SUMMARY OF CHANGES

Date: September 23, 2014

Document: NCI Protocol #9144, PhII-121: "A Phase II Study of Bevacizumab Alone or in Combination with TRC105 for Advanced Renal Cell Cancer."

Note: The following is a Summary of Changes between the 6.20.14 and 9.23.14 versions of protocol

Section	**Description of Change (v. 6.20.14 to v. 9.23.14)**
Footer	Changed protocol version to September 23, 2014. Dates in the footers were also changed to 9.23.14v.
8.1.1	Updated the pharmaceutical information per the request for amendment for TRC105
5.1	Added the following per the request for amendment for TRC105 "Although there is not a weight restriction for enrollment purposes, the maximum weight for dose calculation in this study is 85 kg for women and 100 kg for men such that the administered dose should not exceed 850 mg for women and 1,000 mg for men."

NCI Protocol #: 9144

Local Protocol #: PhII-121

TITLE: A Phase II Study of Bevacizumab Alone or in Combination with TRC105 for Advanced Renal Cell Cancer

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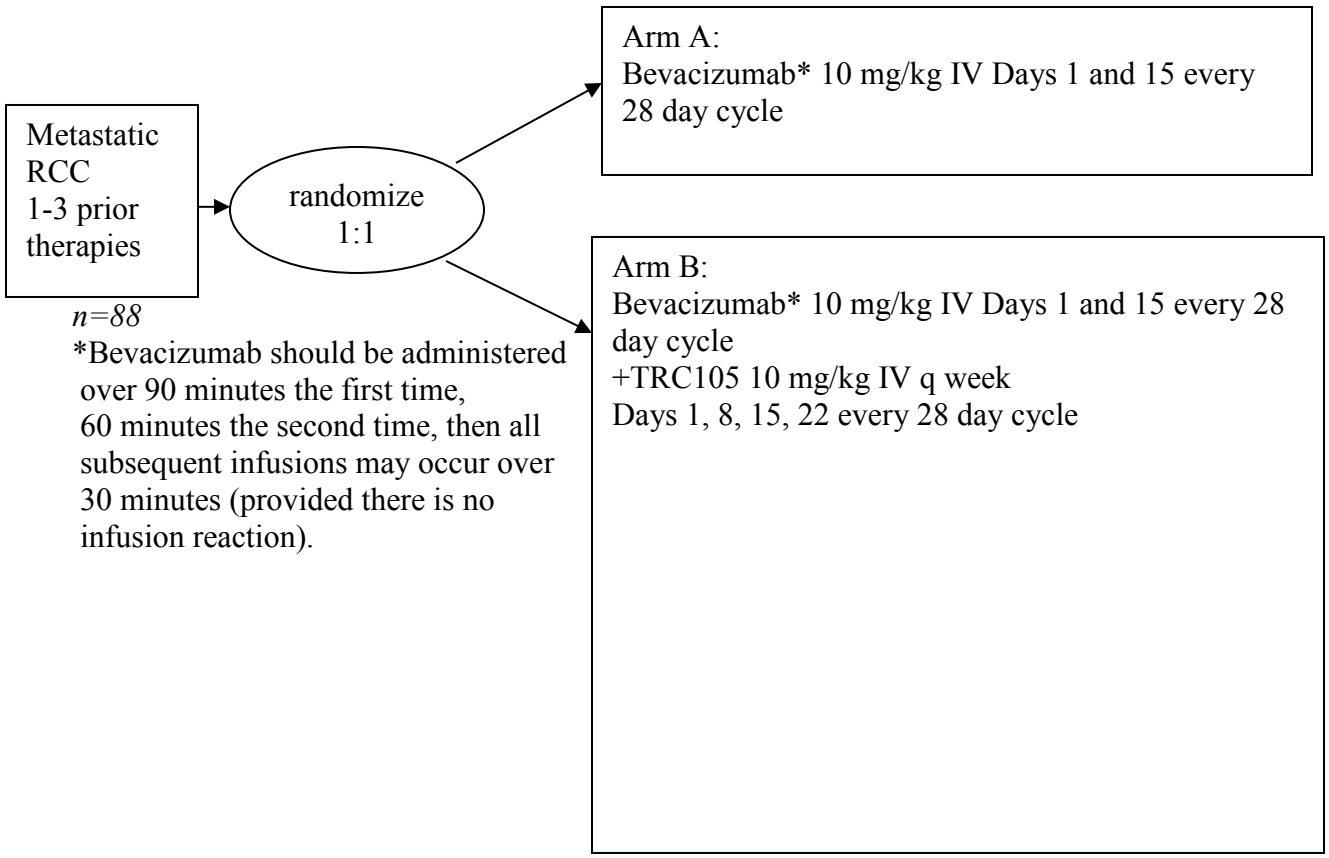
NCI Supplied Agent: TRC105 NSC 754227(IND# 115362)

Commercially available Agent: Bevacizumab (Genentech)

Protocol Type / Version # / Version Date:

December 1, 2011 – initial protocol
February 7, 2012 – Response to Consensus Review
March 6, 2012 – Response to Follow Up Review
May 14, 2012 – Amendment
May 29, 2012 – Response to Follow Up Review (Disapproved)
June 11, 2012 – Response to Follow Up Review
July 12, 2012 – Disapproved
July 26, 2012 – Response to disapproval
July 30, 2012 – Respond to recommendations
November 19, 2012 – disapproved
December 13, 2012 – Response to disapproval
March 7, 2013 – Amendment
July 2, 2013 – RRA Amendment
July 31, 2013 – Amendment
January 13, 2014 - Amendment
June 10, 2014 – Disapproved
June 20, 2014 – Response to disapproval
September 23, 2014 – Amendment request

SCHEMA



n=88

*Bevacizumab should be administered over 90 minutes the first time, 60 minutes the second time, then all subsequent infusions may occur over 30 minutes (provided there is no infusion reaction).

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1. OBJECTIVES

1.1. Primary Objectives

To compare the progression-free survival at 12 and 24 weeks for bevacizumab alone or in combination with TRC105.

1.2. Secondary Objectives

Secondary endpoints will include toxicity and RECIST response rate for the combination compared to single agent bevacizumab.

Correlative endpoints:

To evaluate tumor tissue expression of CD105, TGFβ-RII, ACVRL1 and TGFBR1 kinase from pre- and post-treatment tissue samples in order to determine whether CD105 and stem cell activation occurs after exposure to anti-VEGF therapy as predicted by laboratory models, and whether exposure to TRC105 affects these changes. A primary goal of tissue analysis will be to generate preliminary data to correlate levels of CD105, TGFβ-RII, ACVRL1 and TGFBR1 in tissue with response to bevacizumab in combination with TRC105 compared to bevacizumab alone. To compare the soluble CD105 levels at baseline and after treatment between the group receiving bevacizumab alone and the group receiving bevacizumab in combination with TRC105.

To compare TGFβ-RII levels at baseline and after treatment between the group receiving bevacizumab alone and the group receiving bevacizumab in combination with TRC105.

To evaluate whether circulating tumor cells (CTCs) can be detected in this patient population using parylene membrane filter technology, and whether changes in CTC counts and CD105 expression on CTCs during therapy correspond to imaging and clinical response.

2. BACKGROUND AND RATIONALE

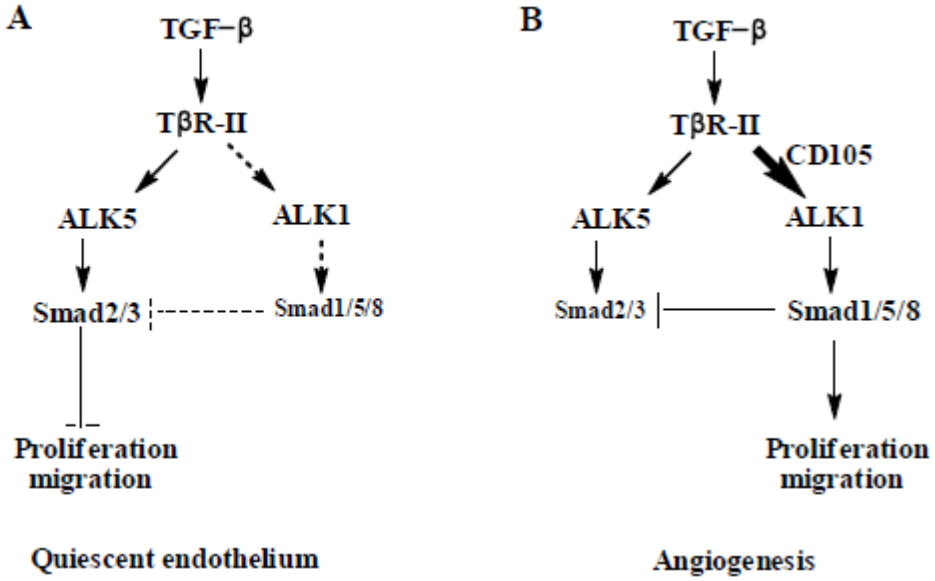
2.1. Renal Cancer

Renal cell cancer (RCC) causes over 13,000 deaths annually in the United States, and the incidence is rising [Jemal]. Standard chemotherapy has not been associated with significant responses, and the responses associated with immune therapies such as Interleukin-2 and interferon-α are limited by toxicity and low overall response rates [MRC, Linehan]. Targeting the unique biology of von Hippel Lindau inactivation (pro-angiogenic vascular endothelial growth factor, VEGF, and mammalian target of rapaycin, mTOR, activity) has led to the emergence of far more successful therapies which prolong progression-free survival and favorably impact overall survival. As a result of research involving VHL related proteins, bevacizumab, everolimus, pazopanib, sorafenib, sunitinib, temsirolimus have all been incorporated as standard

therapies in RCC. Nevertheless, many RCC patients fail to respond to VEGF or mTOR inhibition, and in responders resistance inevitably develops such that the disease ultimately progresses. Additional therapies are therefore needed, and there is particular interest in targeting angiogenic pathways that could allow continued proliferation in the presence of VEGF inhibition. CD105 represents one such target.

CD105 is a transmembrane receptor, a member of the TGFβ receptor family, which plays an important role in angiogenesis. It is induced by hypoxia via Hif1, and confers protection to cells against apoptosis triggered by hypoxia [Li]. While it is not expressed in vasculature of normal tissues, it is overexpressed in the neovasculature of malignant tissues, making it an attractive target. [Fonsatti]. Activation of CD105 by TGFβ results in stimulation of endothelial cell proliferation through the TBR-II/ACVRL1/TGFBR1 heterotetrameric receptor complex. [Lebrin] In addition, tumor cells themselves can express CD105, in particular renal cancer cells [Sandlund], and higher expression is associated with poorer outcomes [Dallas] Furthermore, the presence of CD105 may be a marker of an aggressive, tumor-generating population of RCC cells. When injected into SCID mice, CD105+ RCC cells generated tumors 100% of the time, compared to 10% for CD105- cells [Bussolati]. When grown clonally, CD105+ cells expressed other characteristic stem cell markers, including CD44, CD90, CD146, CD73, CD29, vimentin, nestin, nanog, musashi, oct4 and the renal embryonic marker Pax2; they did not express pan-cytokeratin, nor the endothelial marker vonWillebrand factor. Thus, CD105 represents an independently valuable therapeutic target that may facilitate elimination of more resistant RCC.

Figure 1: Model of Regulation of Angiogenesis by CD105 (Endoglin)



[From the TRC105 investigator brochure]

* Note ALK1 is also known as ACVRL1. ALK5 is also known as TGFBR1

2.2. TRC105

TRC105 is a chimeric (human:murine) IgG1 kappa monoclonal antibody against CD105. It is composed of two light chains of 213 amino acids each and its molecular weight is approximately 148 kDa.

50 patients were treated in the phase I study of TRC105. HAMA and HACA formation was rare in patients treated with the NS0-derived product but did not occur in those treated with the CHO-produced antibody. For the NS0-derived product, the dose was escalated from 0.01 to 1 mg/kg every 2 weeks. The CHO-derived product was used to complete dose escalation from 0.3 to 15 mg/kg every two weeks and then 10 and 15 mg/kg weekly and is the clinical material being used in continued development of TRC105. Serum concentrations expected to saturate CD105 binding were continuously achieved at 15 mg/kg every 2 weeks. Accumulation was noted at the dose level of 15 mg/kg/week and was associated with hypoproliferative anemia. This has led to the selection of the dose of 10 mg/kg weekly as the single agent recommended Phase 2 dose. Dose escalation with bevacizumab was reported at ASCO 2012. TRC105 and bevacizumab were dosed in 19 patients at TRC105 doses of 3 mg/kg, 6 mg/kg and 8 mg/kg weekly with the approved dose of bevacizumab. Tolerability (i.e., a decreased frequency of headaches) was improved when the initial dose of TR105 was delayed one week following the initial dose of bevacizumab and split into two doses during the first week of administration. Following ASCO, dose escalation continued to the single agent recommended Phase 2 dose of 10 mg/kg of TRC105, which was administered safely and without dose limiting toxicity in combination with the approved dose of bevacizumab of 10 mg/kg.

Early evidence for significant activity was noted in the phase I trial, with one complete PSA response associated with bone scan normalization and pain resolution in a man with metastatic castration-resistant prostate cancer that has been durable for >3 years. There was an additional minor response in a patient with uterine cancer, and several patients experienced prolonged disease stabilization. Antitumor activity was also observed in the Phase Ib trial of TRC105 and bevacizumab. Tumor marker reductions and radiographic responses were noted in multiple patients who progressed after prior bevacizumab treatment, who were then treated with TRC105 weekly and 10 mg/kg bevacizumab every two weeks.

2.3. Bevacizumab

Bevacizumab was approved by the FDA for the treatment of metastatic RCC after two randomized, phase III trials documented significantly longer progression-free survival for patients treated with bevacizumab + interferon-α compared to interferon-α alone [Escudier, Rini]; overall survival is also favorably affected.

While bevacizumab was approved in combination with interferon, early studies with the agent in RCC documented efficacy as a single agent. In a randomized phase II

trial comparing placebo to 3 mg/kg or 10 mg/kg of bevacizumab in metastatic RCC patients, the progression-free survival at 4 months was 64% for the 10 mg/kg dose compared to 39% for 3 mg/kg and 20% for placebo and the hazard ratio for time to disease progression was 2.55 ($p<0.001$) representing significant prolongation [Yang]. This more-than-doubling reflects the magnitude of effect seen in the interferon combination trial though the absolute duration cannot be compared across trials, especially since the phase II trial included cytokine pre-treated patients, whereas the registrational trial [Escudier] was in therapy-naïve patients. Further evidence in support of single-agent bevacizumab as an appropriate control arm comes from the fact that intergroup CTSU E2804 trial had bevacizumab alone as its control arm [NCT00378703].

The most common side effects related to bevacizumab in RCC patients treated at the dose of 10 mg/kg every 2 weeks included hypertension (14% overall; 8% grade 3), proteinuria (25% overall; 3% grade 3), malaise (13%, only grade 1 and 2), and epistaxis (8%, only grade 1 and 2) [Yang]. In the registrational trial combining bevacizumab with interferon adverse effects must be put in the context of the high rate of events in the placebo plus interferon arm; the toxicities which were significantly greater in the bevacizumab plus interferon arm included bleeding (33% compared to 9% for placebo, and 3% grade 3 or worse), proteinuria (18% compared to 3% for placebo, and 7% was grade 3 or worse), hypertension (26% compared to 9% for placebo and 3% grade 3 or worse), and thromboembolic events (3% compared to <1% for placebo and 2% grade 3 or worse) [Escudier]. Gastrointestinal perforation was a rare but serious adverse event seen only in the bevacizumab-treated patients. In this trial we have chosen to utilize bevacizumab without interferon as our control arm, in part to minimize toxicity, but also for simplicity and to isolate the added effect of TRC105.

2.4. Rationale

One escape mechanism that may allow RCC to progress despite VEGF inhibition is signaling through other proliferative pathways which are upregulated by the expression of HIF-1α, such as expression of the CD105 receptor [Sanchez-Elsner]. Specifically, the expression of CD105 has been shown to be upregulated after cancer cells are exposed to treatment with a VEGF antibody [Bochner, Davis]. This escape mechanism makes targeting of CD105 attractive. In addition, the upregulation of CD105 as a result of VEGF ligand inhibition may allow TRC105 to be more effective by increasing the density of CD105 expression on the cell surface. In vitro data indicates that combined use of TRC105 and bevacizumab is more effective than either agent alone in VEGF stimulated tumor cell sprouting studies. (unpublished data) This makes the combination of CD105 inhibition with VEGF inhibition highly attractive in RCC.

We will evaluate the combination of TRC105, a monoclonal antibody against CD105, plus bevacizumab compared to bevacizumab alone in pre-treated metastatic renal cancer patients with a primary endpoint of progression-free survival at 12 and 24

weeks. The doses were chosen based on results from a phase Ib trial combining bevacizumab and TRC105. Seven patients were treated at the top dose level (10 mg/kg bevacizumab + 10 mg/kg TRC105) without the development of DLT. Thus, this is a safe dosing schema for phase II study.

2.5. Correlative Studies Background

Hypoxia is known to upregulate CD105 expression [Li], which increases signaling via the TGFβ-RII and activin-like receptor kinase ACVRL1/TGFBR1 heterodimer. Higher CD105 expression (measured by immunohistochemistry) has been associated with higher risk of metastasis and death in several solid tumors [Schimming, Mineo, Dales]. While subjects with high expression of CD105 may have poorer prognosis, we anticipate that subjects with higher expression of CD105 activity will be more likely to respond to TRC105 and less likely to respond to bevacizumab alone.

In addition to the importance of being inducible by CD105, TGFβ signaling via TGFBR1 has taken on new significance as it is identified as one of the pathways for epithelial-to-mesenchymal transition (EMT) [Kalluri], a hallmark of aggressive cancer. Increased expression of TGFβ mRNA in kidney cancer tissue compared to normal kidney tissue may indicate that this is an autocrine growth pathway [Gomella]. **Tumor tissue will be evaluated for expression of TGFβ-RII** activity using immunohistochemistry and immunofluorescence. Given that CD105 and other hypoxia-induced growth factors signal via this receptor, and it has been implicated in the epidermal to mesenchymal transition (EMT), we hypothesize that higher expression will be associated with a poorer overall prognosis. Since it may represent an escape pathway for VEGF inhibition, we hypothesize that elevated baseline expression will be associated with a higher likelihood of response to TRC105 and lower likelihood of response to bevacizumab alone.

Given that TGF can signal via TGFBR1 to activate angiogenesis or through alternate receptor pathways including ACVRL1 to reduce angiogenesis, the differential expression of these proteins may prove markers of which cancers are more angiogenesis-driven. We postulate that elevated baseline tissue expression of TGFBR1 would be associated with a better prognosis due to higher likelihood of response to bevacizumab, but that higher expression of ACVRL1 would be associated with lower overall treatment response.

Measuring VEGF after exposure to bevacizumab has proven difficult, since the agent interferes with the assay [Kindler], though immunodepletion may allow detection of a decrease despite an apparent increase related to antibody-bound ligand [Loupakis]. Thus, finding other molecular changes induced during response or progression on bevacizumab remains a high priority. Suppression of VEGF signaling in preclinical models results in upregulation of CD105 expression. CD105 is an integral component of TGFβ signaling; suppression of CD105 may result in a compensatory increase in its upstream activator TGFβ. This compensatory increase could represent a surrogate marker for effective CD105 suppression and tumor response. Circulating sCD105 has been found at high levels in metastatic solid tumors [Takahashi]. **We will explore serum levels of sCD105 and TGFβ in metastatic RCC patients**, and

correlate baseline levels with prognosis and likelihood of response to TRC105. We anticipate that subjects assigned to combination therapy (Arm B) will have lower levels of sCD105 and TGFβ at post-treatment time points compared to Arm A, where we expect serum levels of both factors to increase..

Although **circulating tumor cells (CTCs)** have not yet been validated as a prognostic marker in RCC, they have proved to be strongly prognostic for prostate and breast cancer patients [deBono, Cristofanilli]. Using CD45 autoMACS depletion, investigators have been able to identify CTCs in a high percentage of patients with localized RCC undergoing nephrectomy, which correlated with presence of nodal involvement and synchronous metastases [Bluemke]. Given that targeted therapy for RCC results primarily in disease stabilization rather than dramatic regression of tumor burden, it can be difficult to measure the degree of response or benefit. Reduction in CTCs could be a very useful objective measure by which to gauge response in this setting. We will use blood samples from baseline and after 6 weeks and 12 weeks to enumerate CTCs using a parylene membrane filter technology developed by USC in conjunction with CalTech [Zheng]. We will evaluate whether changes in CTC counts reflect subsequent changes on radiographic imaging to determine whether changes in CTC counts could predict for ultimate radiographic response versus progression. In addition, CTCs will be evaluated for CD105 expression by IHC to investigate whether exposure to TRC105 has an effect on CD105 expression. Reduction in CTCs which express CD105 could correspond to elimination of cancer cells with more "stem-like" properties, a population resistant to standard therapy, which could account for resistance to VEGF-targeted therapy in RCC.

3. PATIENT SELECTION

3.1. Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed Renal Cancer All histologic subtypes will be eligible

3.1.2 Patients must have metastatic disease which is measurable, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) to ≥ 20 mm in the long axis by chest x-ray, ≥ 10 mm in the long axis by spiral CT, MRI, calipers, or clinical exam, or ≥ 15 mm in the short axis for lymph nodes. See Section 11 for the evaluation of measurable disease.

3.1.3 Patients must have received at least 1 prior systemic therapy for renal cancer but no more than 4 prior therapies. They must have documented intolerance to or progression despite at least 1 systemic therapy.
Therapy administered in the adjuvant setting counts toward the prior systemic therapy total. If adjuvant therapy is the patient's only prior therapy the disease must have recurred during treatment or within 3 months of

discontinuation.

Allowable prior therapies include VEGF TKIs, mTOR inhibitors, and cytokine therapy (ex: IL2).

At least 2 weeks must have elapsed from the last dose of the prior systemic therapy for biologics and 4 weeks for chemotherapy (6 weeks for nitrosoureas or mitomycin C)." Also note that at least 3 weeks should have elapsed since prior TKI administration**.**.

3.1.4 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of TRC105 and anti-angiogenic therapy would be anticipated to have uniquely adverse effects in growing tissues, patients <18 years of age, children are excluded from this study.

3.1.5 ECOG performance status ≤2 (see Appendix A).

3.1.6 Life expectancy of greater than 6 months.

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

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	≤ institutional upper limits of normal (except for Gilbert's)
– AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal
– (except subjects with liver metastases, who can have AST/ALT ≤ 5xULN)	
– Creatinine	GFR (calculated or measured) >50 mL/min
– Hemoglobin	≥9 g/dL

3.1.8 The effects of TRC105 and bevacizumab on the developing human fetus are unknown. For this reason and because anti-angiogenic agents are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 6 months after completion of TRC105 or bevacizumab administration.

3.1.9 Ability to understand and the willingness to sign a written informed consent document.

3.2. Exclusion Criteria

3.2.1 Patients who have had systemic biologic therapy or radiotherapy within 2 weeks prior to entering the study or those who have not recovered from adverse events related to their prior therapy.

3.2.2 Patients who have previously been treated with bevacizumab.

3.2.3 Patients who have previously been treated with TRC105.

3.2.4 Patients who are receiving any other investigational agents.

3.2.5 Known CNS disease except for treated brain metastasis. Treated brain metastases are defined as having no ongoing requirement for steroids and no evidence of progression or hemorrhage after treatment for at least 3 months, as ascertained by clinical examination and brain imaging (MRI or CT). (Stable dose of anticonvulsants are allowed). Treatment for brain metastases may include whole brain radiotherapy (WBRT), radiosurgery (RS; Gamma Knife, LINAC, or equivalent) or a combination as deemed appropriate by the treating physician. Patients with CNS metastases treated by neurosurgical resection or brain biopsy performed within 3 months prior to Day 1 will be excluded.

3.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to TRC105 or bevacizumab.

3.2.7 Patients on full-dose anticoagulation will be excluded due to the risk of bleeding. Antiplatelet therapy will not be exclusionary.

3.2.8 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, unhealed wound, gastrointestinal fistula, symptomatic congestive heart failure, unstable angina pectoris, myocardial infarction, cerebrovascular accident

3.2.9 Pregnant women are excluded from this study TRC105 and bevacizumab are anti-angiogenic agents with significant potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with TRC105 and bevacizumab, breastfeeding should be discontinued if the mother wishes to participate in the study.

3.2.10 Patients with a history of bleeding diathesis or inherited coagulopathy are excluded due to the risk of bleeding and thrombosis associated with bevacizumab. In addition, those with a history of DVT or pulmonary embolus within 1 year and still requiring active anticoagulation will be excluded; those

with a more remote history of DVT or pulmonary embolus may be eligible but the risk of recurrent thrombosis should be considered.

3.2.11 Patients with history of hereditary hemorrhagic telangiectasias (HHT-1 and HHT-2).

3.2.12 Serious or non-healing wound, ulcer, or bone fracture OR history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 6 months prior to day 1.

3.2.13 Invasive procedures defined as follows:

- Major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to Day 1 therapy
- Anticipation of need for major surgical procedures during the course of the study
- Core biopsy within 7 days prior to D1 therapy

3.2.14 Patients with clinically significant cardiovascular disease are excluded.

- Inadequately controlled HTN (SBP >160mmHg and/or DBP >90 mmHg despite antihypertensive medication)
- History of CVA within 6 months
- Myocardial infarction or unstable angina within 6 months
- New York heart association grade II or greater congestive heart failure
- Serious and inadequately controlled cardiac arrhythmia
- Significant vascular disease (e.g. aortic aneurysm, history of aortic dissection)
- Clinically significant peripheral vascular disease

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3.2.15 Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies.

3.2.16 Patients with psychiatric illness/social situations that would limit compliance with study requirements will be excluded.

3.3. Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

Accrual Targets

Ethnic Category	Sex/Gender				
	Females		Males		Total
Hispanic or Latino	7	+	12	=	19
Not Hispanic or Latino	19	+	50	=	69
Ethnic Category: Total of all subjects	26 (A1)	+	62 (B1)	=	88 (C1)

Racial Category						
American Indian or Alaskan Native	0		+	0	=	0
Asian	4		+	7	=	11
Black or African American	1		+	3	=	4
Native Hawaiian or other Pacific Islander	0		+	0	=	0
White	21		+	52	=	73
Racial Category: Total of all subjects	26	(A2)	+	62 (B2)	=	88 (C2)

4. REGISTRATION PROCEDURES

4.1. General Guidelines

Eligible patients will be entered on study centrally at the California Cancer Consortium Data Coordinating Center at the City of Hope. All sites should call the Data Coordinating Center at (626) 256-4673 extension 65928 to verify study status.

Following registration, patients should begin protocol treatment within 5 business days to allow for drug shipment via Priority Mail. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Data Coordinating Center should be notified of cancellations as soon as possible.

Each participating institution will order DCTD-supplied agents directly from CTEP, DCTD. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded to the City of Hope Data Coordinating Center (DCC) FAX (626-256-8654).

4.2. Registration Process

To register a patient, the following documents should be completed by the research nurse or data manager and faxed to the data coordinating center for the California Cancer Consortium (626) *256- 8654.*

- Copy of required laboratory tests (labs, CT, x-ray, pathology, etc)
- Signed patient consent form
- HIPAA authorization form
- Eligibility Screening Worksheet
- Registration Form

The research nurse or data manager at the participating site will then call (626)256-4673 ext 65928 the Study Coordinator to verify eligibility. To complete the registration process, the Coordinator will

- assign a patient study number
- register the patient on the study

- assign the patient a dose
- fax or e-mail the patient study number and dose to the participating site
- call the research nurse or data manager at the participating site and verbally confirm registration.

5. TREATMENT PLAN

5.1. Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications 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.

TREATMENT ARM A					
Agent	***Premedications Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Bevacizumab	none	10 mg/kg in 100 mL NS	IV over 90 minutes the 1st time, 60 minutes for the 2nd infusion, then 30 minutes for all subsequent infusions	Days 1 and 15	*28 days (4 weeks)*

TREATMENT ARM B					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Bevacizumab	none	10 mg/kg in 100 mL NS	IV over 90 minutes the 1st time, 60 minutes for the 2nd infusion, then 30 minutes for all subsequent infusions	Days 1 and 15	*28 days (4 weeks)*
TRC105*	Dexamethasone Acetaminophen Famotidine Diphenhydramine (or equivalent)	10 mg/kg in 500 mL NS	All doses IV Days 1, 8, 15, 22 every 28 day cycle (except Cycle 1 Day 1)	Days 1, 8, 15, 22 (cycle 1 day 8) will	

			Use PVC/DEHP-free tubing with 0.22 micron low protein-binding in-line filter	be split into two doses: 3 mg/kg cycle 1 day 8 and 7 mg/kg cycle 1 day 11.)	

- Start and stop times for infusion of study drug will not be captured, however it is recommended that infusion times occur as delineated, with a +/- 10 minute window.

***** Although there is not a weight restriction for enrollment purposes, the maximum weight for dose calculation in this study is 85 kg for women and 100 kg for men such that the administered dose should not exceed 850 mg for women and 1,000 mg for men.

5.1.1 **TRC105**

Patients should be encouraged to drink abundant fluid prior to the first treatment. IV hydration prior to and during therapy is left to the discretion of the Investigator, but should be considered for patients that may be volume depleted. Vital signs should be monitored every 30 minutes during the TRC105 infusion (+/- 10 minutes).

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

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 i.v. bag and transport of the TRC105 study drug to the patient will be performed as per standard study site procedures.

Because the study opened with a lower starting dose of TRC105 (8 mg/kg) there may be patients who start treatment at the lower dose. Once the amendment to use full dose TRC105 (10 mg/kg) has been approved by the IRB, subjects who are on treatment may be offered dose escalation of TRC105 to the 10 mg/kg dose for subsequent cycles.

5.1.2 **Bevacizumab**

No premedications are required. While infusion reactions are possible, they are extremely rare. nevertheless, the recommended infusion time is no shorter than 30 minutes, and standard practice frequently includes administering the first dose over 90 minutes, the 2nd over 60 minutes, and then all subsequent

infusions over 30 minutes, provided no infusion reactions are noted.

In Arm B, when bevacizumab and TRC105 are administered on the same day, the bevacizumab is given first followed by TRC105 premeds followed by TRC105. The first time both drugs will be given on the same day should be study day Cycle 1 Day 15.

5.2. General Concomitant Medication and Supportive Care Guidelines

There are no known drug-drug interactions for the study medications. However, because these are vascular-targeted therapies, caution is warranted with anticoagulation. Full-dose anticoagulation will exclude patients from enrollment in the study; if a subject develops an indication for full-dose anticoagulation, the appropriateness of their continuation on study therapy should be carefully assessed in consultation with the principal investigator.

5.3. Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for up to 12 cycles, or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), specifically arterial thrombotic event, symptomatic grade 4 venous thrombosis, grade 4 hemorrhage, grade 4 hypertension, grade 4 proteinuria, GI perforation or wound dehiscence.
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Pregnancy

5.4. Duration of Follow Up

Patients will be followed for 4 weeks after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.5. Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.3 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

6.1. Comprehensive Adverse Events and Potential Risks List (CAEPR)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The SPEER is a list of events that are protocol-specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_CTEP-AERS for further clarification. Frequency is provided based on 123 patients.. Below is the CAEPR for TRC105.

NOTE: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously via CTEP-AERS. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

7.1.2 CAEPRs for Bevacizumab (rhuMAb VEGF, NSC 704865)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3540 patients*. Below is the CAEPR for

bevacizumab (rhuMAb VEGF).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, August 1, 2013[1]

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term) [n= 3540]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)	
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
CARDIAC DISORDERS			
		Acute coronary syndrome[2]	
	Cardiac disorders - Other (supraventricular arrhythmias)[3]		***Cardiac disorders - Other (supraventricular arrhythmias)[3] (Gr 3)***
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction[2]	
		Ventricular arrhythmia	
		Ventricular fibrillation	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Colitis		***Colitis (Gr 3)***
	Constipation		***Constipation (Gr 3)***
	Diarrhea		***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
		Gastrointestinal fistula[4]	
	Gastrointestinal hemorrhage[5]		***Gastrointestinal hemorrhage[5] (Gr 2)***
	Gastrointestinal		

	obstruction[6]		
		Gastrointestinal perforation[7]	
		Gastrointestinal ulcer[8]	
	Ileus		
	Mucositis oral		***Mucositis oral (Gr 3)***
	Nausea		***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 3)***
	Infusion related reaction		***Infusion related reaction (Gr 2)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 3)***
	Pain		***Pain (Gr 3)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr 2)***
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[9]		***Infection[9] (Gr 3)***
		Infections and infestations - Other (necrotizing fasciitis)	
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Injury, poisoning and procedural complications – Other (anastomotic leak)[10]	
	Wound complication		***Wound complication (Gr 2)***
	Wound dehiscence		***Wound dehiscence (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Cardiac troponin I increased		
Neutrophil count			***Neutrophil count decreased (Gr***

decreased			***3)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 3)***
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 3)***
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[11]		
	Myalgia		***Myalgia (Gr 3)***
	Osteonecrosis of jaw[12]		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 3)***
		Intracranial hemorrhage	
		Ischemia cerebrovascular[2]	
	Peripheral sensory neuropathy[13]		
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
	Hematuria		***Hematuria (Gr 3)***
	Proteinuria		***Proteinuria (Gr 2)***
		Renal and urinary disorders - Other (Nephrotic Syndrome)	
		Urinary fistula	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Reproductive system and breast disorders - Other (ovarian failure)[14]			
		Vaginal fistula	
	Vaginal hemorrhage		***Vaginal hemorrhage (Gr 3)***

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		***Allergic rhinitis (Gr 3)***
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	
	Cough		***Cough (Gr 3)***
	Dyspnea		***Dyspnea (Gr 2)***
	Epistaxis		***Epistaxis (Gr 3)***
	Hoarseness		***Hoarseness (Gr 3)***
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Urticaria		***Urticaria (Gr 2)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event		***Thromboembolic event (Gr 3)***
		Vascular disorders - Other (arterial thromboembolic event)[2,15]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]The risks of arterial thrombosis such as cardiac or CNS ischemia are increased in elderly patients and in patients with a history of diabetes.

[3]Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation and atrial flutter.

[4]Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[5]Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites

under the GASTROINTESTINAL DISORDERS SOC.

[6]Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[7]Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, Small intestinal perforation, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[8]Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[9]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[10]Anastomotic leak may include Gastric anastomotic leak; Gastrointestinal anastomotic leak; Large intestinal anastomotic leak; Rectal anastomotic leak; Small intestinal anastomotic leak; Urostomy leak; Vaginal anastomotic leak

[11]Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.

[12]Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.

[13]Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.

[14]Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level <30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.

[15]Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack and stroke.

Also reported on bevacizumab (rhuMAb VEGF) trials but with the relationship to bevacizumab (rhuMAb VEGF) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura); Bone marrow hypocellular;

Disseminated intravascular coagulation; Hemolysis
CARDIAC DISORDERS - Atrioventricular block complete; Atrioventricular block first degree; Cardiac arrest; Myocarditis; Pericardial effusion; Restrictive cardiomyopathy; Right ventricular dysfunction
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (tympanic membrane perforation); Hearing impaired; Tinnitus; Vertigo
ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism
EYE DISORDERS - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (blindness); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (corneal epithelial defect); Eye disorders - Other (floaters); Eye disorders - Other (ischemic CRVO); Eye disorders - Other (macular pucker); Eye disorders - Other (transient increased IOP > or =30 mm Hg); Eye disorders - Other (vitreous hemorrhage); Eye pain; Keratitis; Optic nerve disorder; Photophobia; Retinal detachment; Retinal tear; Retinopathy; Watering eyes
GASTROINTESTINAL DISORDERS - Ascites; Chelitis; Colonic stenosis; Dry mouth; Dysphagia; Enterocolitis; Esophageal pain; Esophageal stenosis; Flatulence; Gastrointestinal disorders - Other (peritonitis); Oral pain; Pancreatitis; Proctitis; Rectal mucositis; Rectal stenosis;Typhlitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema face; Edema limbs; Edema trunk; Facial pain; Fever; Flu like symptoms; Gait disturbance; Injection site reaction; Localized edema; Multi-organ failure; Sudden death NOS
HEPATOBILIARY DISORDERS - Cholecystitis; Gallbladder necrosis; Gallbladder obstruction; Hepatic failure; Hepatic necrosis
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (aseptic meningitis)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Arterial injury; Bruising; Burn; Dermatitis radiation; Fracture
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood antidiuretic hormone abnormal; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Electrocardiogram QT corrected interval prolonged; Forced expiratory volume decreased; GGT increased; INR increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Bone pain; Chest wall pain; Fibrosis deep connective tissue; Generalized muscle weakness; Head soft tissue necrosis; Joint effusion; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone); Musculoskeletal and connective tissue disorder - Other (myasthenia gravis); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Neck pain; Pain in extremity; Pelvic soft tissue necrosis; Soft tissue necrosis lower limb
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Arachnoiditis; Ataxia; Central nervous system necrosis; Cerebrospinal fluid leakage; Cognitive disturbance; Depressed level of consciousness;

Dysesthesia; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Facial nerve disorder; Hydrocephalus; Leukoencephalopathy; Memory impairment; Nervous system disorders - Other (increased intracranial pressure); Paresthesia; Peripheral motor neuropathy; Pyramidal tract syndrome; Seizure; Somnolence; Tremor; Vasovagal reaction
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Libido decreased; Psychosis
RENAL AND URINARY DISORDERS - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Renal and urinary disorders - Other (dysuria); Renal and urinary disorders - Other (ureterolithiasis); Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain; Erectile dysfunction; Irregular menstruation; Pelvic pain; Vaginal discharge
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Atelectasis; Hypoxia; Nasal congestion; Pulmonary fibrosis; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (dry nares); Respiratory, thoracic and mediastinal disorders - Other (pulmonary infarction)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Nail loss; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders - Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Skin ulceration; Stevens-Johnson syndrome
VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension; Lymphocele; Phlebitis; Vasculitis

Note: Bevacizumab (rhuMAb VEGF) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

6.2. Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- For expedited reporting purposes only:
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.

- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

6.3. Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse EventReporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note:

"Any death occurring ***within 30 days*** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours."

"Any death occurring ***greater than 30 days*** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably or definitely related to the investigational agent/intervention."

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same

name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

6.4. Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must also be reported in routine study data submissions and a copy of the report must be sent to the Data Coordinating Center at the City of Hope (cccp@coh.org).**

6.5. Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm. CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

6.6. Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

7. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational and commercial agents administered in this study can be found in Section 7.1.

7.1. CTEP-provided agent: TRC105 NSC 754227 (IND# TBD)

8.1.1 Descriptive information

Classification: Chimeric IgG1 kappa monoclonal antibody

M.W.: Approximately 148 kDa

Mode of Action: TRC105 is a chimeric IgG1 monoclonal antibody to human

CD105, a transmembrane receptor that is selectively expressed at high levels on proliferating endothelial cells. Upon binding to the endothelial cell CD105 receptor, TRC105 changes the downstream signal from a proliferative to a quiescent one. TRC105 also induces endothelial cell antibody-dependent cell-mediated cytotoxicity and apoptosis. In addition targeting angiogenesis, TRC105 may have direct antitumor activity by inducing ADCC and apoptosis of CD105-positive cancer cells.

Route of Administration: Intravenous infusion.

Availability
TRC105 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

TRC105 is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.2 Agent Ordering and Agent Accountability

8.1.2.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime

8.1.2.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

7.2. Bevacizumab

8.2.1 Descriptive information

Bevacizumab (Avastin®, Genentech) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay systems. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. Avastin has an approximate molecular weight of 149 kD. Bevacizumab is produced in a mammalian cell (Chinese Hamster Ovary) expression system in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. Bevacizumab is FDA approved for the treatment of metastatic RCC.

Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for intravenous infusion. Bevacizumab is supplied in 100 mg and 400 mg preservative-free, single-use vials to deliver 4 mL or 16 mL of Bevacizumab (25 mg/mL). The 100 mg product is formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. The 400 mg product is formulated in 960 mg α,α-trehalose dihydrate, 92.8 mg sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water for Injection, USP.

Bevacizumab is typically administered intravenously over 90 minutes for the first infusion, 60 minutes for the second infusion, and 30 minutes for all subsequent infusions provided no allergic infusional reactions are noted. This dosing may be adjusted to match institutional standard practices.

8.2.2 Agent ordering and accountability

Bevacizumab is commercially available.

8. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

8.1. Background on Correlative Studies

For additional information about techniques,etc please see Appendix E.

Rationale. The rationale and hypotheses for correlative studies may be found in section 2.5 of the protocol. The correlative studies are exploratory, with markers that have been selected rationally based on the mechanism of action of the two drugs being administered. The primary goal of the tissue analyses will be to generate preliminary data, potentially identifying a biomarker for response. Those who agree to a repeat biopsy will give us the opportunity to evaluate for proof of principle, evaluating how expression of CD105 and its signaling pathway change after expression to VEGF antibody (bevacizumab) alone or with the added blockade of CD105 (TRC105). We will also evaluate for changes in serum factors and CTC expression induced by treatment, which will generate preliminary data about whether the agent in fact hits the target, and elucidate potential mechanisms of resistance to therapy.

Techniques. Standard technique will be used for immunohistochemical (IHC) analysis, utilizing the commercially available primary murine antibodies against CD105 (Abcam) and TGFβ-RII (Abcam), and immunofluorecence using primary murine antibodies against ALK-1 and ALK-5 (Santa Cruz Biotech). Following deparaffinization, antigen retrieval will be performed with heating during incubation with citrate buffer. IHC will be visualized using 3,3'- diaminobenzidine (DAB; DAKO, Japan) and immunofluorescence with fluorescein antimouse IgG (Invitrogen). We have chosen IHC and immunofluorescence because these are the methods for assessing CD105, TGFβ-RII, and ALK-1 and ALK-5 which have been reported in the literature. This is also considerably less costly than expression by RT-PCR from microdissected paraffin embedded specimens. Applying ACIS to the interpretation will enhance the reproducibility and reliability of the results.

Standard ELISA kits will be used for serum TGFβ and sCD105 (R&D systems, Minneapolis, USA) and samples collected throughout the study will be run in batches. CTCs will be run on microfilters developed by USC and CalTech. We have chosen this platform because it allows for additional sophisticated assays of the captured cells, such as interrogation of captured cells for expression by IHC or RNA by PCR [Xu 2010, Xu 2011]. Also, since enumeration of CTCs by the commercially available Veridex (CellSearch®) assay has not been shown to have prognostic value in RCC, it is not considered standard, and would not be held as the gold standard for this disease. Validation of the USC/CalTech microfilter platform in comparison to the Veridex assay has been completed as part of the randomized phase III clinical trial SWOG S0421 (results pending).

Competence of the laboratories which will perform the assays. The Pinski laboratory has published multiple studies using immunohistochemistry [Daneshmand, Quek, Liu]. The Pinski laboratory has also published studies using ELISA to evaluate protein expression [Wang]. Circulating tumor cells will be processed in the circulating tumor cell core of the USC Norris Comprehensive Cancer Center under the guidance of Dr. Amir Goldkorn.

Concern for human subjects. In order to minimize adverse events related to venipuncture for the study subjects, every effort will be made to draw study correlative

bloodwork at the same time as clinically necessary laboratory tests are being performed. Tissue which has previously
been obtained by biopsy or surgery will be utilized for all subjects, and extra biopsy will be an optional part of the study. Only subjects with safely accessible tumors (ex: palpable lymph nodes or subcutaneous nodules) will be considered for participation in the extra biopsy. Results of the correlative studies will not be routinely provided to subjects or treating physicians since they have not been validated for clinical decision-making, however, results may be provided to treating physicians who request the results.

Banking of specimens. In order to maximize the value of clinically annotated biological specimens obtained as part of this study, all unused tissue and blood will be banked. However, tissue blocks which are submitted will NOT be banked, but will be returned so that they would be available to subjects should they need additional analysis of their tissue in the future. Subjects who participate in the voluntary extra biopsy will have those tissue blocks banked. Banking of specimens will be handled by the USC Norris Pathology Core.

8.2. Correlative Studies: instructions

9.2.1 **Tissue Studies**: CD105, TGFβ-RII, ACVRL1 and TGFBR1 using immunohistochemistry and immunofluorescence

9.2.1.1 Collection

For all subjects, paraffin-embedded tissue blocks or unstained slides from a prior biopsy or nephrectomy specimen will be requested. Please select a section that contains tumor. If blocks are provided, the USC Norris Pathology Core will cut 10 x 5 micron sections and return the blocks. If slides are provided, request 9 unstained slides (5 micron thick) plus 1 H&E from the same block.

For subjects who agree to a repeat biopsy after therapy in order to compare tissue expression before and after treatment, a core needle biopsy is required to provide adequate tissue; if a core biopsy cannot be safely obtained the subject should not be asked to participate in the optional repeat biopsy aspect of the protocol. Blocks or unstained slides should be prepared as above.

9.2.1.2 Handling

Blocks should be wrapped in bubble wrap or send in padded envelope. Slides should be packaged in slotted plastic box and wrapped in bubble wrap or sent in a padded envelope.

9.2.1.3 Shipping

Blocks or slides should be shipped to:

Dr. Tanya Dorff
USC Norris Cancer Center
1441 Eastlake Ave. #3440
Los Angeles, CA 90033

9.2.2 **Serum Studies**: TGFβ and sCD105 levels (ELISA)

9.2.2.1 Collection

At each correlative time point (baseline, Cycle 2 Day 1, and Cycle 4 Day 1 (about week 13)), draw 2 x 7.5 mL serum separator tubes.

9.2.2.2 Handling

The serum separator tubes should be allow blood to clot by standing vertically at room temperature for 30 minutes. Then centrifuge specimen at 1000-1400xg for 20 minutes. Remove the top layer (serum) by pouring into 1 mL aliquots and place in **-80oC** freezer. These shipments may be batched. Samples can be placed in a -20oC freezer for short term storage.

9.2.2.3 Shipping

If shipping a batch of ONLY serum tubes, please ship to the laboratory of Jacek Pinski:

Jacek Pinski Laboratory
USC Norris Cancer Center Room 5432
1441 Eastlake Ave.
Los Angeles, CA 90033

9.2.3 **Circulating Tumor Cells – DO NOT COLLECT UNTIL FUNDING HAS BEEN OBTAINED. Sites will be notified on when samples can be collected.**

9.2.3.1 Collection

At each correlative time point (baseline, Cycle 2 Day 1, and Cycle 4 Day 1 (about week 13)) draw 1 x 7.5 mL EDTA-containing tube.

9.2.3.2 Handling

The EDTA tube should be left unspun and shipped immediately on ice. Please alert the Goldkorn laboratory when samples have been collected

(323) 442-7721.

Note: there has been no noted difference in yield of CTCs from samples processed immediately compared to those processed after shipment.

9.2.3.3 Shipping

Blood samples should be shipped to the laboratory of Dr. Amir Goldkorn if they contain any EDTA tubes.

Amir Goldkorn Laboratory
9171 HSC
NRT 6505
Los Angeles, CA 90033

9.2.4 **Pharmacokinetics and Immunogenicity (Arm B only)**

9.2.4.1.1 Collection

Immunogenicity samples will be collected at cycle 1 day 8 (before dose), end of study, and end of study +28 days (when possible).

Pharmacokinetics will be collected pre- and post-dose of TRC105 on cycle 1 day 15, cycle 2 day 1, end of study, and end of study +28 days (when possible).

See Appendix G for processing and shipping samples.

8.3. Outcome measures for correlative studies

All data will be recorded using study ID #s only, without protected health information. Data will be recorded in CAFÉ, the electronic database managed by the USC Norris Cancer Center Clinical Investigator Support Office (CISO).

Tissue: IHC will be evaluated for intensity by an experienced pathologist, Dr. Debra Hawes, using ACIS. ACIS, the automated cellular imaging system, provides a reproducible quantification of staining, both % of cells staining as well as intensity. Both will be recorded. IHC will be run in batches of 14 subjects intermittently during the study duration or within 3 months after study closure.

Serum: Standard ELISA kits will be used (R&D systems, Minneapolis, USA) and samples collected throughout the study will be run in batches during the study duration or within 3 months after study closure.

Circulating Tumor Cells: Because the results are best when specimens are processed immediately, CTC samples will be processed on microfilters immediately upon receipt. IHC staining for CD105 will occur in batches, however. The following data will be

recorded for each time point: number of CTCs detected, expression of CD105 at baseline and after therapy. This will only be done if funding has been obtained to collect the CTC samples.

9. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. Scans and x-rays must be done ≤ 28 days prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Contrast is not required for imaging but is left to the discretion of the treating physician. Visits for Day 8 and Day 11 will only occur for patients on Arm B.

	Pre-Study	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 11	Cycle 1 Day 15	Cycle 1 Day 22	Cycle 2 Day 1 & 15	Cycle 2 Day 8 & 22	Cycle 3 Day 1& 15	Cycle 3 Day 8 & 22	Cycle 4 Day 1 & 15	Cycle 4 Day 8 & 22	Cycles 5-12 Day 1& 15	Cycles 5-12 Day 8& 22	Off Study[c]
TRC105			B (3 mg/kg)	B (7 mg/kg)	B	B	B	B	B	B	B	B	B	B	
Bevacizumab		A & B			A & B		A & B		A & B		A & B		A & B		
Informed consent	X														
Demographics	X														
Medical history	X														
Concurrent meds	X		X	X	X (May be done by telephone for Arm A)										
Physical exam	X				X		X		X		X		X		X
Vital signs[g]	X		X	X	X		X		X		X		X		X
Height	X														
Weight	X				X		X		X		X		X		X
Performance status	X				X		X		X		X		X		X
CBC w/diff, plts	X				X		X		X		X		X		X
Serum chemistry[a]	X				X		X		X		X		X		X
LDH					X		X		X		X		X		
Urine dipstick OR protein & creatinine	X				X		X		X		X		X		X
PT/PTT	X														
Adverse event eval.			X	X	X (may be done by telephone for patients on Arm A)										
Tumor measurements	X				Every 12 weeks										
Radiologic evaluation	X				Every 12 weeks										
B-HCG	X[b]														
Correlative Blood	X[d]*						X[e]*				X[f]*				
Pharmacokinetics (Arm B)					X		X (day 1 only)								
Immunogenicity (Arm B)			X												X

Tissue blocks /unstained slides	X														

All treatment, clinical and laboratory observations are +/- 3 days. Baseline H&P (or cycle 1, day 1 h&p) should include tobacco history including number of years smoked, number of cigarettes per day, and years since quitting, as applicable.

All imaging is +/- 7 days except for baseline imaging. Baseline imaging should be done within 28 days prior to registration and should consist of at least a CT, CT/PET, or MRI covering the chest, abdomen and pelvis. Bone scans should be done as appropriate. As much as possible, repeat imaging should use the same modality as baseline/previous studies so that comparison can be made accurately.

"A" and "B" (as opposed to "X") denote the treatment group to which the patient is assigned.
TRC105 = 10 mg/kg IV q week (GROUP B only)
Bevacizumab = 10 mg/kg IV q 2 weeks (BOTH GROUPS A & B)

a= include electrolytes, creatinine, albumin, total protein, AST/ALT, alkaline phosphatase, and bilirubin
b = for women of childbearing potential only
c = off study evaluation
d= may be drawn at cycle 1, day 1
e = only on day 1
f = only on day 1
g = Vital signs should be monitored every 30 minutes during the TRC105 infusion (+/- 10 minutes).

*At each correlative time point (baseline, Cycle 2 Day 1 (about week 5), and Cycle 4 Day 1 (about week 13), draw 2 x 7.5 mL serum separator tubes. Pharmacokinetic samples are to be drawn on cycle 1 day 15 before and after TRC105 dose, and cycle 2 day 1 before and after dose and off-study, as well as 28 days after off-study if feasible. Immunogenicity samples are to be drawn at cycle 1 day 8 and off-study, as well as 28 days after off-study if feasible.

10. MEASUREMENT OF EFFECT

10.1. Antitumor Effect – Solid Tumors

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.

For the purposes of this study, patients should be re-evaluated for response every 12 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4-6 weeks following initial documentation of objective response.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with Bevacizumab alone or with TRC105.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded, except for lymph nodes) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or 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 will not be considered measurable.

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.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or involved 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.

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.

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.

11.1.3 Methods 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.

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.

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.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine

relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers There are no tumor markers to be followed for RCC patients.

Cytology, Histology The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1 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.

11.1.4.2 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: Persistence of one or more non-target lesion(s).

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).

11.1.4.3 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.

For Patients with Measurable Disease (*i.e.*, Target Disease)

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

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.1.5 Duration of Response

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.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

11.1. Data Reporting

12.1.1 Method

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

12.1.2 Responsibility for Data Submission

Study participants are responsible for submitting CDUS data and/or data forms to the Coordinating Center for the California Cancer Consortium quarterly. The date for submission to the Coordinating Center one month before the CDUS deadlines (i.e. December 31, March 31, June 30, September 30). CDUS does not accept data submissions from the participants on the study.

11.2. CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix B.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

11.3. Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the

Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the

protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

12. STATISTICAL CONSIDERATIONS

12.1. Study Design/Endpoints

The primary endpoint will be progression-free survival, evaluated using the two-point analysis (12 and 24 weeks) proposed by [Freidlin]. Secondary endpoints will include toxicity, RECIST response rate and investigation of correlative markers.

The main endpoint of interest will be whether the combination arm has a greater PFS than single agent bevacizumab. Planning is based on the supposition of 12-week PFS of 61% on the control arm and 78% on the combination arm. This improvement of 17% corresponds to reducing the hazard of progression in half by adding TRC105 to Bevacizumab. The corresponding hypothesized PFS at 24 weeks would be 37% on the single-agent arm and 60% on the combination arm. A randomized design is needed

due to the paucity of data for progression-free survival of bevacizumab in the second and third-line setting.

While there are limited data for outcomes with 2nd and 3rd line therapy in RCC, published phase II and retrospective data for the use of sunitinib or sorafenib after prior VEGF-targeted therapy document median progression-free survival of 16-34 weeks [DiLorenzo, Motzer 2006, Zimmerman]. Our planning hypotheses, described above, correspond to median PFS of 17 weeks on the single agent arm, and 33 weeks on the combination arm.

Enrollment of 88 patients, at a rate of one patient per week, would provide approximately 80% power for a one-sided test at the 0.10 level of significance, based conservatively on a single evaluation. We propose to use the two-point analysis (12 and 24 weeks) proposed by Freidlin et al [Freidlin] for unblinded randomized trials using PFS, which will increase power. An interim analysis for futility will be done after 44 patients have been evaluated. The 1-sided p-value at the interim analysis must be less than 0.43 to continue. There will be no early stopping for efficacy. With 44 patients per arm, the fraction of patients progression-free at 12 weeks can be estimated with a standard error of approximately 7.5 percentage points, although exact binomial lower confidence bounds will be calculated.

In addition to the planned interim analysis for futility, the study will receive routine review at monthly meetings of the California Cancer Consortium Data Coordinating Center to ensure adequacy of enrollment, tolerability of treatment, and suitability of enrolled subjects (e.g. adequate expected survival).

12.2. Sample Size/Accrual Rate

The sample size will be 88 patients. We anticipate accrual of 4 patients per month. Enrollment will be monitored at the regular monthly meetings of the consortium Data Coordinating Center. The protocol PI and consortium contract PI will receive a written notification from the DCC if, at 6, 12, 18, or 24 months into the trial, enrollment is less than half of the planned rate. Recognizing that this study may be impacted by the current enrollment cap on the N01 contract, plans for dealing with underenrollment may include expanding participation to additional sites, or closure of the trial.

12.3. Stratification Factors

Randomization will be blocked and stratified to maintain balance with respect to clear-cell versus non-clear-cell disease, and ECOG performance status of 0 or 1 versus 2.

12.4. Analysis of Secondary Endpoints

Correlative Endpoints: The data generated from the correlative studies during this protocol will be exploratory in nature.

13.4.1 Tissue studies

Baseline levels of CD105, TGFβ-RII, TGFBR1 and ACVRL1 will be correlated with response.

13.4.1.1 For **CD105**, the reported median number of cells staining positive per core is 5 (range 0-79) and staining in at least one of 2 tissue cores had some staining positivity in 75% [Sandlund]. We anticipate that patients whose tumors have higher levels of CD105 staining will be more likely to respond to TRC105 plus bevacizumab, and may be less likely to respond to bevacizumab alone. If 5 subjects on the combination arm were to respond, and all 5 had above-median staining, the association would be significant ($p=0.024$) by a one-sided version of Fisher's exact test. While this provides an example of a detectable effect, without invoking a detailed model, the planned analysis will use a rank-sum test for improved power. Generalized linear models for ordered categorical data will be used to address the treatment and staining interaction using the full dataset.

13.4.1.2 For **TGFβ-RII**, the expression in kidney cancer has not yet been well described. Given that CD105 and other hypoxia-induced growth factors signal via this receptor, and it has been implicated in the epidermal to mesenchymal transition (EMT), we will explore the associate of this receptor's expression with outcomes in study patients.

13.4.1.3. For **TGFBR1 and ACVRL1**, again there are not published reports of extent of expression in renal carcinoma. However, given that TGF can signal via ALK-5 to activate angiogenesis or through alternate receptor pathways including ALK-1 to reduce angiogenesis, the differential expression of these proteins may prove markers of which cancers are more angiogenesis-driven, which could rationally affect response to therapy and/or prognosis.

13.4.2 Serum studies

The change in serum levels of sCD105 will be compared between groups A & B. We anticipate that subjects assigned to combination therapy (Arm B) will have lower levels of sCD105 at post-treatment time points compared to Arm A, where we expect levels to increase. Both baseline levels of sCD105 and changes during treatment will be correlated with response, using the approach described above.

(CTCs: The change in number of CTCs from baseline to repeat time points will be correlated with radiographic response. The change in expression of CD105 on CTCs will be compared between groups.) – ON HOLD pending funding

12.5. Reporting and Exclusions

13.5.1 Evaluation of toxicity – All patients will be evaluable for toxicity from the time of their first treatment with Bevacizumab and TRC105.

13.5.2 Evaluation of response – All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria and were randomized will be included in the main analysis of the response rate. Patients in response categories 4-9 will be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

Subgroup analyses will include evaluation of progression-free survival among those categorized as good risk or intermediate risk by Motzer criteria compared to those categorized as poor risk. Additionally, clear cell and non-clear cell subjects will be analyzed as separate subgroups.

12.6. Safety Monitoring

Safety and toxicity will be reviewed monthly at the CCCP Data Coordinating Meetings, in which all toxicities (especially Grade 3+) are assembled and reviewed. In addition, every time a patient dies within 30 days of last treatment, this death will be reviewed to ascertain whether the death could be attributed primarily to the treatment, to disease progression, or another cause. If the attribution for the death is most likely due to treatment, then a careful review of the trial data will be mandated. Based on the review, a decision will be made to continue the study unchanged or to modify the regimen and amend the protocol. Finally, at approximately every 6 months, at the time of the DSMC review, all deaths on both arms will be tabulated for overall review.

13. DATA AND SAFETY MONITORING PLAN

13.1. Oversight of CCCP Phase I and Phase II Trials

The Californian Cancer Consortium with Pittsburgh (CCCP) will oversee the development and conduct of all Phase I and II trials that are undertaken as part of this consortium. However, it is also the CCCP policy to take advantage of reviews and infrastructure provided by CTEP as well as the Protocol Review and Monitoring Systems (PRMSs) that are in place at each participating Cancer Center. In addition to these institutional mechanisms for review and oversight, to ensure that the CCCP

objectives and priorities are addressed and that highest quality clinical research prevails, the following policies and procedures are in place.

14.1.1 Review of Trials Prior to Activation

Prior to developing a protocol, the concept for a Phase I or Phase II trial is discussed at a monthly CCCP teleconference. While this discussion is informal, no concept is given the go-ahead without approval by CCCP leadership (i.e. the grant PI's at each of the 4 member institutions, for both the Phase I U01 and Phase II N01). Discussion includes the scientific merit of the proposal, the compatibility with the CCCP priorities, and the ability to complete the study in a timely fashion. Once the protocol document is completed, the protocol is reviewed by the collaborating statistician, by the CCCP Project Coordinator (to verify adherence to boilerplate and formatting requirements), as well as the CCCP leadership; at this stage, the plans to monitor safety and (if appropriate) efficacy are carefully reviewed.

This is done before the document is submitted for review by CTEP and/or other sponsors, as well as the CCCP institutional PRMSs and IRBs.

14.1.2 Review of Safety, Conduct, and Data While Trial is Open to Accrual

14.1.2.1 Ongoing Review

The protocol principal investigator (PI) is responsible for monitoring the conduct and progress of this Phase I trial, including the ongoing review of accrual, data and toxicities, as well as the accumulation of reported adverse events from other trials testing the same drug(s). The participating clinicians and their designees are responsible for timely submission of adverse event reports and case report forms. The Data Coordinating Center for the CCCP Consortium is responsible for providing the PI with access to the submitted case report form data in summary and detail in a timely fashion. Although the PI is responsible for evaluating the cumulative reported adverse events and the impact that these have on the continued conduct of the trial, it is the Operations Office of the CCCP that distributes all submitted SAE reports to the appropriate individuals, including the local protocol principal investigators, at each of the participating institutions.

The Data Coordinating Center (DCC) posts a summary (accrual, toxicities, and responses) of each CCCP initiated trial on the CCCP website. In this way, each PI has access to up-to-date information on the status of his or her trial. In consultation with the collaborating statistician, the PI is responsible for review of:

14.1.2.1.1 For Phase I trials, all dose limiting toxicities and decisions regarding dose escalation, expansion, as

well as decisions to terminate escalation, and

14.1.2.1.2 For Phase II trials, the toxicities and therapeutic endpoints referred to in the statistical plan.

The DCC meets monthly to review data management and data quality issues – completeness of data submissions as well as accuracy. Any issues identified and the corrective plans are presented at the next CCCP teleconference meeting for review and approval.

14.1.2.2 Oversight

Oversight of the conduct of CCCP trials occurs at several levels:

14.1.2.2.1 The Operations Office for the CCCP flags all trials that are approaching a decision in terms of toxicity (for both Phase I and Phase II trials) or responses (for Phase II trials). Decisions are made by the PI with input from the statistician and discussion with the principal investigator of the funding mechanism (U01 Cooperative Agreement or N01 Contract, as appropriate) or his or her designee, and are communicated to the participating centers by the CCCP Operations Office.

14.1.2.2.2 At the monthly teleconferences, the status of each open protocol is reviewed.

14.1.2.2.3 For CTEP sponsored Phase I trials, data are reported to the NCI-designated clinical trials monitoring service (CTMS) which will audit patients' records on each protocol – at each CCCP institution; this audit is initiated by CTEP. For all other CCCP trials, the CCCP will contract with Theradex to audit patient records at each CCCP institution.

14.1.2.2.4 An independent CCCP DSMC will review CCCP trials every 6 months. This DSMC will consist of 4 voting members (2 medical oncologists or hematologists involved in Phase I/II cancer clinical trials but not participating in CCCP studies, a statistician, and a patient advocate) and a non-voting CCCP statistician.

14.1.2.2.4.1 DSMC meetings will take place twice a year. Additional meetings will be convened if necessary.

14.1.2.2.4.2 This DSMC will review each CCCP trial in terms of accrual, toxicity/safety, and adherence to trial

design, audit results, and likelihood of successful completion.

14.1.2.2.4.3 The DSMC will report to the CCCP leadership. The CCCP Operations Office will distribute the DSMC reports to the PI of each open study and the U01 and N01 institutional PI's for submission to local oversight committees as required per each institution's policy.

14.1.3 **Review of Manuscripts and Abstracts based on CCCP Trials**

All meeting abstracts and manuscripts must be approved, and signed off by the collaborating statistician and the CCCP leadership. Copies of the final, published abstracts and manuscripts must be maintained in the CCCP operations office – along with a copy of the frozen data files on which the analyses were based.

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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.

APPENDIX B: CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.

- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  1. The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  2. The Coordinating Center must be designated on the title page.
  3. Central registration of patients is required. The procedures for registration must be stated in the protocol.
  4. Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  5. Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  6. Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX C: INFORMATION ON POSSIBLE INTERACTIONS WITH OTHER AGENTS FOR PATIENTS AND THEIR CAREGIVERS AND NON-STUDY HEALTH CARE TEAM

The patient _____ is enrolled on a clinical trial using the experimental agent **TRC105**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

Because TRC105 is an antibody, it is not known to interact with many other medications. However, it does increase the risk of bleeding, and this side effect could be made worse by using other drugs which "thin the blood" at the same time.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**.

Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is _____ and he or she can be contacted at _____.

INFORMATION ON POSSIBLE DRUG INTERACTIONS

You are enrolled on a clinical trial using the experimental agent **_____.** This clinical trial is sponsored by the NCI. _____ interacts with drugs that are processed by your liver. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicine or if you start taking a new medicine.
- Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

_____ interacts with a specific liver enzyme called **CYP_____**, and must be used very carefully with other medicines that interact with this enzyme.

- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP_____**."
- Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis/table.asp for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____**.**

APPENDIX D: CCCP REGISTRATION PROCEDURES FOR PHASE II TRIALS

1. Registrations for Phase II protocols must be made through the Data Coordinating Center (DCC) office at the City of Hope between the hours of 8:30 a.m. to 4:30 p.m. Pacific Time, Monday through Friday (except holidays).
2. Patients must be registered within 5 days (to allow for drug shipment via Priority Mail) prior to initiation of protocol therapy.
3. A patient failing to meet all protocol requirements may not be registered. If you have any questions regarding eligibility, contact the City of Hope Data Coordinating Center (DCC) at (626) 256-HOPE (4673), ***extension 65928.***
4. Prestudy laboratory tests, scans and x-rays must be completed prior to registration according to study calendar/protocol.
5. Patients must sign an informed consent prior to registration.
6. Confirm that the patient meets all inclusion and exclusion eligibility criteria for a protocol.
7. Complete the Eligibility Checklist.
8. Verify that all required prestudy tests were performed.
9. Fax the completed Eligibility Checklist, signed and dated informed consent, pathology report, and relevant laboratory results to the City of Hope Consortium Coordinator for confirmation of eligibility. The FAX number is (626) 256-8654.
10. Call the City of Hope Consortium Coordinator at (626) 256-HOPE (4673), extension 65928 to confirm the FAX arrival. If the Consortium Coordinator is not in the office, have them paged at (626) 423-5365.
11. If the patient qualifies, the City of Hope Consortium Coordinator will call the registering institution to complete the registration/randomization procedure and assign the patient's study ID number.
12. Once a patient has been registered, the Data Coordinating Center will provide a "Confirmation of Registration" to the center registering the patient via email.

For questions regarding eligibility call City of Hope California Cancer Consortium,
Data Coordinating Center
(626) 256-HOPE (4673), extension 65928

APPENDIX E: INFORMATION ABOUT CORRELATIVE STUDIES

Immunohistochemistry and Immunofluorescence.
Deparaffinization will be performed using xylene, followed by rehydration with graded EtOH solutions (100%, 95%, 85% for 5 min 3x, 2x, and 1x respectively). Antigen retrieval will be performed in 0.001M citrate buffer (pH 7) and incubation in the pressure cooker for 5 minutes. Non-specific protein binding will be performed using albumin for 30 minutes, then endogenous peroxidase will be blocked using 3% H2O2 in distilled water. Commercially available primary murine antibodies against CD105 (Abcam) and TGFβ-RII (Abcam) diluted 1:100 will be applied and incubated overnight at 4°C. For ALK-1 and ALK-5 (Santa Cruz Biotech) primary murine antibodies for immunofluorecence will be diluted 1:100 and incubated overnight at 4°C.

Secondary antibody diluted 1:500 will be applied (mouse-horseradish peroxidase) and incubated for 1 hour at room temperature. IHC will be visualized using 3,3'- diaminobenzidine (DAB; DAKO, Japan) with hematoxylin counter-stain, and immunofluorescence with fluorescein antimouse IgG (Invitrogen). We have chosen IHC and immunofluorescence because these are the methods for assessing CD105, TGFβ-RII, and ALK-1 and ALK-5 which have been reported in the literature.

Slides will be read by an experienced pathologist (DH), and IHC will be graded 0-2+ based on intensity of staining. The pathologist will also use ACIS, and analysis will be performed using the ACIS output which is an arbitrary number from 0-100 which represents the intensity of staining.

ELISA.
Standard ELISA kits will be used for serum TGFβ and sCD105 (R&D systems, Minneapolis, USA) and samples collected throughout the study will be run in batches.

Circulating Tumor Cells (CTCs).
CTCs will be run on microfilters developed by USC and CalTech, using technique which has been previously reported [Xu 2010, Xu 2011]. Briefly, 7.5ml peripheral blood will be drawn by standard venipuncture into 1 CellSave tube. The tube will be kept at room temperature and delivered to the Goldkorn laboratory, where it will be subjected to Ficoll-Paque centrifugation to deplete red blood cells and to isolate the "buffy coat" layer containing CTC and white blood cells (WBC). Then, the buffy coat will be passed through the slot microfilter using a constant low-pressure delivery apparatus. The microfilter-captured cells will be fixed in 1% formalin and subjected to immunofluorescent staining for cytokeratin (Cam 5.2, BD), CD105, and DAPI. Captured CTC ($DAPI^+Cam5.2^+$) will be enumerated by a blinded independent observer using the Nuance multispectral imaging platform. Because there are fewer cells anticipated than are typically available in tissue samples, percent of cells staining IHC+ will be reported in addition to an intensity score.

APPENDIX F: CCCP SPECIMEN SUBMISSION FORM

To be emailed to sites separately once study is activated.
Please email cccp@coh.org to request the form.

APPENDIX G: Laboratory Manual for TRC105 Pharmacokinetic & TRC105 HAMA/HACA Sample Collection

Please contact the cccp@coh.org for the latest version of the laboratory manual.