 mg/kg or 10.0 mg/kg of TRC105 (c- SN6j). In summary, TRC105 was well-tolerated by nonhuman primates when dosed up to 30 mg/kg weekly for five doses as a 30 minute intravenous infusion in a GLP study or up to 10 mg/kg twice weekly for six doses as an intravenous bolus. The highest dose tested, 30 mg/kg weekly for five doses, produced no indications of a drug-related effect in a GLP study and is the NOEL.

TRC105 Nonclinical Pharmacokinetics and Immunogenicity

Toxicokinetics and immunogenicity were studied following the administration of TRC105 by intravenous infusion over 30 minutes weekly for five doses to cynomolgus monkeys, at doses of 3 mg/kg, 10 mg/kg and 30 mg/kg. The mean central distribution volume was 0.029, 0.040 and 0.038 L/kg in animals given 3 mg/kg, 10 mg/kg and 30 mg/kg of TRC105, respectively, by intravenous infusion over 30 minutes. The mean steady-state volume of distribution was 0.075, 0.087 and 0.076 L/kg in animals given 3 mg/kg, 10 mg/kg and 30 mg/kg of TRC105, respectively. As expected, the central volume of distribution for TRC105 was similar to the serum volume in monkeys. Both the central and steady-state distribution volumes were consistent with distribution volumes of other chimeric antibodies (e.g., rituximab and cetuximab). The mean terminal half-life of TRC105 was 133, 149 and 153 hours among the anti-TRC105 antibody negative animals in the 3, 10, and 30 mg/kg dose groups, respectively. Steady-state was attained by 5 weeks in each dose group. The mean serum TRC105 Cmax was 83, 135 and 104 μg/mL in the 3 mg/kg dose group on Study Days 1, 22 and 29, respectively. In the 10 mg/kg dose group the mean Cmax values were 212, 346 and 306 μg/mL, and were 834, 1113 and 957 μg/mL in the 30 mg/kg dose group on Study Days 1, 22, and 29, respectively. A single monkey dosed with 30 mg/kg of TRC105 tested positive for the formation of MACA (monkey

anti-chimeric antibodies; i.e., antibodies reactive with the human portion of TRC105) on Study Days 36, 43, and 50, but not Study Day 57. All animals that tested negative for MAMA (monkey anti-murine antibodies; i.e., antibodies reactive with the murine portion of TRC105) before dose administration on Study Day 1 also tested negative when subsequent samples were obtained throughout the remainder of the study. Several other animals tested positive for MAMA prior to the first dose administration on Study Day 1 and also tested positive (at lower titers) at frequent times throughout the 57 day study period.

TRC105 Nonclinical Efficacy

TRC105 was studied *in vivo* for its ability to inhibit angiogenesis using a murine model of choroidal neovascularization (CNV). C57B/L6 mice were given an intravitreal injection of TRC105 in one eye and PBS in the contralateral eye. TRC105 demonstrated dose-dependent inhibition of CNV in C57B/L6 mice. The highest dose administered (5 μg in1 μL) inhibited CNV by over 50% versus control.

2.4.2 TRC105 Clinical Safety, Pharmacokinetics and Efficacy

TRC105 is being studied in an ongoing monotherapy phase I trial in patients with advanced solid cancer. To date, a total of 43 patients have been treated at escalating doses of 0.01, 0.03, 0.1, 0.3, 1, 3, 10 and 15 mg/kg TRC105 every two weeks.

TRC105 Clinical Safety

Grade 3/4 adverse events possibly related to TRC105 were reported in four patients including one patient with a grade 4 gastrointestinal bleed and three patients with grade 3 infusion reactions. One patient with peptic ulcer disease had a gastric ulcer hemorrhage 4 days after the initial TRC105 infusion at 0.1 mg/kg that required transfusion of two units of packed red blood cells. This was the only serious bleeding event. Three patients developed grade 3 TRC105 infusion reactions at 0.3 and 1 mg/kg. Because of this, the phase I protocol was modified to require dexamethasone-based premedication before each infusion. None of the ten patients that received 3 mg/kg, 10 mg/kg or 15 mg/kg every 2 weeks experienced grade 3 or higher infusion reactions. Two patients, both at 10 mg/kg, experienced transient grade 2 infusion reactions that did not prevent them from receiving the prescribed dose. Other adverse events considered possibly related to TRC105 have been rare and limited to grade 1 or 2.

Table 2: Possibly Related Events

Possibly Related Events (N=41)				
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal hemorrhage				1
Infusion related reaction		5	3	
Fatigue	1	3		
Anemia		1		
Blood bilirubin increased		1		
Proteinuria		1		
Flushing	2			
Arthralgia	1			
Constipation	1			
Diarrhea	1			
Headache	1			
Hyperuricemia	1			
Micturition urgency	1			
Nausea	1			
Vaginal hemorrhage	1			
Vomiting	1			
Diarrhea	1			
Dysgeusia	1			

TRC105 Pharmacokinetics

Serial TRC105 serum concentrations were measured in 24 patients at doses up to 10 mg/kg every two weeks. TRC105 concentrations known to engage ADCC (>1 ng/mL) were detected transiently in all patients, and concentrations that saturate CD105 receptors (>200 ng/mL) were achieved at 0.3 mg/kg and higher. The 200 ng/mL target concentration was maintained for 1 day at 1 mg/kg, 5 days at 3 mg/kg, and 7 days at 10 mg/kg. Up to three additional cohorts will be studied in phase I including 15 mg/kg and 20 mg/kg every two weeks, and 10 mg/kg weekly.

TRC105 Clinical Pharmacokinetics (N=24)

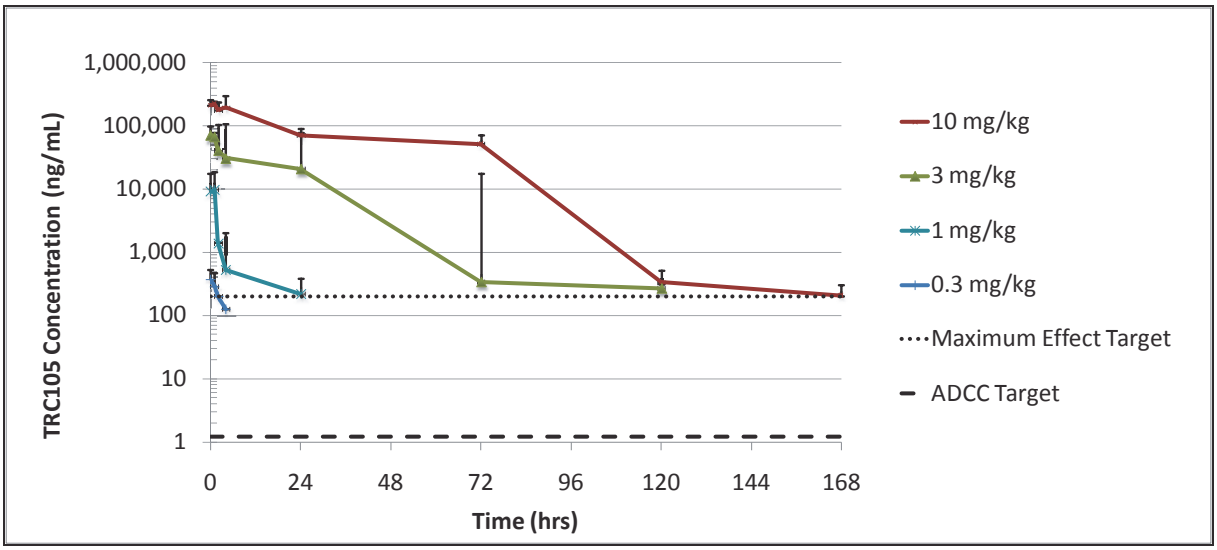

Figure 2

TRC105 Immunogenicity

Thirty-nine patients have been evaluated for HAMA as part of the ongoing Phase 1 monotherapy trial. HAMA was detected in one patient at 0.03 mg/kg after 10 doses of TRC105 and one patient at 0.3 mg/kg after 6 doses of TRC105 that was produced in NS0 cells. Neither HAMA nor HACA were detected in patients dosed with the CHO-derived TRC105 supply that will be used in this study and for future development.

TRC105 Clinical Efficacy

Early evidence of clinical activity includes stable disease for greater than two months in 13 of 35 evaluable patients (37%), with stable disease for greater than four months in 4 of those patients (11%). One patient with castrate-refractory prostate cancer remains on study after 34 cycles (136 weeks) of TRC105 with a complete PSA response and bone scan normalization, and one ovarian cancer patient was treated for 6 cycles (24 weeks) with stable disease and CA125 decrease of 16%. In addition, decreases in circulating tumor markers were seen in 6 of 20 patients (30%) with available markers.

Results from Phase I portion of current trial

Enrollment on the phase I portion of this study has been completed as of Amendment M. Twenty patients have been enrolled, with two patients remaining on the sixth cohort (20 mg/kg every 2 weeks). PSA declines were seen in a total of 7 patients.

One patient in cohort 2 (3 mg/kg every 2 weeks) had a PSA decline of 6%. In cohort 3, (10 mg/kg every 2 weeks), two patients had PSA declines of 50% and 17%, while in cohort 4 (10 mg/kg weekly), PSA declines were seen in two patients (20% and 59% respectively). In cohort 5, (15 mg/kg every two weeks), one patient had a PSA decline of 41%. Lastly, in cohort 6, one patient had PSA decline of 19%. In the first 5 cohorts, 13 patients had soft tissue disease and 9 patients had stable disease status post two cycles of treatment.

One patient in cohort 5 (15 mg/kg IV every two weeks) experienced a grade-4 infusion reaction. This serious adverse event (SAE) was the only dose-limiting toxicity to occur on the protocol as of Amendment M. In addition to this adverse event there was one occurrence of grade 3 fever and three occurrences of grade 3 hypotension considered to be possibly related to TRC105. Other AEs were limited to grade 1 or grade 2 in severity, the most frequent being headache (13/20), epistaxis (9/20), fever (8/20), nausea (7/20), flushing (7/20), anemia (6/20), chills (5/20), vomiting (5/20), infusion related reaction (4/20), bone pain (4/20), oral hemorrhage (4/20).

2.4.3 TRC105 Physical, Chemical, and Pharmaceutical Properties and Formulation

Physical, Chemical and Pharmaceutical Properties

TRC105 is a chimeric anti-CD105 IgG1 antibody consisting of human Cκ and Cγ1 constant regions with murine Vκ and VH regions. TRC105 is composed of two light chains of 213 amino acids and two heavy chains of 448 amino acids and has an approximate molecular weight of 148 kDa.

Formulation

TRC105 is a sterile, clear colorless to slightly yellow opalescent solution for intravenous infusion. The solution may contain small amounts of visible particulates. TRC105 will be filtered through a 0.2 μm low protein binding filter at the clinical site prior to administration. Each single-use vial contains a 5 mg/mL solution. TRC105 is formulated as a preservative-free solution containing sodium chloride, monobasic sodium phosphate monohydrate, anhydrous dibasic sodium phosphate, and Sterile Water for Injection. Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH. TRC105 is formulated to be isotonic with a pH of 6.2 – 8.2.

Storage Conditions

TRC105 should be stored refrigerated 2 °C to 8 °C (36 °F to 46 °F). Preparations of TRC105 in infusion containers are stable for up to 8 hours at room temperature.

Manufacturing Process

The TRC105 production cell line for initial phase I clinical testing was a NS0 cell line. The manufacturing process used bioreactors with media containing bovine sera from the US or New Zealand. A high producing CHO cell line was subsequently developed for phase I and later stage clinical development using media that is free of animal-derived components. The manufacturing process uses conventional purification and filtration steps and concludes with the formulation of TRC105 in phosphate buffered saline. The purity of TRC105 is greater than 95%. Only CHO derived material will be used in this study.

3 PATIENT SELECTION

3.1 ELIGIBILITY CRITERIA

3.1.1 Histopathological Confirmation

Patients must have histopathological confirmation of prostate cancer by the Laboratory of Pathology of the NCI, Pathology Department of the National Naval Medical Center or Pathology Department of Walter Reed Army Medical Center prior to entering this study. Patients whose

pathology specimens are no longer available may be enrolled in the trial if the patient has a clinical course consistent with prostate cancer and available documentation from an outside pathology laboratory of the diagnosis. In cases where original tissue blocks or archival biopsy material is available, efforts will be made to contact referring physicians and outside pathology departments to have the material forwarded to the research team for use in correlative studies.

3.1.2 Metastatic Progressive Castrate-Resistant Prostate Cancer

Patients must have metastatic progressive castrate-resistant prostate cancer defined as progressive disease (see below) despite surgical castration or ongoing use of gonadotropin-releasing hormone agonists with confirmed castrate levels of testosterone.

Criteria of progression for trial eligibility are defined from the Prostate Cancer Clinical Trials Working Group-2 [53]. Clinically progressive prostate cancer must be evidenced and documented by any of the following parameters:

1. Two consecutively rising PSA values at a minimum of 1-week intervals (2.0 ng/mL is the minimum starting value for PSA)
2. Appearance of one or more new lesions on bone scans
3. Progressive measurable disease by RECIST 1.1

Patients on flutamide for at least 6 months must have disease progression at least 4 weeks after withdrawal. Patients on bicalutamide or nilutamide for at least 6 months must have progression at least 6 weeks after withdrawal.

All patients enrolled will be required to have measurable or non-measurable disease on imaging studies.

3.1.3 Prior Treatments

Phase II study patients enrolled onto Arm 1 (chemotherapy-naïve) may not have received any prior chemotherapy or antiangiogenic therapy for metastatic prostate cancer. Those patients enrolled onto Arm 2 must have evidence of disease progression (per criteria stated above) despite prior docetaxel. Any number of prior treatment lines is acceptable.

3.1.4 Age

Age >18 years

3.1.5 Life Expectancy

Life expectancy of greater than 3 months.

3.1.6 ECOG

ECOG performance status 0-2 (see Appendix A)

3.1.7 Normal Organ and Marrow Function

Patients must have normal organ and marrow function as defined below:

- Absolute neutrophil count $\geq$1,500/mcL
- Platelets $\geq$100,000/mcL

- Total bilirubin ≤ 1.5 x upper normal limits or < 3 mg/dl in subjects with Gilbert's Syndrome
- AST/ALT ≤ 2.5 × upper limit of normal
- Creatinine ≤ 1.5 x upper normal limits OR creatinine clearance ≥ 40 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal, as calculated by the Cockcroft Gault formula.

3.1.8 Acute Toxicity Recovery

Patients must have recovered from any acute toxicity related to prior therapy, includingsurgery. Toxicity should be ≤ grade 1 or returned to baseline.

3.1.9 Suppression of Testosterone Production

All patients who have not undergone bilateral surgical castration must continue suppression of testosterone production by appropriate usage of GnRH agonists or antagonists.

3.1.10 No Other Invasive Malignancies

Patients must not have other invasive malignancies (within the past 2 years with the exception of non-melanoma skin cancers or non-invasive bladder cancer).

3.1.11 Adequate Contraception

Enrolled patients must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, the duration of study participation and 3 months after the end of the treatment.

3.1.12 Written Informed Consent

Patient must be able to understand and willing to sign a written informed consent document.

3.1.13 Steroids

Patients on a stable dose of steroids of 10 mg/day or less can continue on steroids if they are on peptic ulcer disease prophylaxis with an H2-blocker or proton pump inhibitor

3.1.14 Anticoagulants

Patients on an anticoagulant can be enrolled as long as the INR does not exceed 3.

3.2 EXCLUSION CRITERIA

3.2.1 Prior Treatment

Patients who have had chemotherapy, large field radiotherapy, or major surgery must wait 3 weeks prior to entering the study.

3.2.2 Agents Not Approved by the FDA

Patients may not be receiving any agents not approved by the FDA within the past 4 weeks.

3.2.3 Brain Metastases

Patients with known brain metastases will be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.4 Proteinuria

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.

3.2.5 Uncontrolled Intercurrent Illness

Uncontrolled intercurrent illness including, but not limited to, hypertension (systolic BP > 160, diastolic BP > 100), ongoing or active systemic infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.6 Hemorrhage

Hemorrhage within 30 days of dosing

3.2.7 History of Peptic Ulcer Disease or Gastritis

History of peptic ulcer disease or gastritis within 6 months of TRC105 administration, unless patient has received adequate treatment for peptic ulcer disease and has evidence of complete resolution documented by EGD

3.2.8 QTc

QTc > 500 msec

3.2.9 HIV Disease

Known HIV-positive patients are excluded

3.2.10 History of Hypersensitivity Reaction

History of hypersensitivity reaction to human or mouse antibody products

3.2.11 History of Familial Bleeding Disorders

Patients with a history of familial bleeding disorders.

3.2.12 Hereditary Hemorrhagic Telangiectasia

Patients with a history of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)

3.3 INCLUSION OF WOMEN AND MINORITIES

Men of all races and ethnic groups are eligible for this trial. Women are excluded by the nature of the disease.

3.4 BASELINE EVALUATION

3.4.1 Imaging Studies

Imaging studies (baseline – obtained within one month prior to enrollment):

- Technetium 99 Bone Scintigraphy
- CT scan of chest, abdomen and pelvis

3.4.2 Laboratory Evaluation

Laboratory evaluation (baseline – obtained within 16 days prior to dosing)

- Hematological profile: CBC with differential and platelet count, PT, aPTT, fibrinogen.
- Biochemical profile: electrolytes, BUN, creatinine, urine protein-creatinine ratio (UPC), AST, ALT, total bilirubin, calcium, phosphorus, albumin, magnesium, uric acid, albumin, amylase and testosterone level. This is to be ordered as an acute care panel, hepatic panel, mineral panel, uric acid and total protein.
- Tumor marker profile: PSA (baseline – within 7 days prior to dosing)
- CTC (baseline and at week 12)
- FcGRIII (baseline)
- INR if patient is on an anticoagulant

3.4.3 History and Physical Exam

History and physical exam with vital signs within 1 week prior to dosing.

3.4.4 EKG

Electrocardiogram (baseline – obtained within 16 days prior to dosing)

3.5 REGISTRATION PROCEDURES

3.5.1 On-Study Registration

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://intranet.cancer.gov/ccr/welcome.htm) must be completed and faxed to 301-480-0757. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail. Please note, it is very important for all registrars to acquire encrypted e-mail from NIH Help Desk, since the verification of registration includes patient's information. A recorder is available during non-working hours.

3.5.2 Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a patient is taken off-study. An off-study form from the web site (http://intranet.cancer.gov/ccr/welcome.htm) main page must be completed and faxed to 301-480-0757.

4 TREATMENT PLAN

4.1 PHASE I LEAD-IN

The primary objective of this phase I lead-in is to define the maximum tolerable dose (MTD) of TRC105, given as an intravenous infusion on day 1 and day 15 or days 1, 8, 15, and 22 (+/- 2 days) of each 28 day cycle, to be administered in the phase II portion of the study.

This open-label, non-randomized, dose-finding evaluation of TRC105 will be conducted in all patients with progressive metastatic castrate resistant prostate cancer. Escalating doses of TRC105, based on a modified Fibonacci scheme [51], will be given intravenously every 2 weeks, on days 1 and 15 for Cohorts 1, 2, 3, 5, and 6 or weekly on days 1, 8, 15 and 22 of each 28 day cycle for Cohort 4 . Intra-patient dose escalation will not be permitted. The starting dose of TRC105 will be 0.3 mg/kg (one dose level below the highest level studied to date). The maximal potential TRC105 dose that will be studied in this trial is 20 mg/kg. The starting dose for TRC105 was based on preliminary results from the ongoing phase I trial and toxicology studies in nonhuman primates. In preclinical studies in cynomolgus monkeys, the no observed event level (NOEL), at which there was no clinical, clinical pathologic or histopathologic evidence of toxicity was determined to be 30 mg/kg given by 30 minute intravenous infusion weekly for five doses. This NOEL of 30 mg/kg in monkeys dosed weekly for five doses in an intravenous toxicity study is twice the maximum clinical dose of 20 mg/kg.

The planned dose escalation schedule is as follows:

Table 3: Planned Dose Escalation

Cohort	Phase I Dose	Planned Number of Patients
1	1.0 mg/kg every 2 weeks	3-6
2	3 mg/kg every 2 weeks	3-6
3	10 mg/kg every 2 weeks	3-6
4	10 mg/kg weekly	Up to Six Patients
5	15 mg/kg every two weeks	3-6
6	20 mg/kg every two weeks	3-6

Each cohort in the phase I portion of the study is planned to have at least 3 patients to evaluate for toxicity, with the exception of cohort 4. Once amendment F is approved by the NCI Institutional Review Board, enrollment will proceed directly to cohort 5. Existing patients in Cohort 4 will continue to be treated weekly. Three patients will be treated at a given dose level and observed for acute toxicity for one course of treatment before any more patients are entered. If none of the three patients at a given dose level experience dose-limiting toxicity (DLT), defined as any grade 3 or higher hematologic (excluding anemia) or non-hematologic toxicity considered to be possibly related to TRC105, then the next cohort of three patients will be enrolled at the next higher dose. Toxicities will be graded using the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE). If two or more of the three patients experience DLT that is considered to be at least possibly related to TRC105, then three more patients are treated at the next lower dose unless six patients have already been treated at

that dose. If one of three patients treated at a dose experiences DLT that is considered to be at least possibly related to TRC105, then three more patients are enrolled at that same level. If the incidence of DLT among those six patients is one in six, then the next cohort of three patients is treated at the next higher dose. In general, if two or more of the six patients treated at a dose level experience DLT, then the MTD is considered to have been exceeded, and three more patients are treated at the next lower dose as described above [51]. The MTD is defined as the highest dose studied for which the incidence of DLT was less than 33% [51]. For MTD determination, dose-limiting toxicities will be evaluated throughout the first 28 days of treatment (Cycle 1). Patients who exit the study for reasons other than drug-related toxicity prior to completion of the 28-day DLT evaluation period will be replaced to ensure an adequate safety assessment of each cohort. If at the first dose level more than one DLT is observed in the first three subjects, or more than two DLTs in six subjects are observed, the study will be stopped.

4.2 PHASE II

Patients in phase II will receive a TRC 105 dose of 20 mg/kg on day 1 and day15 (± 2 days) of each 28 day dosing cycle as determined in the phase I portion of this study. Patients in this portion of the study will be stratified in to two arms as described below.

Two treatment arms (strata):

1. Chemotherapy-naïve (including no prior antiangiogenic therapy)
2. Post-docetaxel disease progression

This phase II portion of the study is an open-label, two-stage, two-arm design. Patients will be treated with TRC105 as an intravenous infusion at 20 mg/kg every two weeks of each 28 day cycle. In both phases of this trial, patients will be treated with TRC105 until progressive disease (as defined below) or intolerable toxicity. Subjects enrolled onto this study will all have evidence of disease progression despite castrate levels of testosterone, and will then be stratified into two arms, either chemotherapy-naïve or chemotherapy-refractory. This is in order to allow for an adequate number of patients to be enrolled such that the impact of TRC105 in each stratum can be assessed independently. The primary objective of this phase II study is to determine if single-agent TRC105, when administered at 20 mg/kg every two weeks to patients with castrate-resistant prostate cancer, is associated with a 6-month progression-free survival probability of 30% in two separate strata of patients: those who are chemotherapy naïve and those who are chemotherapy-refractory with evidence of disease progression despite prior docetaxel. The primary endpoint for both strata of patients is progression-free survival (PFS) per radiologic and clinical criteria. PSA increases will not be used to determine progression.

Advanced prostate cancer is characterized by a poor ability to measure response due to immeasurable bone-only metastases [52]. Because of the uncertainties associated with assessing response in bone and the controversy surrounding the clinical significance of post-therapy changes in PSA, the Prostate Cancer Working Group (PCWG)-2 [53] recommends that phase II trials focus on a clinically relevant improvement in time to progression as a means of providing the most useful way to assess whether to proceed from a phase II to a phase III trial [53]. Time-to-event end points, with an emphasis on PFS as a composite endpoint constituted by radiological or symptomatic progression, are currently recommended by the Prostate Cancer Working Group-2 guidelines [53]. According to a retrospective analysis by Halabi et al [54], composite PFS appears to be a useful intermediate surrogate for overall survival.

In this phase I/II trial, radiographic progression is defined as the first occurrence of either two distinct new lesions on bone scan or progression of measurable disease by RECIST criteria [1]. Regarding metastatic bone and soft tissue lesions, new lesions seen by the end of cycle 2 or before cycle 3 (after the first re-staging evaluation) may represent disease that was not detected on the pre-study scan, and a confirmatory scan will be required at the next scheduled re-staging evaluation unless clinically not indicated. This is consistent with recommendations of the Prostate Cancer Clinical Trials Working Group-2 [53]. For more information, please refer to sections 11.1.6 and 11.1.8. Objective response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [Eisenhauer EA, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1) 2009; Eur J Ca 45:228-247]. Clinical progression is defined as any bone-related event (pathologic fracture, spinal cord compression, need for palliative radiation, surgery or kyphoplasty to any neoplastic bone lesion) or a deterioration of performance status, typically to an ECOG score of greater than two. The utilization of composite PFS as a primary endpoint, and the definition of progression as noted above, is consistent with prior trials performed both at the NCI and in the extramural setting [52, 55] as well as the current recommendations from the Prostate Cancer Clinical Trials Working Group-2 [53].

4.3 TRC105 ADMINISTRATION

At the outset of the study, the patient may be admitted to the inpatient service for a period of approximately 24 hours to complete research studies including PK measurements. Otherwise, treatment will be administered on an outpatient basis. Reported adverse events (AEs) and potential risks are described in Section 2.4.2. Appropriate dose modifications for TRC105 are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Pre-medications are to be given approximately 30 minutes to two hours prior to the start of each TRC administration:

- Acetaminophen 650 mg PO x 1
- Dexamethasone 20 mg IV x 1 (see below for tapering schedule)
- Famotidine 20 mg iv (or similar H2 blocker) x1
- Cetirizine 10 mg i.v. or p.o. x1 (or similar oral or intravenous antihistamine)

Thirty minutes after completing pre-medications, TRC105 will be administered intravenously utilizing an infusion pump. TRC105 must be administered using a low protein binding, non-DEHP infusion set with a 0.2 micron downstream filter. The attachment of the infusion pump administration set to the IV bag and transport of the study drug to the patient will be performed as per standard study site procedures.

On Cycle 1 Day 1, TRC105 will be infused over a period of four hours. For patients who complete one 4 hour infusion without the development of infusion reaction, the subsequent TRC105 infusion may be reduced to 2 hours. For patients who complete one 2 hour infusion without the development of infusion reaction, subsequent TRC105 infusions may be reduced to 1 hour. The TRC105 infusion must be given over at least 1 hour.

After the minimum TRC105 infusion duration of 1 hour has been safely administered, the dexamethasone should be gradually tapered as tolerated with each subsequent infusion and eventually discontinued if possible (see below table). The dexamethasone dose should not be reduced unless the prior infusion was well-tolerated (no infusion reaction of any grade).

Table 4: Recommended Dexamethasone Taper Schedule

Infusion	**Dexamethasone Dose and Schedule**
First 1 hr infusion	20 mg i.v. 30 minutes to 2 hours prior to each infusion
Second 1 hr infusion	10 mg i.v. 30 minutes to 2 hours prior to each infusion
Third 1 hr infusion	5 mg IV 30 minutes to 2 hours prior to each infusion
Subsequent infusions	No dexamethasone

[a]The dexamethasone dose should not be reduced unless the prior infusion was well-tolerated (no infusion reaction of any grade).

Patient with infusion related events of any grade should be managed appropriately. The immediate next dose should be infused at the same infusion rate. If tolerated, subsequent doses may be decreased per protocol. Patients who experience a grade 3 or higher hypersensitivity reaction will be taken off study. Each infusion of TRC105 must be completed within 8 hours of reconstitution. The dose level and infusion start and stop times must be recorded in the source documents.

4.3.1 Management of TRC105 Infusion Reactions

If a patient experiences a grade 2, 3 or 4 adverse reaction during infusion, the infusion should be stopped and the patient treated accordingly. Antipyretic, antihistamine and other therapies should be administered as indicated. If appropriate, the infusion may be restarted at half of the previous rate when the patient is able to continue. Infusion reactions will be recorded as AEs in the case report form. Interventions should be documented as concomitant medications or concomitant treatments as appropriate.

4.3.2 TRC105 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 identification of the 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.

4.4 CONCURRENT MEDICATIONS

Non-steroidal anti-inflammatory drugs (NSAIDS) are allowed while on protocol therapy. However, all patients who receive NSAIDS should also receive peptic ulcer disease prophylaxis with an H2 or proton pump inhibitor.

4.5 DURATION OF THERAPY

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Progressive disease as defined in Section 11.0,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s)
- Patient decides to withdraw from treatment
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.6 FOLLOW-UP CRITERIA

- All study subjects will be followed for overall survival only once active treatment has been completed (as indicated above).
- Follow-up will be annual telephone contact to assess survival status. Every attempt will be made to contact patient/subject including: contacting referring physician, contacting emergency contact patient identified on admission, checking SSDI (Social Security Death Index)

4.7 OFF-STUDY CRITERIA

- Patient choice
- Voluntary withdrawal of consent to participate in the study or the follow up period.
- Grade 4 non-hematologic toxicity or intolerable, persistent toxicity following two successive dose reductions as outlined in section 6
- Patient noncompliance with the study.
- Patient death

5 DOSE LIMITING TOXICITIES

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting and determination of DLT. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at http://ctep.cancer.gov. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

Dose limiting toxicities (DLTs) are defined as any grade 3 or higher hematologic (excluding anemia) or non-hematologic toxicity considered to be possibly related to TRC105. Anemia will not be considered as a DLT. Three patients should have completed at least 1 cycle of therapy prior to considering dose escalation in the next cohort of patients, with the exception of cohort 4. Once amendment F has been IRB approved, enrollment will proceed directly to cohort 5.

Determination of DLT for the purpose of dose escalation enrollment will be based on toxicities observed in the first 28 days of treatment (cycle 1) and must be considered as at least possibly related to study drug. Evaluation for toxicity will continue throughout the study and should dose limiting toxicities occur beyond the cycle one, consideration will be given to halting the dose escalation and re-evaluating lower dose levels.

Infusion reactions that are allergic or vaso vagal in nature will not require that the dose level below is expanded.

Table 5: Dose Escalation Table

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level
$\geq$ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. If 0 of these 3 patients experience DLT, proceed to the next dose level. If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
$\leq$1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

If $\geq$2 patients experience a DLT at any dose level, at any time in the Phase I study, then subsequent patients will be enrolled at the next lower dose level.

6 DOSING DELAYS AND DOSE MODIFICATIONS

Toxicities will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at: http://ctep.cancer.gov.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

As this trial allows patients to receive treatment indefinitely, patients may have the dose of TRC105 temporarily withheld and potentially resume treatment as long as they do not fulfill the off-study criteria outlined in section 4.6

Dose reductions and dose interruptions will be allowed during both the phase 1 and 2 portions of this study. Patients who experience a DLT that is at least possibly related to TRC105 will have their dose held until the toxicities have resolved as outlined in the tables and text below. For selected DLTs, upon re-initiation of treatment with TRC105, patients will have their dose reduced to the next lower dose level. No dose reductions below 0.3 mg/kg will be allowed. Patients will be removed from the study if dose-limiting toxicity does not resolve as outlined in the tables and text below within 28 days.

The following adjustments will only apply if the toxicities reported are attributed by the investigators to be at least possibly related to TRC105

Dose Adjustment based on hematologic toxicities

Table 6: Hematologic Toxicities Dose Adjustment

Toxicity	**Dose Adjustment**
Grade 0, 1, 2 neutropenia	No action
Grade 3 neutropenia without concomitant fever	Hold TRC105 until ANC ≥ 1000 Check weekly CBC/differential May resume treatment at current dose level
Grade 3 neutropenia with concomitant fever (temperature ≥ 38.5^{o}C)	Hold TRC105 until ANC ≥ 1000 Check weekly CBC/differential All subsequent cycles at next lower dose level
Grade 4 neutropenia without fever	Hold TRC105 until ANC ≥ 1000 Check weekly CBC/differential All subsequent cycles at next lower dose level

Additional management steps to be followed are based on whether the patient had received growth factor support during the cycle in which grade 4 neutropenia was documented.

For those patients with grade 4 neutropenia not already supported by pegfilgrastrim, the following guidelines apply:

1. Hold TRC105 until ANC ≥1000 as noted above
2. Consider administration of filgrastrim once grade 4 neutropenia is noted, with duration of growth factor support to be determined by physician discretion.
3. Once ANC ≥1000, TRC105 may be re-started at next lower dose level
4. Subsequent cycles of treatment may be accompanied by administration of pegfilgrastrim

For those patients who experience grade 4 neutropenia in a cycle during which prophylactic growth factor support was administered, the following guidelines apply:

1. Once ANC ≥1000, re-start TRC105 at next lower dose level
2. Continue administration of prophylactic pegfilgrastrim unless, at physician discretion, there is justification to withhold.

Dose adjustment based on hematologic toxicities

Table 7: Hematologic Toxicity Dose Adjustment

Toxicity	**Dose Adjustment**
Grade 0, 1 thrombocytopenia	No action
Grade 2, 3 thrombocytopenia without bleeding	Hold treatment until platelet count ≥ 75,000 May resume at current dose level
Grade 3 thrombocytopenia with bleeding	Hold treatment until platelet count ≥ 75,000 All subsequent cycles at next lower dose level
Grade 4 thrombocytopenia	Hold treatment until platelet count ≥ 75,000 All subsequent cycles at next lower dose level

Grade 1 Toxicity

Treatment with TRC105 need not be interrupted. For symptoms that last more than 7 days and have been found to be intolerable to the patient, the dose of TRC105 may be reduced to the next lower dose level.

Grade 2 Non-Hematologic Toxicity

For nausea, vomiting and diarrhea, maintain dosing with symptomatic treatment. Patients who have a subjective intolerable grade 2 event may have a dose interruption. Re-initiation of TRC105 at the same dose is allowed if and when the adverse event resolves to grade 1 or baseline; dose reduction is not required. For persistent nausea, vomiting or diarrhea despite symptomatic treatment that remains unacceptable (intolerable) to the patient, reduce dose of TRC105 to the next lower dose level. For any grade 2 toxicity, the dose need not be reduced unless side effects become intolerable to the patient. Patients with intolerable or limiting toxicity after two successive dose reductions will be removed from the study. Electrocardiogram evaluation will be performed as clinically indicated

Grade 3 Non-Hematologic Toxicity

Hold TRC105 and re-evaluate at least bi-weekly until toxicity improves to ≤ grade 1 or pre-treatment baseline. Reduce dose of TRC105 by one dose level. Treatment will be discontinued in patients who experience grade 3 non-hematologic toxicities that do not resolve to grade 1 or baseline within 4 weeks. Hypokalemia and hypomagnesemia that can be corrected within 48 hours to grade 2 or less will not require a dose reduction.

Dose Adjustment based on non-hematologic toxicities

Table 8: Non-Hematologic Toxicities Dose Adjustment

Toxicity	**Dose Adjustment**
Grade 0, 1, 2	No action
Grade 3 non-hematologic toxicity (except untreated nausea and vomiting)	Hold treatment until ≤ grade 1 or pre-treatment baseline All subsequent cycles at next lower dose level

Grade 4 Non-hematologic Toxicity

Patients with clinical grade 4 non-hematologic toxicity thought to be at least possibly related to the IND will be taken off treatment.

Patients with intolerable or limiting toxicity following two successive dose reductions will be removed from study.

Unacceptable toxicities that have not resolved at time of "off treatment" must be followed until stabilization or resolution.

Proteinuria

Proteinuria, as demonstrated by a 24 hour protein of ≥ 2000 mg. Urine protein will be screened by urine protein-creatinine ratio (UPC).

Table 9: Proteinuria

Proteinuria	[Proteinuria should be monitored by urine analysis for urine protein creatinine (UPC) ratio prior to every other cycle of TRC105]	
	UPC ratio < 3.5	Continue TRC105
	UPC ratio ≥ 3.5	Hold TRC105 until it UPC recovers to < 3.5.
	Grade 4 or nephrotic syndrome	Discontinue TRC105.

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form with the exception of grade 1 events occurring in the Phase II portion of the protocol.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug. AEs that are considered treatment related, expected, continuing, but not resolvable by 30 days after treatment completion (e.g., alopecia) will not be followed after the 30-day period.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

7.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the

pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.1.5 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.6 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.1.7 Protocol Deviation (NIH definition)

A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IRB.

7.1.8 Protocol Violation (NIH definition)

Any change, divergence, or departure from the study procedures in an IRB-approved research protocol that has a major impact on the subject's rights, safety, or well-being and/or the completeness, accuracy or reliability of the study data.

7.1.9 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to:

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; AND
- Is related or possibly related to participation in the research; AND

- Places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 NCI-IRB REPORTING

7.2.1 NCI-IRB Expedited Reporting of Adverse Events, Unanticipated Problems, and Deaths

The Protocol PI will report to the NCI-IRB:

- All unexpected serious adverse events that are possibly, probably, or definitely related to the research
- All deaths, except deaths due to progressive disease
- All Protocol Violations or Deviations
- All Unanticipated Problems

Reports must be received by the NCI-IRB within 7 working days of PI awareness via iRIS.

7.2.2 NCI-IRB Requirements for PI Reporting of Adverse Events at Continuing Review

The protocol PI will report to the NCI-IRB:

- All Grade 2 unexpected events that are possibly, probably or definitely related to the research;
- All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
- All Grade 5 events regardless of attribution;
- All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

7.2.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that require a sponsor recommended change to the protocol or the consent form or in the opinion of the PI increases risks to study participants will need to be reported to the NCI IRB.

7.3 IND SPONSOR REPORTING CRITERIA

An investigator must immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event.

Study endpoints that are serious adverse events (e.g. all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g. death from anaphylaxis). In that case, the investigator must immediately report the death to the sponsor.

7.4 REPORTED ADVERSE EVENTS RELATED TO TRC105

Clinical safety experience is based on data from 43 subjects with advanced incurable solid tumors treated with escalating doses of TRC105 in the phase I clinical study 105ST101 and 20 subjects in the phase I portion of the current study, NCI 10C0062.

- BLOOD/BONE MARROW – anemia

- CONSTITUTIONAL SYMPTOMS – fatigue, fever, chills, flushing, dysgeusia
- GASTROINTESTINAL – diarrhea, nausea, vomiting
- RENAL – proteinuria
- PAIN – arthralgia
- VASCULAR – Gastrointestinal hemorrhage, oral hemorrhage, hypotension
- LABORATORY – hyperuricemia
- NERVOUS SYSTEM – headache
- RESPIRATORY, THORACIC, MEDIASTINAL – epistaxis
- GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS – infusion related reaction

7.5 FDA REPORTING CRITERIA

7.5.1 IND Safety Reports to the FDA (Refer to 21 CFR 312.32)

7.5.1.1 Expedited reporting to the FDA

The Sponsor will notify FDA via phone, fax, or email of any unexpected fatal or life-threatening suspected adverse reactions as soon as possible but no later than 7 calendar days of initial receipt of the information. This will be followed with a written report within 15 days using the MedWatch Form 3500a.

The study Sponsor will notify FDA in writing of any suspected adverse reaction that is both serious and unexpected as soon as possible but no later than 15 calendar days after initial receipt of the information using the MedWatch Form 3500a. If FDA requests any additional data or information, the sponsor must submit it to the FDA as soon as possible, but no later than 15 calendars days after receiving the request.

The study Sponsor will also report expeditiously as above:

- any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug
- clinical important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

7.5.2 FDA Annual Reports (Refer to 21 CFR 312.33)

The study Sponsor will submit a brief report annually of the progress of the trial within 60 days of the anniversary date that the IND went into effect as indicated in 21CFR 312.33, and any associated FDA correspondences regarding the IND annual report.

7.5.3 Expedited Adverse Event Reporting Criteria to the IND Manufacturer (Tracon Pharmaceuticals, Inc.)

- The study IND holder will notify TRACON in a written IND Safety Report (MedWatch, Form 3500A) of any *unexpected* fatal or life threatening experience

associated with the use of TRC105 as soon as possible but in no event later than 7 calendar days of initial receipt of the information.

- The IND holder will also notify TRACON in a written IND Safety Report (MedWatch, Form 3500A) of any serious adverse events *associated* with the use of TRC105 that is both *serious* and *unexpected* as soon as possible and in no event later than 15 calendar days after initial receipt of the information.
- SAEs that do not require expedited reporting to the FDA will be reported to TRACON quarterly in the form of a spreadsheet generated from the CCR C3D Oracle Clinical database.

7.6 DATA AND SAFETY MONITORING PLAN

7.6.1 Principal Investigator/Research Team

A safety monitoring committee made up of the Principal Investigator, William L. Dahut, M.D., a Lead Associate Investigator, David E. Adelberg, M.D. and Research Nurse Ann Pierpoint, R.N., will review the events of every patient on the protocol every week. Follow-up of both on-going and previously treated patients and the reported adverse events in a given week will be reviewed (i.e., adverse events, protocol adherence, tumor responses, and potential new patient eligibilities). Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations and violations will be immediately reported to the IRB using iRIS and if applicable to the Sponsor.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.6.2 Sponsor Monitoring Plan

This trial will be monitored by personnel employed by Harris Technical Services on contract to the NCI, NIH. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

At least 25% of enrolled patients' will be randomly selected and monitored at least biannually or as needed, based on accrual rate. The patients selected will have 100% source document verification done. Additional monitoring activities will include: adherence to protocol specified study eligibility, treatment plans, data collection for safety and efficacy, reporting and time frames of adverse events to the NCI IRB and FDA, and informed consent requirements. Written reports will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

8 PHARMACEUTICAL INFORMATION

8.1 COMPOSITION OF TRC105

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

8.2 TRC105 PACKAGING AND LABELING

TRC105 will be supplied at 5 mg/mL in PBS in sealed 15 mL glass vials containing 15 mL. Vials of TRC105 are labeled with the following:

Table 10: Label Text Approval Form

Section I: Label Information
Study No.: 105ST101 **Countries: US** **Languages: English** **Label Text:** **TRC105** **NSC #754227** **75 mg per vial (5 mg/mL, 15 mL vial)** Store refrigerated at 2-8°C For Intravenous Use Only. Single-use vial Lot: XXXXXXX Mfg Date: XX/XX/XXXX Caution: New Drug--Limited by Federal (or United States) law to investigational use. TRACON Pharmaceuticals, Inc., San Diego, CA 92122 USA (X) New Request (__) Amendment No: **Product Development:** Change: Prepared By: Sharon Real Date: 21 March 2011

Section II: Label Text Approvals	
Clinical Operations:	
Approved By:	Date:
Regulatory Affairs:	
Approved By:	Date:

For information regarding current formulation, please refer to section 2.4.3. TRC105 Physical, Chemical, and Pharmaceutical Properties and Formulations.

8.3 TRC105 Storage and Shipping

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

8.4 TRC105 Preparation

TRC105 will be prepared in the pharmacy and diluted into normal saline in polyolefin plastic bags. TRC105 will be administered using an in-line 0.2 micron low protein binding filter. Compatibility studies support the use of tubing that is polyethylene lined and non-DEHP. Following dilution in normal saline, TRC105 will be administered at room temperature within 8 hours of reconstitution. Depending on the dose and patient weight, multiple vials may 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 to be administered can be rounded up or down to the nearest 0.1 mL. If an increment of 0.05 mL is calculated, the volume should be rounded up. The calculated volume of TRC105 is to be a concentration between 0.03 mg/mL and 5 mg/mL (undiluted). The diluted TRC105 must be gently inverted several times in order to ensure a homogeneous solution. Preparations of TRC105 in infusion containers are stable for up to 8 hours at room temperature.

8.5 TRC105 Handling and Disposal

The Investigator should not return clinical study materials to TRACON unless specifically instructed to do so by TRACON. All used or expired vials of TRC105 should be retained. A TRACON representative will periodically conduct an accountability of the used or expired vials and authorize their destruction.

If the participating pharmacy is prohibited by institutional policy from retaining open or expired vials, the Site Pharmacist will then be responsible for documenting the destruction of the vials and completing an Investigational Drug Product Destruction Form.

8.6 ADVERSE EVENTS

Please refer to section 2.4.2 TRC105 Clinical Pharmacology, Toxicity and Efficacy**,** under the heading TRC105 Clinical Safety for all information relating to adverse events from TRC105.

9 CORRELATIVE/SPECIAL STUDIES

9.1 PHARMACODYNAMIC STUDIES OF TRC105

9.1.1 Background:

1. TRC105 is a human/murine chimeric IgG1 monoclonal antibody that binds to human CD105, thus inhibiting angiogenesis and tumor growth. However, there is no current human clinical data to support such biological activity.
2. Via the detection of plasma VEGF and PlGF (placenta-derived growth factor), we have been able to consistently detect elevated levels of both proteins following an array of anti-angiogenic therapies, including the anti-VEGF antibody bevacizumab, VEGFR2 inhibitors, and their combinations in clinical studies.
3. The data quality for determining plasma levels of VEGF and PlGF is exceptional, allowing the detection of small changes of levels of these proteins associated with systemic hypoxia. Such analysis would provide the necessary support for the putative mechanism of action of the agent under investigation.

9.1.2 Implementation:

Blood samples will be taken at various time points pre- and post-TRC105 treatment and be used to measure levels of surrogate biomarkers for the demonstration of mechanism of action of the investigational agent.

Collection and Processing of Specimen(s):

Plasma: Two 4ml EDTA tubes (BD, Franklin Lakes, NJ) are collected from patients pre- dose on cycle 1 day 1, cycle 1 day 15, and cycle 2 day 15. Immediately place tubes on wet ice and then refrigerate. The date and **exact** time of each blood draw should be recorded on the tube. The samples need to be processed within 2 hours of collection. Please page 102-11964 (Gareth Peters or alternate tech) for immediate pick-up. Contact Dr. Figg's Blood Processing Core (BPC) in 10/5A09 at 301-402-3622 or 301-594-6131 with any questions. The tubes are centrifuged in the BPC at 2400rpm for 5 minutes at 4ºC. The plasma layer from each tube is transferred into a separate 2ml cryovial, immediately frozen on dry ice, and stored at -80ºC. The frozen samples will be transferred to Dr. Cao's lab at Bldg 37, Rm. 6134 in batches (tel: 301-435-9039).

Pharmacodynamic Tests and Data Analysis:

Plasma levels of angiogenic factors will be performed for sCD105, VEGF, PlGF, bFGF and sVEGFR1 (soluble VEGF receptor 1). The analysis will be done with assays developed on electrochemiluminescence platform that provides ultra-high sensitivity and very large signal dynamic range. Purified protein standard will be used for generating standard curves for concentration determination. Data analysis will be performed with Prism (GraphPad, San Diego, CA) to determine the medium value, interquartile range, and p value in paired t test.

sCD105 collected predose C1D1, C1, D15 and C2, D15 will require one additional lavender tube and to be processed by Dr. Figg's lab. The National Cancer Institute will batch and ship sCD105 samples to Dr. Seon at Roswell Park Cancer Institute.

TRC105 interferes with the R & D Systems sCD105 kit, so plasma for sCD105 to be stored at NCI and batch shipped for analysis to:

Jill Duzen
Seon Laboratory
CGP bldg. Room L5-126
Roswell Park Cancer Institute
Elm and Carlton Streets
Buffalo, NY 14263
Phone: 716-845-4482

Correlations:

If the induction of VEGF and PlGF can be observed, correlative studies will be performed between the induced levels of angiogenic factors and the dose levels of TRC105 in the phase I segment of the trial. If responses can be established in phase II, correlative studies will be performed between the initial levels of the angiogenic factors, or the degree of their induction with the clinical responses.

Sample Data Collection:

All samples sent to the Clinical Pharmacology Program (CPP) will be barcoded, with data entered and stored in the Patient Sample Data Management System (PSDMS) utilized by the CPP (the Blood Processing Core is part of the CPP). This is a secure program, with access to the PSDM System limited to defined CPP personnel, who are issued individual user accounts. Installation of PSDMS is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen. All CPP personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.

PSDMS creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without PSDMS access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

Sample Storage and Destruction:

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the CPP and offsite at NCI Frederick Central Repository Services (Fisher BioServices) in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in the PSDM System. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the CPP. It is the responsibility of the NCI Principal

Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e. broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the PSDMS. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

9.1.3 Pharmacodynamic assessment of circulating endothelial cells and immune subsets:

Two 8cc CPT-citrate tubes (blue/black tiger top) will be drawn for analysis of circulating endothelial progenitor cells (CEP), mature circulating endothelial cells (CEC) and circulating tumor cells (CTC). CEC samples will be collected from patients pre- dose on cycle 1 day 1, cycle 1 day 15 and cycle 2 day 15. CTC samples will be collected from patients at baseline, prior to dose cycle 4 (green top). As soon as possible after the patient is scheduled please send email notification to the Trepel lab: Jane Trepel at trepel@helix.nih.gov; Min-Jung Lee at leemin@mail.nih.gov that the sample is scheduled. After the sample is drawn please call the Trepel lab at 301-496-1547 to communicate that the sample is ready. Keep the sample on the unit at room temperature. The sample will be picked up by the lab. CEC, CEP, and CTC will be analyzed by multiparameter flow cytometry. If cell number permits, the sample may be analyzed for changes in immune cell subsets, including regulatory T cells and CD8+/IL-17+ T cells, which may reflect changes in TGF-beta biology. The impact of TRC105 on TGF-beta biology may also be assessed by examination of TGF-beta/Smad signaling in endothelial cells and immune cells. If tumor biopsies are available they may be examined for the same parameters as peripheral blood, i.e. mature endothelial cells and endothelial progenitor cells, immune subsets and TGF-beta signaling. Viable cells will be prepared using the Miltenyi GentleMACS Dissociator or by hand using mechanical dissociation and dissociative enzymes as needed for the tumor sample. Serum osteopontin may also be measured in, using ELISA (Pass, H et al. *N Engl J Med* 353:1564-1573, 2005), Luminex or similar technology. Serum osteopontin will be collected Cycle 1 Day 1 and Cycle 2 Day 15 in a 5 ml, red top tube.

FcGRIII will be collected at baseline (lavender top tube).

9.2 PHARMACOKINETIC STUDIES OF TRC105

Serum concentrations of TRC105 will be determined to assess pharmacokinetics of TRC105 and correlate with clinical response and toxicity. Serial samples will be obtained for pharmacokinetic analysis on C1D1 and C1D15 at the following time points:

- Predose on C1D1 and C1D15 – **phase I and phase II**
- Immediately at the end of infusion on C1D1 and C1D15 – **phase I and phase II**
- 1, 2, 8, 24 and 48 h after the end of C1D1 and C1D15 infusions – **only in phase I**
- During Cycle 2 and Cycle 3, trough and peak pharmacokinetic samples will be collected:
- Predose on C2D1, C2D15, C3D1 and C3D15
- Immediately at the end of infusion on C2D1, C2D15, C3D1 and C3D15

At each timepoint, a venous blood sample will be collected in a 4 mL serum vacutainer tube (red top). Page the Clinical Pharmacology Program on 102-11964 for immediate pickup (Dr. Figg's Lab - Building 10, Room 5A09; Tel: 301-402-3622).

Upon arrival in the Clinical Pharmacology Program, samples will be centrifuged, and the serum transferred into cryovials for storage at -80C. In addition, samples will be barcoded as described in section 9.1.2.

The samples will be batch shipped to and analyzed by WuXi Apptec, Attention Theodora Solomos (4751 League Island Blvd., Philadelphia, PA 19112), Telephone 215-218-5500 ext. 5662.

The pharmacokinetic characteristics of TRC105 in patients with CRPC will be evaluated using the WinNonlin software (Pharsight, Mountain View, CA). The maximum concentration, time to maximum concentration, the area under the curve extrapolated to infinity, clearance, and the apparent terminal half-life will be calculated.

9.3 IMAGING STUDIES

9.3.1 Time Efficient Automatic Lesion Identification and Measurement on CT

Metastatic tumor burden and treatment response is commonly evaluated on serial CT scans with subjective target lesion selection and measurement on baseline and post-treatment exams (RECIST). Subjective measurement error has been studied showing false categorization of partial response based on two measurements of the same lesion [56]. Semi-automated RECIST measurements of malignant lymph nodes produce reliable results when compared to manual measurements [57]. It is generally believed that assessment on thin section data on the most tumors possible [58] would be the optimal approach to assessing response to therapy. However, with manual protocols, the detection and measurement of additional lesions compounds the total time investment in the evaluation that has been rarely feasible. Various software programs have recently been developed to address this deficiency.

We aim to assess time savings of semi-automated lesion localization and measurement on serial images of metastatic cancer patients as compared to the current manual process. The automated software that will be used is available in the PACS (Picture Archiving and Communications System) at NIH provided by Carestream Health (Rochester, NY) and called the Lesion Management Application (LMA). The application has advanced serial image co-registration as well as refined registration for lesion identification (based on original exam). The program semi-automatically segments and measures the lesion targeted by the radiologist on baseline CT, then automatically localizes and measures the lesion on the subsequent exam. Preliminary results demonstrate that target lesions can be identified, segmented, and measured (including RECIST *and* volume) in most cases. Routine inclusion of tumor measurements should greatly assist

providers in quickly evaluating the efficacy of cancer therapies. Tumor evaluation by volume determination on serial CT studies can be enhanced and made more effective by semi-automated detection of previously identified and measured target lesions.

We will retrospectively assess CT scans acquired for tumor response evaluations via automated volumetric measurements obtained using LMA. We will also assess the accuracy and consistency of target lesion localization, segmentation, and resultant measurements, to include volumes, on serial CT studies.

10 STUDY CALENDAR

All baseline and follow-up evaluations can be performed during the last week of the prior cycle.

Table 11: Bi-Weekly Dosing

	Pre-study	Cycle 1						Cycle 2	Cycle 2 +		Off Treatment
Day		**1**	**2**	**3**	**15**	**16**	**17**	**15**	**1**	**15**	
TRC105[a]		X			X				X	X	
Premedications[b]		X			X				X	X	
Informed consent	X										
Demographics	X										
Medical history	X	X			X				X	X	X
Adverse event evaluation		X			X				X	X	X
Concurrent meds	X	X			X				X	X	X
Physical exam	X	X			X				X	X	X
Vital signs	X	X			X				X	X	X
Height	X										
Weight	X	X			X				X	X	
Performance Status	X	X			X				X	X	X
CBC w/differential, Platelets	X	X			X				X	X	X
PT, PTT, Fibrinogen	X	X			X				X	X	X
Serum chemistry [c]	X	X			X				X	X	X
ECG	X										
Urine Protein-creatinine Ratio (UPC)[d]	X										
Testosterone	X										
PSA	X	X			X				X	X	X
Restaging radiologic Evaluation[e]	X										
Pharmacokinetics[f]	X	X	X	X	X	X	X		X	X	
Angiogenic biomarkers[g]	X				X			**X**		X	
Serum Osteopontin		X						X		X	
Pharmacodynamics[h]	X										

a: TRC105: Dose as assigned; administered I.V. every two weeks. One cycle = 28 days
b: Premedications: Acetaminophen 650 mg, dexamethasone 20 mg iv, Famotidine 20 mg iv (or similar H2 blocker) x1, Cetirizine 10 mg iv or po x1 (or similar oral or intravenous antihistamine) 30 minutes to two hours prior. For details and dexamethasone tapering schedule please refer to section 4.3
c: Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, albumin, total protein, calcium, magnesium, phosphorous, AST, ALT, alkaline phosphatase, total bilirubin, uric acid
d: 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. UPC will be performed every other cycle
e: CT chest, abdomen, pelvis; radionuclide bone scintigraphy; refer to section 11for frequency of imaging studies
f: See section 9.2 for details as to pharmacokinetic timepoints to be drawn.
g: see section 9.1 for details as to pharmacodynamic timepoints/angiogenic biomarkers to be drawn.
h. See Section 9.1.3 for details; CEC drawn pre-dose on C1D1, C1D15, C2D15; CTC drawn pre-C1D1 and pre C4D1; FcGRIII drawn at baseline.

Table 12: Weekly Dosing for Phase I Cohort 4 Only

	Pre-study	**Cycle 1**									**Cycle 2+**				**Off Treatment**
Day		**1**	**2**	**3**	**8**	**15**	**16**	**17**	**22**	**24**	**1**	**8**	**15**	**22**	
TRC105[a]		X			**X**	X			**X**	X	X	X	X	**X**	
Premedications[b]		X			**X**	X			**X**	X	X	X	X	**X**	
Informed consent	X														
Demographics	X														
Medical history	X	X				X					X		X		X
Adverse event evaluation		X				X					X		X		X
Concurrent meds	X	X				X					X		X		X
Physical exam	X	X				X					X		X		X
Vital signs	X	X				X					X		X		X
Height	X														
Weight	X	X				X					X		X		
Performance Status	X	X				X					X		X		X
CBC w/differential, Platelets	X	X				X					X		X		X
PT, PTT, Fibrinogen	X	X				X					X		X		X
Serum chemistry [c]	X	X				X					X		X		X
ECG	X														
Urine Protein-creatinine Ratio (UPC)[d]	X														
Testosterone	X														
PSA	X	X				X					X		X		X
Restaging radiologic Evaluation[e]	X														
Pharmacokinetics[f]	X	X	X	X	X	X	X	X	X		X		X		
Angiogenic biomarkers[g]	X					X							X		
Serum Osteopontin		X											X		
Pharmacodynamics[h]	X														

a: TRC105: Dose as assigned; administered I.V. every week. One cycle = 28 days
b: Premedications: Acetaminophen 650 mg, dexamethasone 20 mg iv, Famotidine 20 mg iv (similar H2 blocker), Cetirizine 10 mg iv (or similar oral or intravenous antihistamine 30 minutes to two hours prior. For details and dexamethasone tapering schedule please refer to section 4.3
c: Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, albumin, total protein, calcium, magnesium, phosphorous, AST, ALT, alkaline phosphatase, total bilirubin, uric acid
d: 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. UPC will be performed every other cycle
e: CT chest, abdomen, pelvis; radionuclide bone scintigraphy; refer to section 11for frequency of imaging studies
f: See section 9.2 for details as to pharmacokinetic timepoints to be drawn.
g: see section 9.1 for details as to pharmacodynamic timepoints/angiogenic biomarkers to be drawn.
h. See Section 9.1.3 for details; CEC drawn pre-dose on C1D1, C1D15, C2D15; CTC drawn pre-C1D1 and pre C4D1; FcGRIII drawn at baseline.

11 MEASUREMENT OF EFFECT

Re-staging bone scans and CT scan of chest, abdomen, and pelvis will be required every two months for the first four months of the study (following cycles two and four), and then after every 3 cycles of treatment. If screening CT scan is negative for soft tissue disease, repeat CT imaging will not be required. Confirmatory scans should also be obtained 4 weeks following initial documentation of objective response (CR or PR).

Objective response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [Eisenhauer EA, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) 2009; Eur J Ca 45:228-247].

Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

11.1 RESPONSE CRITERIA FOR RADIOGRAPHIC STUDIES

11.1.1 Measuring of Soft Tissue Disease

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

a. Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm

Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions)

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

b. Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD (Stable Disease, SD)

Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD)

Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

c. Evaluation of Best Overall Response

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.

Table 13: Evaluation of Best Overall Response

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR Non-PD Not evaluated	No	PR	

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
SD	Non-CR Non-PD Not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	
*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion. **Only for non-randomized trials with response as primary endpoint. ***In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression				

d. Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration*." Every effort should be made to document the objective progression even after discontinuation of treatment.

e. In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesions be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

11.1.2 Confirmatory Measurement/Duration of Response

a. Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed at least 4 weeks after the

criteria for response are first met.

b. Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are

met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

11.1.3 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

11.1.4 Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

11.1.5 Non-Measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

11.1.6 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

11.1.7 Non-Target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.8 Metastatic Bone Lesions

Disease progression is considered if a minimum of two new lesions is observed on bone scan. New lesions seen by the end of cycle 2 or before cycle 3 (with the first re-staging bone scan) may represent disease that was not detected on the pre-study scan, and a confirmatory scan will be required at the next scheduled re-staging bone scan unless clinically not indicated. If confirmed, progression should be dated by the initial time when the lesions are first detected. If new lesions are seen after cycle 2, but no additional lesions are seen on confirmatory scans, the scans from post-cycle 2 would serve as the baseline scan to evaluate for disease progression, (ref: Scher, HI et al. J Clin Onc, 26 (7), 2008)

11.1.9 Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.1.10 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

11.1.11 Methods of Measurement

Chest X-ray - Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

CT and MRI - CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. For this study helical Multi-detector CT will be performed with cuts of 5 mm in slice thickness for chest, abdomen and pelvis lesions and 2-3 mm thickness for head and neck lesions.

12 STATISTICAL CONSIDERATIONS

The primary objectives of this study are twofold. First, define the maximum tolerable dose (MTD) of TRC105 given as an intravenous infusion every two weeks or every week of each 28 day cycle that will be administered in the phase II portion of the study. Secondly, determine if single-agent TRC105, when administered to patients with castrate-resistant prostate cancer at 20

mg/kg every two weeks, the MTD determined in phase I, is associated with a 6-month progression-free survival probability of 30% in two separate strata of patients: those who are chemotherapy naïve (and have not received prior antiangiogenic therapy) and those who are chemotherapy-refractory with evidence of disease progression despite prior docetaxel.

Published data from previous trials of patients with similar eligibility requirements demonstrated that the median time-to-progression in patients with chemotherapy-naïve, PSA-progressive, castrate-resistant prostate cancer is approximately three months [12, 59, 60]. For CRPC patients with evidence of post-docetaxel disease progression, the median progression-free survival (using similar end points as listed here) with agents in the second-line setting has ranged from 2.5 months [55, 61] up to 19 weeks [52]. In a phase II study of sorafenib in patients with progressive metastatic CRPC [62], approximately 10% of patients were progression – free at 6 months [62]. Based on these results, it would be useful to demonstrate whether TRC105 is able to induce progression free survival in 30% of patients at the 6 month (approximately day 180) evaluation time point.

The study will initially contain a phase I dose escalation portion, which will enroll all patients with progressive metastatic castrate-resistant prostate cancer. The study will evaluate patients in six cohorts of escalating dose levels.

As of the date of amendment 10-C-0062G, 17 patients were enrolled onto the first 5 dose levels and the dose level 6 could potentially enroll up to 6 patients, based on a standard 3+3 design. Thus, a maximum of 23 patients will be needed to complete the phase I evaluation, after all six dose levels are tested.

The phase II portion of the study will be conducted separately in two different patient strata, those who are chemotherapy-naïve for metastatic disease and those who have evidence of post-docetaxel disease progression. Given that the impact of treatment with TRC105 may be different according to prior exposure to chemotherapy, and the influence of prior chemotherapy on PFS is uncertain, patients will be stratified based on whether they are chemotherapy-naïve or have disease progression despite prior docetaxel-based chemotherapy. This is in order to allow for an adequate number of patients to be enrolled such that the impact of TRC105 in each stratum can be assessed independently. The two strata will have identical designs since, in each stratum, the goal is to target a modest level of activity. In each stratum of patients, the objective will be to determine if a 6 month progression free survival probability of 30.0% can be identified. If this is found to be true in either or both strata, then further evaluation in a definitive phase III trial will be considered appropriate.

The phase II portion of the trial will be conducted in each stratum using a two-stage optimal design (Simon R, Controlled Clinical Trials, 10:1-10, 1989). Using alpha=0.10 and beta=0.10 as acceptable error probabilities, the trial will target 30% as the desirable proportion of patients who are still without progression by radiographic or clinical criteria at the 6th monthly evaluation (p1=0.30), and will be considered inadequate if only a fraction consistent with 10% are without progression by the same evaluation time (p0=0.10).

Initially, 12 patients will be enrolled in each stratum and evaluated for progression. Six patients who are treated at 20 mg/kg (the phase I MTD) will be included, in the appropriate strata, among the initial 12 for each of the two strata. The enrollment will be temporarily halted after the 12th patient is enrolled in a stratum unless we know that 2 patients have passed the 6 month point without progression. If 2 or more of the first 12 patients enrolled in a given stratum have not

progressed at the 6th evaluation (day 180, approximately), then enrollment will continue until a full 35 patients have been enrolled in that stratum. If, among the first 12 patients enrolled, 0 or 1 are able to be progression free at the 6 month evaluation, then no further patients will be enrolled into that stratum once such a determination has been made. Enrollment may continue to the other stratum if one stratum has ended accrual. If 6 or more of the total cohort of 35 patients in a stratum have been found to be progression free at 6 months, then this will indicate an adequate progression free probability to justify further consideration of TRC105 in this population of patients. On the other hand, if 2 to 5 of 35 are progression free at 6 months, this will be considered insufficient. Under the null hypothesis (10% progression free at 6 months), the probability of being able to stop accrual after 12 patients have been evaluated at 6 months is 66%.

In addition to evaluation of the proportion of patients that are progression free at 6 months, the progression free survival for patients in the phase II portion of the trial will also be analyzed via a Kaplan-Meier curve. As well, the overall response rate will be reported for the phase II patients in each stratum, and the overall survival will be reported using a Kaplan-Meier curve. These results will also be compared between the two strata, but in an exploratory manner. The study will include an early stopping rule in the phase II portion of the trial. If among the first 10 patients, in both strata combined, two grade 4 GI bleeding events occur, then accrual will stop unless an amendment to modify the treatment is approved, because 2/10 is consistent with a 45% event rate (the upper one sided 90% CI on 2/10 is 45%), which would be considered excessive.

Secondary endpoints, including all correlations between circulating endothelial cells, pharmacokinetic parameters and such pharmacodynamic endpoints as toxicity and response, will be performed in an exploratory fashion, focusing on the patients enrolled in the phase II portion of the study, using non-parametric analyses unless data are clearly normally distributed, and will not be adjusted for multiple comparisons. Changes in molecular markers of angiogenesis before and after administration of TRC105, including serum for soluble CD105, will be evaluated using a Wilcoxon signed rank test. All findings with potentially important levels of statistical significance will be reported as hypothesis generating and suggestive of future confirmatory studies.

Toxicity information will be reported as the maximum grade of each type of toxicity obtained for a given patient, separately by stratum and separately by dose level as appropriate, for all toxicities with at least a possible attribution to TRC105.

Based on previous efforts in recruiting patients with this disease onto trials at the NCI, it is anticipated that up to 30 or more patients per year may be able to enroll onto this protocol. Allowing for up to 23 patients in the phase I portion of the trial, and up to 64 additional patients in the phase II portion (70 for the two strata – 6 who could be included from cohort 6 , the MTD cohort from the phase I portion) a total of up to 87 total subjects may be required to be enrolled. Thus, it is expected that accrual of up to 87 total patients can be completed in approximately 3 to 4 years. In order to allow for a small number of in-evaluable patients, the accrual ceiling will be set at 90 patients.

13 HUMAN SUBJECTS PROTECTIONS

13.1 RATIONALE FOR SUBJECT SELECTION

Subjects treated on this study, will be individuals with metastatic prostate cancer, which has recurred (or persisted) after appropriate standard treatment. Individuals of any race or ethnic group will be eligible for this study. Eligibility assessment will be based solely on the patient's medical status. Recruitment of patients onto this study will be through standard CCR mechanisms. No special recruitment efforts will be conducted.

13.2 PARTICIPATION OF CHILDREN

Individuals under the age of 18 will not be eligible to participate in this study because they are unlikely to have prostate cancer, and because of unknown toxicities in pediatric patient.

13.3 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

The potential benefit to a patient that goes onto study is a reduction in the bulk of their tumor and improvement in their bony lesions, which may or may not have favorable impact on symptoms and/or survival. Potential risks include the possible occurrence of any of a range of side effects which are listed in the Consent Document. The procedure for protecting against or minimizing risks will be to medically evaluate patients on a regular basis as described in Section 10.

13.4 RISKS/BENEFITS ANALYSIS

For patients with castrate-resistant prostate cancer, median survival is in the range of 12-18 months. Potential risks include the possible occurrence of any of a range of side effects listed in section 7. Risk of serial biopsies: All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection and visceral injury) that will be explained fully during informed consent. If patients suffer any physical injury as a result of the biopsies, immediate medical treatment is available at the NIH's Clinical Center in Bethesda, Maryland. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

13.5 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

Patients will meet with an associate or principal investigator on the trial in the Prostate Cancer Clinic, during the initial evaluation for this study. During that meeting, the investigator will inform patients of the purpose, alternatives, treatment plan, research objectives and follow-up of this trial. The investigator will then provide a copy of the IRB-approved informed consent document that is included in this protocol. The patient will be allowed to take as much time as he wishes, in deciding whether or not he wishes to participate. If a prolonged period of time expires during the decision making process (several weeks, as an example), it may be necessary to reassess the patient for protocol eligibility. The original signed consent goes to Medical Records; copy placed in research record (NIH policy).

All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on the study.

13.6 PATIENT RECORDS AND QUALITY ASSURANCE

Protocol related data will be entered into the NCI C3D database. Medical records will be maintained to include but not limited to:

- Signed, Dated Consent Form
- Completed Eligibility Checklist
- Source documents verifying eligibility criteria
- Pre-study lab, radiology, pathology reports, histopathological results
- Interim monitoring test results
- Physician notes/progress notes documenting physical evaluations, PS, history, prior therapy
- Physician/Nursing notes documenting vital signs, adverse event assessment,
- Treatment administration forms-In-patient/Out-patient
- PK Collection Forms
- Response evaluation- results/tumor measurements
- Biologic correlate sample collection/analysis
- Off study summary

14 APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

References

1. Eisenhauer EA, Therasseb P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) 2009; Eur J Ca 45:228-247
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. CA Cancer J Clin. 2009 Jun 9. [Epub ahead of print]
3. http://seer.cancer.gov/csr/1975_2006/results_single/sect_01_table.01.pdf Horner MJ, Ries LAG, Krapcho M, Neyman N, Aminou R, Howlader N, Altekruse SF, Feuer EJ, Huang L, Mariotto A, Miller BA, Lewis DR, Eisner MP, Stinchcomb DG, Edwards BK (eds). *SEER Cancer Statistics Review, 1975-2006*, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2006/, based on November 2008 SEER data submi*ssion, posted to the SEER web site, 2009*.
4. Huggins C, Hodges C. Studies on prostatic cancer: I. The effect of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1941; 1: 293 – 297
5. Grossfeld GD, Stier DM, Flanders SC, Henning JM, Schonfeld W, Warolin K, et al. Use of second treatment following definitive local therapy for prostate cancer. Data from the CaPSURE database. J Urol 1998;160:1398–404.
6. Figg WD, Feuer JA, Bauer KS. Management of hormone-sensitive metastatic prostate cancer. Update on hormonal therapy. Cancer Pract 1997;5:258–63. [PubMed: 9250085]
7. Aragon-Ching JB, Dahut WL. J Cancer Ther. 2007 May ; 5(A): 151–160
8. Petrylak DP, et al. Docetaxel and Estramustine Compared with Mitoxantrone and Prednisone for Advanced Refractory Prostate Cancer. N Engl J Med 2004;351:1513-20.
9. Tannock IF, de Wit R, Berry WR et al. Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer. N Engl J Med 2004; 351:1502 – 12
10. Berthold DR, Pond GR, Soban F, et al. Docetaxel Plus Prednisone or Mitoxantrone Plus Prednisone for Advanced Prostate Cancer: Updated Survival in the TAX 327 Study. J Clin Oncol 2008; 26:242 - 245
11. Schnadig ID, Beer TM, Optimal timing of chemotherapy in androgen independent prostate cancer. Urologic Oncology: Seminars and Original Investigations 2009; 27: 97-100
12. Small, EJ, Schellhammer PF, Higano CS et al. Placebo-Controlled Phase III Trial of Immunologic Therapy with Sipuleucel-T (APC8015) in Patients with Metastatic, Asymptomatic Hormone Refractory Prostate Cancer. J Clin Oncol 2006; 24:3089-3094
13. Folkman, J. Tumor angiogenesis: therapeutic implications. N. Engl. J. Med., *285:* 1182–1186, 1971.
14. Folkman J. Anti-angiogenesis: new concept for therapy of solid tumors. Ann Surg. 1972;175:409–416.
15. Folkman J. Tumor angiogenesis: a possible control point in tumor growth. Ann Intern Med. 1975;82:96 –100

16. Folkman, J, Shing Y Angiogenesis. J Biol Chem 1992; 267(16): 10931-4.

17. Carmeliet, P. Angiogenesis in health and disease. Nat Med 2003; 9(6): 653-60.

18. Weidner N, Folkman J, Pozza F, et al. Tumor angiogenesis: a new significant and independent prognostic indicator in early-stage breast carcinoma. *J Natl Cancer Inst.* 1992;84:1875–1887.

19. Macchiarini P, Fontanini G, Hardin MJ, et al. Relation of neovascularisation to metastasis of non-small-cell lung cancer. *Lancet.* 1992;340: 145–146.

20. Weidner N, Semple JP, Welch WR, et al. Tumor angiogenesis and metastasis–correlation in invasive breast carcinoma. *N Engl J Med.* 1991;324:1– 8.

21. Jaeger TM, Weidner N, Chew K, et al. Tumor angiogenesis correlates with lymph node metastases in invasive bladder cancer. *J Urol.* 1995; 154:69 –71.

22. Weidner N, Carroll PR, Flax J, et al. Tumor angiogenesis correlates with metastasis in invasive prostate carcinoma. *Am J Pathol.* 1993;143:401–409.

23. D'Amato RJ, Loughnan MS, Flynn E, et al:Thalidomide is an inhibitor of angiogenesis. Proc Natl Acad Sci U S A 91:4082-4085, 1994

24. Bauer KS, Dixon SC, Figg WD: Inhibition of angiogenesis by thalidomide requires metabolic activation, which is species-dependent. Biochem Pharmacol 55:1827-1834, 1998

25. Figg WD, Dahut W, Duray P, et al. A randomized phase II trial of thalidomide, an angiogenesis inhibitor, in patients with androgen-independent prostate cancer. *Clin Cancer Res.* 2001; 7:1888 –1893.

26. Dahut WL, Gulley JL, Arlen PM, et al. Randomized phase II trial of docetaxel plus thalidomide in androgen-independent prostate cancer. *J Clin Oncol.* 2004;22:2532–2539.

27. Figg WD, Retter A, Steinberg SM, et al. In reply. *J Clin Oncol.* 2005; 23:2113–2114.

28. Ning YM, Arlen PM, Gulley JL, et al. Phase II Trial of Thalidomide (T), Bevacizumab (Bv), and Docetaxel (Doc) in Patients (pts) with Metastatic Castration-Refractory Prostate Cancer (mCRPC). J Clin Oncol 2008; 26: (May 20 suppl; abstr 5000)

29. Duff SE, Li C, Garland JM, et al. CD105 is important for angiogenesis: evidence and potential applications. FASEB J. 2003; 17, 984 – 992

30. Dallas NA, Samuel S, Xia L, et al. Engodlin (CD105): A Marker of Tumor Vasculature and Potential Target for Therapy. Clin Cancer Res 2008;14(7): 1931-1937

31. Fonsatti E, Maio M. Highlights on endoglin (CD105): from basic findings towards clinical applications in human cancer. Journal of Translational Medicine 2004; 2:18

32. Li DY, Sorensen LK, Brooke BS, et al. Defective Angiogenesis in Mice Lacking Engolin. Science 1999; 284: 1534-1537

33. Barbara NP, Wrana JL, Letarte M. Endoglin is an accessory protein that interacts with the signaling receptor complex of multiple members of the transforming growth factor-beta superfamily. J Biol Chem 1999; 274:584-94.

34. Lebrin F, Goumans M-J, Jonker L, et al. Endoglin promotes endothelial cell proliferation and TGF-β/ALK1 signal transduction. EMBO J 2004; 23:4018-28.

35. Guo B, Slevin M, Li C, et al. CD105 inhibits transforming growth factor-beta-SMAD3 signaling. Anticancer Res 2004; 24:1337-45.

36. Warrington K, Hillarby MC, Li C, et al. Functional role of CD105 in TGF-beta1 signaling in murine and human endothelial cells. Anticancer Res 2005; 25:1851-64.

37. Li C, Gardy R, Seon BK, et al. Both high intratumoral microvessel density determined using CD105 antibody and elevated plasma levels of CD105 in colorectal cancer patients correlate with poor prognosis. Br J Cancer 2003; 88:1424-31

38. El-Gohary YM, Silverman JF, Olson PR, et al. Endoglin (CD105) and Vascular Endothelial Growth Factor as Prognostic Markers in Prostatic Adenocarcinoma. Am J Clin Pathol 2007; 127: 572 – 579

39. Wikstrom P, Lissbrant IF, Stattin P, et al. Endoglin (CD105) is Expressed on Immature Blood Vessels and Is a Marker for Survival in Prostate Cancer. Prostate 2002, 51: 268 – 275

40. Fujita K, Ewing CM, Chan DYS, et al. Endoglin (CD105) as a urinary and serum marker of prostate cancer. Int J Cancer: 124, 664 – 669 (2009)

41. Bockhorn M, Tsuzuki Y, Xu L, et al. Differential vascular and transcriptional responses to antivascular endothelial growth factor antibody in orthotopic human pancreatic cancer xenografts. Clin Cancer Res 2003; 9:4221-6.

42. Buhring, HJ, Muller CA, et al. Endoglin is expressed on a subpopulation of immature erythroid cells of normal human bone marrow. Leukemia 1991; 5(10): 841-7.

43. St-Jacques S, Cymerman U, et al. Molecular characterization and in situ localization of murine endoglin reveal that it is a transforming growth factor-beta binding protein of endothelial and stromal cells. Endocrinology 1994; 134(6): 2645-57.

44. Rokhlin OW, Cohen MB, et al. Differential expression of endoglin on fetal and adult hematopoietic cells in human bone marrow J Immunol 1995; 154(9): 4456-65.

45. Gougos A, Letarte M. Primary structure of endoglin, an RGD-containing glycoprotein of human endothelial cells. J Biol Chem 1990; 265(15): 8361-4.

46. Chen CZ, Li M, et al. Identification of endoglin as a functional marker that defines long-term repopulating hematopoietic stem cells.Proc Natl Acad Sci USA 2002; 99(24): 15468-73

47. Pece-Barbara N, Cymerman U, et al. Expression analysis of four endoglin missense mutations suggests that haploinsufficiency is the predominant mechanism for hereditary hemorrhagic telangiectasia type 1. Hum Mol Genet 1999; 8(12): 2171-81.

48. Lastres P, Bellon T, et al. Regulated expression on human macrophages of endoglin, an Arg-Gly-Asp-containing surface antigen. Eur J Immunol 1992; 22(2): 393-7.

49. Pece N, Vera S, et al. Mutant endoglin in hereditary hemorrhagic telangiectasia type 1 is transiently expressed intracellularly and is not a dominant negative. J Clin Invest 1997; 100(10): 2568-79.

50. Haruta Y, and Seon BK. Distinct human leukemia-associated cell surface glycoprotein GP160 defined by monoclonal antibody SN6.Proc Natl Acad Sci USA 1986; 83(20): 7898-902.

51. Simon R, Freidlin B, Rubinstein L, et al. Accelerated Titration Designs for Phase I Clinical Trials in Oncology. J Natl Cancer Inst 1997; 89: 1138 – 47

52. Sonpavde G, Periman PO, Bernold D, et al. Sunitinib Malate for Metastatic Castration-Resistant Prostate Cancer Following Docetaxel-Based Chemotherapy. Ann Oncol 2009 Jul 24. [Epub ahead of print]

53. Scher HI, Halabi S, Tannock I, et al. Design and End Points of Clinical Trials for Patients With Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008; 26: 1148 – 1159

54. Halabi S, Vogelzang NJ, Ou SS, et al. Progression-Free Survival as a Predictor of Overall Survival in Men With Castrate-Resistant Prostate Cancer. J Clin Oncol 2009; 27: 2766 – 2771

55. Sartor AO, Petrylak DP, Witjes JA et al. Satraplatin in patients with advanced hormone-refractory prostate cancer (HRPC): overall survival (OS) results from the phase III satraplatin and prednisone against refractory cancer (SPARC) trial. J Clin Oncol 2008; 26 (20 Suppl): (Abstr 5003)

56. Warr D, McKinney S, Tannock I. Influence of measurement error on assessment of response to anticancer chemotherapy: proposal for new criteria of tumor response. J Clin Oncol. 1984 Sep;2(9):1040-6.

57. Keil S, Behrendt FF, Stanzel S, Suehling M, Jost E, Mühlenbruch G, Mahnken A, Günther RW, Das M. RECIST and WHO criteria evaluation of cervical, thoracic and abdominal lymph nodes in patients with malignant lymphoma: manual versus semi-automated measurement on standard MDCT slices. Rofo. 2009 Sep;181(9):888-95. Epub 2009 Jul 6.

58. Schwartz LH, Mazumdar M, Brown W, Smith A, Panicek DM. Variability in response assessment in solid tumors: effect of number of lesions chosen for measurement. Clin Cancer Res. 2003 Oct 1;9(12):4318-23.

59. Small EJ, Meyer M, Marshall ME, et al: Suramin therapy for patients with symptomatic hormone hormone refractory prostate cancer: Results of a randomized phase III trial comparing suramin plus hydrocortisone to placebo plus hydrocortisone. J Clin Oncol 18:1440-1450, 2000

60. Saad F, Gleason DM, Murray R, et al: A randomized, placebo-controlled trial of zoledronic acid in patients with hormone refractory metastatic prostate carcinoma. J Natl Ca Inst 2002; 94:1458-1468

61. Rosenberg JE, Weinberg VK, Kelly WK at al., Activity of second-line chemotherapy in docetaxel-refractory hormone-refractory prostate cancer patients: randomized phase 2 study of ixabepilone or mitoxantrone and prednisone. Cancer 2007; 110 (3): 556 – 563

62. Dahut WL, Scripture C, Posades E, et al. A phase II clinical trial of sorafenib ni androgen-independent prostate cancer. Clin Cancer Res 2008; 14(1): 209 – 214

INSTITUTE: National Cancer Institute

STUDY NUMBER: 10-C-0062 PRINCIPAL INVESTIGATOR: William L. Dahut, M.D.

STUDY TITLE: A Phase I/II Study of TRC105 in Metastatic Castrate Resistant Prostate Cancer (CRPC)

Continuing Review Approved by the IRB on 09/26/11
Amendment Approved by the IRB on 07/25/12 (N) Date Posted to the Web: 8/3/12
Standard – Phase II

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

This is a clinical trial, a type of research study. Your study team will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family or your referring physician. You can also discuss it with your study team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have a cancer that has not responded to standard treatments. There is no known curative option for your cancer. For this reason, we are offering you experimental treatment on this research study. Although we hope that this experimental therapy may be of benefit to you, there is no guarantee that your cancer will respond. Benefit cannot be promised, nor can the chance of benefit be accurately predicted.

Description of Research Study

Why is this study being done?
The purpose of this study is to determine what effects, good and/or bad TRC105, an unproven anticancer drug, has on you and your prostate cancer. This study will also help to determine how TRC105 works in patients who have prostate cancer. TRC105 is an experimental drug, not yet approved by the Food and Drug Administration. This study is being done in collaboration with Tracon Pharmaceuticals, Inc., the makers of TRC105, in an effort to understand the safety of this drug. TRC105 is a man-made antibody (a specialized immune system protein) that blocks the development and growth of new blood vessels, a process called angiogenesis. All solid tumors require new blood vessels to grow. To date 50 patients have been treated with this drug in a phase I study of patients with multiple types of solid tumors. An additional 20 patients with prostate cancer have been treated with this drug in the first portion of this study.

How many people will take part in the study?
About 90 people will take part in this study.

What will happen if you take part in this research study?
TRC105 will be given through a vein (intravenously) every two weeks of each 28 day cycle. Each infusion will take at least one hour. In association with receiving TRC105, we will ask you to take dexamethasone (a steroid agent) before the infusion. If infusion of TRC105 is well tolerated, dexamethasone premedication dosing may be tapered and eventually discontinued. Infusion of any antibody such as TRC105 may cause an allergic-type of infusion reaction and dexamethasone helps to prevent this. The first 20 patients on the trial were divided into 6 groups. Each group received a different dose and were monitored for side effects. Each dose of TRC was well tolerated (there were very few serious side effects). The remaining patients enrolling on trial will receive the highest of these doses. The dose of TRC105 will be adjusted if you experience any significant problems. This will be determined by your study team. To help us to understand how the drug is working, a number of tests will be done, including blood draws to determine the levels of various markers of angiogenesis in the blood both before and at various times after TRC105 administration to evaluate blood flow both before and at various times during treatment with TRC105. The first two doses will be given in the hospital and additional doses will be given in the outpatient clinic (day hospital). When you are hospitalized for the first two doses, you will stay for three days to complete research studies including blood measurements to determine the level of drug in your bloodstream. During this hospitalization, blood will be drawn immediately prior to, and immediately following your first dose of TRC105. Blood will also be drawn at 1 hr, 2 hr, 8 hr, 24 hr, and 48 hours after the end of the TRC105 infusion. You will return every two weeks to the NIH to see a doctor who will monitor your response to the experimental treatment. You will also have blood drawn at each clinic visit prior to, and following TRC105 infusion to measure the level of drug in your body. Each separate blood draw will consist of approximately one tablespoon of blood

The DCE-MRI involves intravenous injection with a special non-radioactive dye (gadolinium chelate) to examine blood flow in a certain part of the body. An intravenous injection involves a needle stick into a vein in the arm. Several attempts may be necessary to place the needle into the vein. In addition to the pain associated with the needle stick there may be some bruising after the needle is removed. Experience with a large number of patients who have received commercially available gadolinium has shown it is without side effects in a large majority of patients. When side effects do occur, they are usually mild and last a short time. These include coolness in the arm during injection, headache, and nausea. More severe reactions (shortness of breath, wheezing, or lowering of blood pressure) have occurred in an extremely small number of patients.

Before you begin the study…
You will need to have the following exams, tests, and procedures to find out if it is safe for you to be in the study. The exams, tests, and procedures are part of regular cancer care and may be done even if you do not join the study. If you recently had some of the tests, they may not need to be repeated. This will be up to your study team.

- Blood tests: measurements of how your liver and kidneys work, measurement of your white blood cells, red blood cells and platelets, your blood sugar and blood electrolytes.
- CT scan of the chest, abdomen, and pelvis within the past 4 weeks
- Bone scan within the past 4 weeks
- Blood counts and chemistries (within 16 days before enrollment)
- PSA (Prostate Specific Antigen) within 7 days of enrollment
- Urine sample for measurement of protein in the urine
- Electrocardiogram

During the study…
If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. Some are part of regular cancer care; other tests are specific to the drug you will be taking.

- Blood tests including blood counts and chemistries
- PSA measurements

You will need these tests and procedures that are also part of regular cancer care. They are being done more often because you are in this study.

- CT scan of the chest, abdomen, and pelvis after cycles 2 and 4, then every 3 months.
- Bone scan after cycles 2 and 4, then every 3 months.

You will need these tests and procedures that are either being tested in this study or being done to see how the study drug is affecting your body.

- Pharmacokinetic sampling- this is the determination of the amount of TRC105 in your bloodstream at different time periods after having been administered the drug.

When you are finished receiving TRC105
Your participation in this study will continue until either you or your study team decides that this medication is not beneficial to you. Your participation is voluntary; so you may stop receiving TRC105 at any time, but we ask that you speak to your study team before stopping. Your study team will be monitoring you and your cancer while you are receiving TRC105. If your prostate cancer is clearly worsening, then your study team will stop treatment with TRC105. At the end of the study, no additional testing will be required. If you stop the drug because of side effects, the study team may request that you continue follow-up and/or testing for this until resolution.

Study Chart

The treatment is given every two weeks over a 28-day period of time called a cycle. The 28 day treatment cycle will be repeated as long as you are tolerating the TRC105 and your cancer is not getting worse. Each cycle is numbered in consecutive order. The chart below shows what will happen to you during Cycle 1 and future cycles. The left-hand column shows the day in the cycle and the right-hand column tells you what will happen on that day. This schedule indicates what will happen to you after you sign consent and start the study.

Cycle 1

Day	What to do and what will happen to you if you are receiving bi-weekly dosing of TRC105
Before starting TRC105	Get routine blood tests. Provide a history of how you feel and undergo a physical examination by a Health Care Provider. Research blood samples will be taken. Optional tumor biopsy (if there is a site that is safe as determined by your study team). You may require overnight admission to the hospital for the biopsy; the decision whether to admit will be discussed with you by your heath care team.
Day 1	Receive dose of TRC105 • Blood draws for research will be obtained on days 1, 2 and 3 including a series of blood draws pre-dose, immediately post-dose and at 1 hr, 2 hr, 8 hr, 24 hr, and 48 hr after drug administration to monitor the level of TRC105 in your bloodstream. You will be hospitalized for these blood tests.
Day 2	If applicable, repeat DCE-MRI following dose of TRC105
Day 3	You will be discharged from the hospital.
Day 15	Return to the NIH clinic (OP12 outpatient clinic) to see your doctor. Provide a history of how you feel and undergo a physical examination by a Health Care Provider. Blood tests and exams including PSA measurement. Blood draws for research will be obtained on days 15, 16 and 17 including a series of blood draws pre-dose, immediately post-dose and at 1 hr, 2 hr, 8 hr, 24 hr, and 48 hr after drug administration to monitor the level of TRC105 in your bloodstream. You will be hospitalized overnight for these blood tests. If you are tolerating the drug well, the dose of cycle 1 will be given at the NIH Clinical Center.
Day 29 (also Cycle 2 Day 1)	Blood tests. Provide a history of how you feel and undergo a physical examination by a Health Care Provider. Research blood samples will be taken. If you are tolerating the drug well, the 1st dose of cycle 2 will be given at the NIH Clinical Center.
Day 43 (also Cycle 2 Day 15)	Blood tests. Provide a history of how you feel and undergo a physical examination by a Health Care Provider. Research blood samples will be taken. If you are tolerating the drug well, the 2nd dose of cycle 2 will be given at the NIH Clinical Center.

Future cycles

Day	What to do and what will happen to you
Every 2 weeks	Blood tests. Return to the NIH Clinical Center and provide a history of how you feel and undergo a physical examination by a Health Care Provider. Research blood samples will be taken immediately prior to, and immediately following, TRC105 infusion. If you are tolerating the drug well, and the cancer is not getting worse, subsequent doses of TRC105 will be administered Call the research nurse or your study doctor if you do not know what to do.

How long will you be in the study?
You will be invited to continue to receive TRC105 until your study team advises you that the medication is not helping your cancer, you are experiencing significant toxicity from the therapy, or you decide that you no longer wish to participate in the study.

Can I stop being in the study?
Yes. You can decide to stop at any time. Tell your study team if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell your study team if you are thinking about stopping so any risks from TRC105 can be evaluated by your study team. Another reason to tell your study team that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Your study team may stop you from taking part in this study at any time if they believe it is in your best interest, if you do not follow the study rules, or if the study is stopped.

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?
To make an informed decision about whether or not to participate in this study, you need to know your options. Alternative treatments to this study, in general, include:

1) No further treatment of the cancer, but treatment of any symptoms that may be causing discomfort,
2) Chemotherapy and/or hormonal therapy with commercially available drugs. Recent studies have shown that a drug known as docetaxel or taxotere in combination with prednisone has survival benefit in prostate cancer. This is now recognized as the standard treatment of prostate cancers that are no longer sensitive to hormonal therapies.
3) Other experimental therapies,
4) Radiation therapy to shrink tumor masses or relieve pain, and
5) Surgery to remove tumor masses.

All of these options may not apply to your particular situation, but it is important that you have explored these options with your regular doctor.

Risk or Discomforts of Participation

What side effects or risks can you expect from being in the study?
You may have side effects while you are taking the study drug. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen so it is important to report changes that you may notice, even if your study team does not ask specifically about them. Side effects may be mild or very serious. Your study team may give you medicines to help lessen side effects. Many side effects go away with those medicines and others can go away soon after you stop TRC105. In some cases, side effects can be serious, long lasting, or may never go away. There are no known long-lasting toxicities from TRC105 at this time. You should talk to your study team about all side effects that you have while taking part in the study.

Preliminary studies have shown that TRC105 has been well tolerated in humans, with some patients reporting fatigue, chills and diarrhea as the more common side effects of TRC105.

Grapefruit juice has been shown to interact with a number of drugs by blocking the activity of the body's cytochrome P450 (CYP450) system. CYP450 is important in breaking down substances in the body, including many drugs. Since the degree to which grapefruit juice interacts with TRC105 in the body is not fully known, please avoid grapefruit juice while receiving TRC105. As other drugs may also interact with the CYP450 system, **please contact the study team prior to starting any new medication**.

Risks and side effects related to TRC105 are detailed in the table below.

Side Effect	Mild	Severe, but not life threatening	Life threatening
Common	Fatigue Bone Pain Back Pain* Lip Pain Anemia (low blood counts) Abdominal pain* Abdominal Distension Constipation Diarrhea Nausea Infusion related reaction Headache		
Uncommon	Loss of appetite* (Anorexia) Vomiting Joint pain Abnormal blood tests related to liver function* Chills Wheezing* Fever Heartburn (dyspepsia)*		

Side Effect	Mild	Severe, but not life threatening	Life threatening
	Taste alteration Flushing Proteinuria (protein in the urine) Swelling of legs* Lowered potassium level* Insomnia* Cough* Coughing up blood* Anal Discomfort Dry Mouth Flatulence Chest Pain Decrease in blood pressure Thirst Eye Infection Nosebleeds Increased heart rate Bleeding from the gums Herpes Zoster		
Rare		Gastric Ulcer Gastrointestinal hemorrhage (bleeding in the digestive tract) Small Intestine Obstruction Severe infusion related reaction	Hepatic Failure Acute Renal Failure

*These side effects are events have occurred on TRC105 trials but it has not yet been determined whether the events were caused by TRC105.

Reproductive risks: You should not father a baby while on this study because the drugs in this study can affect an unborn baby. It is important you understand that you must refrain from intercourse or need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and for how long you should use them after you are no longer receiving the study drug. Typical birth control methods include abstinence from intercourse, barrier contraceptives (condoms, diaphragms), or hormonal agents (oral contraceptive pills).

For more information about risks and side effects, ask your study team.

Potential Benefit

Are there benefits to taking part in the study?
Taking part in this study may or may not make your health better. While doctors hope TRC105 will be more useful against cancer compared to currently available treatments, there is not yet any proof that this is so. We do know that the

information from this study will help doctors learn more about TRC105 as a treatment for cancer. The information will help future cancer patients.

Cost and Reimbursement

What are the costs of taking part in this study?
While you are on study at the National Cancer Institute, we will pay for the medications and treatments associated with the study. We cannot, however, assume the cost of your overall medical care. Any studies done outside of the NCI may require you or your insurance company to cover the cost of the service.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at ://cancer.gov/clinicaltrials/understanding/insurance- . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if you injured because you took part in this study?
It is important that you tell your study team, (Dr. David Adelberg and/or Dr. William Dahut) if you feel that you have been injured because of taking part in this study. You will get medical treatment if you are injured as a direct result of taking part in this study at the NIH.

What are your rights if you take part in this study?
Taking part in this study is your choice. You may choose either to take part or to not take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. You can still get your medical care from our institution if you are eligible and choose to participate in another trial.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Communication
Who can answer my questions about the study?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study coordinator at (301) 402-9137. You may also contact the lead associate investigator, Dr. David Adelberg, at (301) 402-9134, and/or Dr. William Dahut at (301) 435-8183.

If you have any complications when you are not in the Clinical Center (e.g., at home or in a local hotel), you may call the page operator at (301) 496-1211 and ask for the NCI Medical Oncology Branch physician on call or the NIH Patients' Rights Representative who will be available to answer questions concerning your involvement in this study or your rights as a research subject. She is not directly associated with this study and can be contacted at (301) 496-2626.

Research Subjects' Rights

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- Qualified representatives from Tracon Pharmaceuticals, Inc., the pharmaceutical drug sponsors who produce TRC105.

Benefits

Although we hope that this experimental therapy may be of benefit to you, there is no guarantee that your cancer will respond. Benefit cannot be promised, nor can the chance of benefit be accurately predicted. The benefits of research using tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

In addition to the previously noted risks mentioned in this consent form, the greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Optional Studies

We would like to keep some of the blood collected for future research. These specimens will be identified by a number and not your name. The use of your specimens will be for research purposes only and will not benefit you. It is also possible that the stored specimens may never be used. Results of research done on your specimens will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

In the future, people who do research may need to know more about your health. While the NCI may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Your tissue will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future.

If you decide now that your blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your blood. Then any blood that remains will be destroyed.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call the NIH Clinical Center Patient Representative at (301) 496-2626. No matter what you decide to do, it will not affect your care.

1. Someone may contact me in the future to ask me to take part in more research.

Yes No

2. My blood may be kept for use in research to learn about, prevent, or treat cancer.

Yes No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at ://cancer.gov/

- For NCI's clinical trials information, go to: ://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to ://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. The following link contains details on this process ://ethics.od.nih.gov/procedures/COI-Protocol-Review-Guide. . You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the study Lead Associate Investigator, David E. Adelberg, M.D.; Bldg 10 Rm 12N226, Telephone (301) 402-9134 or Principal Investigator, William L. Dahut, M.D.; Building 10, Room 12N226, Telephone (301) 435-8183. If you have any questions about the use of your tissue or blood specimens for future research studies, you may also contact the Office of the Clinical Director, Telephone: (301) 496-4251.

You may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM SEPTEMBER 26, 2011 THROUGH SEPTEMBER 25, 2012.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____