

PHASE 1 STUDY OF TRC105 [ANTI-CD105 (ENDOGLIN) ANTIBODY] THERAPY IN PATIENTS WITH ADVANCED REFRACTORY CANCER

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INTRODUCTION

- TRC105 is a human/murine chimeric IgG1 kappa monoclonal antibody that binds with 5 pM (~1 ng/mL) avidity to human CD105 (endoglin), a membrane receptor required for angiogenesis and over-expressed by the proliferating vascular endothelium of solid tumors (Seon et al, 1997)
- TRC105 inhibits angiogenesis and tumor growth via endothelial cell growth inhibition, ADCC and apoptosis
- Like VEGF, CD105 expression is up-regulated by hypoxia through HIF-1 α and is knockout lethal; mice that lack CD105 die *in utero* from absent vascular development (Li et al, 1999)
- High CD105 expression by tumor vasculature correlates with poor prognosis across more than 10 solid tumor types, including breast, colorectal, prostate and lung cancer
- CD105 expression is increased following VEGF inhibition in preclinical studies of human cancer (Bockhorn et al, 2003; Davis et al, 2004), supplying a rationale for developing TRC105 in combination with VEGF inhibitors
- CD105 is also expressed on cancer stem cells (Bussolati et al, 2008)

OBJECTIVES

- Evaluate the safety and tolerability of escalating doses of TRC105 administered intravenously every 2 weeks to patients with refractory solid cancer
- Evaluate pharmacokinetics, tumor response and immunogenicity

METHODS

STUDY DESIGN

- Phase 1, non-randomized, open-label, dose-finding, first-in-human study conducted at 4 institutions in the United States

KEY INCLUSION CRITERIA

- Adults (age \geq 18 years) with advanced or metastatic solid cancer for whom curative therapy is unavailable
- ECOG performance status of 0 or 1
- Adequate organ function

KEY EXCLUSION CRITERIA

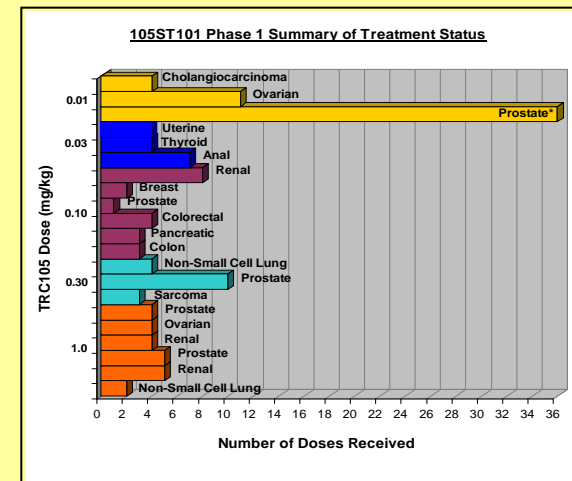
- Receipt of cancer treatment within 4 weeks of study start
- History of primary or secondary brain tumors
- Lung cancer with central chest lesions
- Major surgery within 4 weeks of study start
- Unhealed wounds or bleeding within 30 days of dosing
- Significant pericardial, pleural or peritoneal effusion

RESULTS

Patient Demographics

Characteristic	Number of Patients (n=21)
Median Age	61
Gender	Female: 8 Male: 13
Screening ECOG Performance Status	ECOG 0: 10 ECOG 1: 11
Number of Prior Regimens	Median: 3 Range: 1 to 8
Race	Caucasian: 14 Asian: 2 Black/African American: 3 Hispanic/Latino: 2

Treatment Status



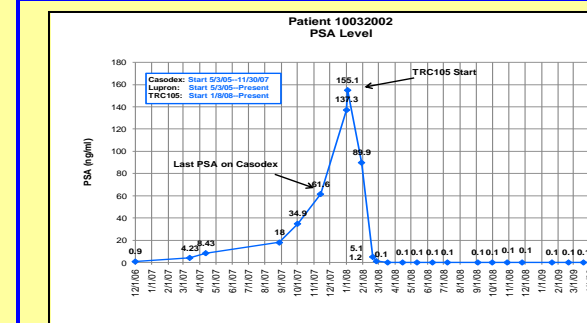
*A prostate cancer patient remains on study after 36 doses (18 x 28-day cycles) of TRC105

Safety

TRC105 Possibly Related Adverse Events				
Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4
Anemia		1		
Diarrhea	2	1		
Gastrointestinal hemorrhage				1 SAE & DLT
Chills	1 Infusion Rxn		1 DLT Infusion Rxn	
Fatigue		2		
Pyrexia		1 Infusion Rxn		
Hyperuricemia	1			
Arthralgia	1			
Dysgeusia	1			
Proteinuria	1			
Vaginal hemorrhage	1			
Dyspnea			1 DLT Infusion Rxn	
Wheezing		1		
Flushing	Mild			

- Two dose limiting toxicities occurred on study
 - Grade 4 gastrointestinal hemorrhage within 1 week of the first TRC105 infusion at 0.1 mg/kg; the bleeding resolved by the time of endoscopy after receiving 2 units of packed red cells, and the protocol was amended to exclude patients with risk factors for peptic ulcer disease
 - Hypersensitivity reaction (Grade 3 chills and Grade 3 dyspnea) during TRC105 infusion at 1.0 mg/kg
- Two patients developed human antimouse antibody, one after 6 doses at 0.03 mg/kg and another after 10 doses at 0.3 mg/kg; both became undetectable at 4 and 12 weeks following treatment discontinuation

Efficacy

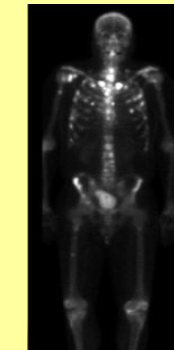


A patient with castrate-refractory prostate cancer and multiple bone metastases treated at 0.01 mg/kg remains on study at Cycle 18 with a complete PSA response and markedly improved bone scans.

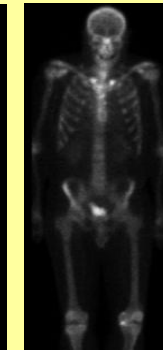
Patient #10032002 Prostate Cancer

Whole-Body Bone Imaging Study

After 3 TRC105 Doses



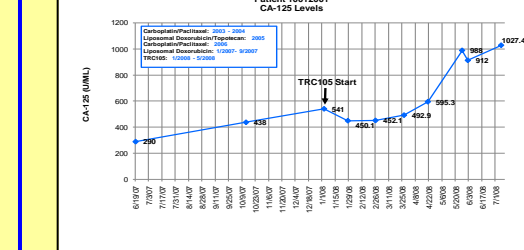
After 12 TRC105 Doses



Patient #10012001 Ovarian Cancer

CA-125 Levels

TRC105 Start

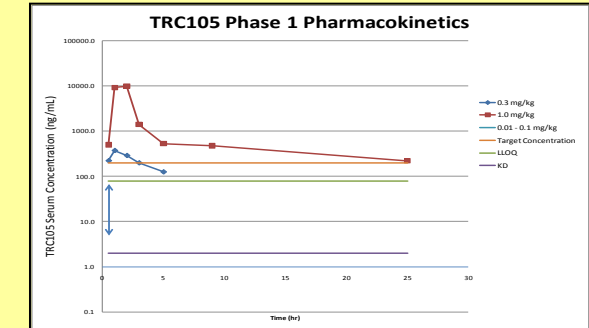


A patient with metastatic ovarian cancer was treated for 6 months at a TRC105 dose of 0.01 mg/kg with radiographically stable disease and a 16% decrease in plasma CA125. Progression at Month 7 was based on a rising CA125.

Summary and Conclusions

- Safety and Immunogenicity
 - TRC105 was tolerated in 21 patients at doses up to 1.0 mg/kg every 2 weeks with evidence of clinical activity
 - Two dose-limiting toxicities were observed: Grade 4 bleeding from a gastric ulcer and Grade 3 hypersensitivity reaction
 - Two of 21 patients (<10%) developed HAMA after 6 and 10 doses of TRC105
- Efficacy
 - One patient with castrate-resistant metastatic prostate cancer remains on study at Cycle 18 (Month 17) with a complete PSA response
 - One patient with ovarian cancer remained on study through Month 6 with stable disease and a 16% decrease in plasma CA125
 - In addition, one patient each at 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg and two at 1.0 mg/kg demonstrated stable disease for \geq 2 months
- Further dose escalation is planned to saturate CD105 binding sites for the full 2-week dosing interval followed by a comprehensive Phase 2 program of TRC105 alone and in combination with other agents

Pharmacokinetics



- TRC105 levels were detected in the first three cohorts at concentrations above the K_D but below levels shown to saturate CD105 binding sites
- TRC105 levels exceeding concentrations shown to saturate CD105 binding sites for 24 hours were achieved in cohort 5 (1.0 mg/kg), with C_{max} >10,000 ng/mL

REFERENCES

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