

EARLY EVIDENCE OF TOLERABILITY AND CLINICAL ACTIVITY FROM A PHASE 1 STUDY OF TRC105 (ANT-CD105 ANTIBODY) IN PATIENTS WITH ADVANCED REFRACTORY CANCER

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UPDATED ABSTRACT

Background: TRC105 is a human/murine chimeric IgG1 monoclonal antibody that inhibits angiogenesis and tumor growth. TRC105 binds human CD105, a proliferation-associated and hypoxia-inducible protein found on the surface of proliferating vascular endothelial cells. Preclinical studies have demonstrated the safety and antitumor activity of TRC105 in multiple tumor types as monotherapy and in combination with cytotoxic chemotherapy. An ongoing phase 1 trial is evaluating the safety and tolerability of single-agent TRC105 in patients with solid cancers.

Methods: Study patients were required to have advanced refractory cancer, ECOG ≤ 1 , and adequate organ function. Patients with CNS or central thoracic cancers were excluded. TRC105 was administered by 60 minute IV infusion every 2 weeks until progression. Cohorts of 3 to 6 patients were planned at doses of 0.01, 0.03, 0.1, 0.3, and 1.0 mg/kg.

Results: A total of 17 patients have been enrolled and treated at each of the planned doses. One patient at 0.1 mg/kg experienced Grade 4 bleeding from a gastric ulcer within 1 week of the first TRC105 infusion. The bleeding was considered possibly related to study treatment and a dose-limiting toxicity. The ulcer bleeding had resolved by the time of endoscopy after 2 units of packed red blood cells. No other Grade 3 or 4 adverse events have been reported. Possibly related grade 1 or 2 adverse events have included grade 2 fatigue, grade 2 dysgeusia, and grade 1 intermittent postcoital vaginal bleeding in a premenopausal woman with locally recurrent ovarian cancer. One patient with castrate-refractory prostate cancer treated at 0.01 mg/kg remains on study without progression in month 11 of TRC105 therapy with a complete PSA response accompanied by improved bone scans. One metastatic ovarian cancer patient also treated at 0.01 mg/kg was treated on study for 6 months with radiographically stable disease and a 16% decrease in plasma CA125. Additionally, one patient each at 0.03 mg/kg, 0.1 mg/kg, and 0.3 mg/kg had stable disease for ≥ 2 months. One patient out of 12 patients treated in the first 3 dose cohorts (0.01, 0.03 and 0.1 mg/kg) developed human antimouse antibody after 6 doses of TRC105 (3 months of treatment). PK analyses indicate TRC105 concentrations known to saturate CD105 binding sites were achieved in cohort 4 (0.3 mg/kg), with $C_{MAX} = 160-2600$ ng/mL.

Conclusion: TRC105 is tolerated at doses that show evidence of clinical activity in advanced refractory cancer. The study continues to enroll patients at 1.0 mg/kg every 2 weeks. These findings suggest that TRC105 is an attractive candidate for further clinical development alone and in combination with other anticancer agents.

INTRODUCTION

TRC105 is a human/murine chimeric IgG1 kappa monoclonal antibody that binds with ~ 2 ng/mL avidity to human CD105 (endoglin), a membrane receptor required for angiogenesis and over-expressed by the proliferating vascular endothelium of solid tumors. Like VEGF, CD105 expression is induced by hypoxia through HIF-1 α and is knock-out "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 cancers. Notably, 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.

OBJECTIVES

- Evaluate the safety and tolerability of escalating doses of the monoclonal antibody, TRC105, when administered intravenously every 2 weeks to patients with solid tumors.
- Evaluate pharmacokinetics, tumor response, and human antichimeric antibody formation.

METHODS

STUDY DESIGN

- Phase 1, non-randomized, open-label, dose-finding, first-in-human study conducted at 4 institutions in the U.S.

KEY INCLUSION CRITERIA

- Adults (age ≥ 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 effusions within 3 months of dosing.

RESULTS

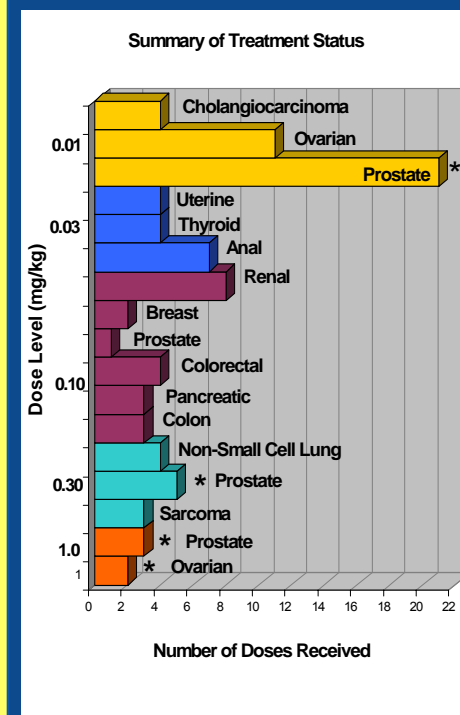
This is an interim analysis of an ongoing study; data have not been audited. A total of 17 patients have been enrolled and have been evaluated as part of this presentation.

Baseline Characteristics

Characteristic	Number of Patients (n=17)
Median Age	60
Gender	Female - 8 Male - 9
Screening ECOG	ECOG 0 - 10
Performance Status	ECOG 1 - 7
Prior Anti-Cancer Therapy*	Median Number of Prior Therapies - 4 Range - 1 to 12 Caucasian - 13 Asian - 1 Black/African American - 2 Hispanic/Latino - 1
Race	

*n=15

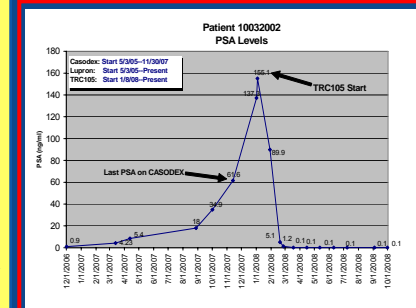
Summary of Treatment Status



*Patient treatment is ongoing

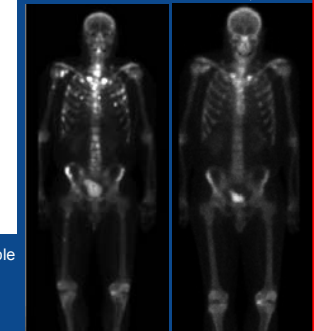
Summary of Response Data

A total of 17 patients have been treated on study to date. One prostate cancer patient treated at 0.01 mg/kg remains on study with a complete PSA response at month 11 of treatment, a second ovarian cancer patient treated at 0.01 mg/kg for 6 months demonstrated a 16% decrease in CA125 (see patient data below). Additionally, one patient each at 0.03 mg/kg, 0.1 mg/kg, and 0.3 mg/kg had stable disease for ≥ 2 months.



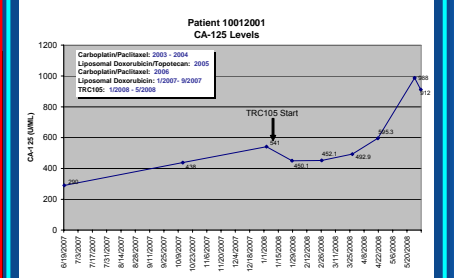
Patient #10032002 Prostate Cancer

Whole-Body Bone Imaging Study
February 11, 2008
June 16, 2008



A castrate-refractory prostate cancer patient with multiple bone metastases treated at 0.01 mg/kg remains on study at Month 11 with a complete PSA response to TRC105 and a markedly improved bone scan.

Patient #10012001 Ovarian Cancer



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

Summary of Safety Data – Related Events

Event	Number of Patients Out of 17 Total Treated			
	Grade 1	Grade 2	Grade 3	Grade 4
Anemia		1		
Arthralgia	1			
Diarrhea	2			
Dysgeusia	1			
Fatigue	1			
Flushing	1	2		
Gastrointestinal bleeding*				1
Proteinuria		1		
Vaginal bleeding**	1			

*A single dose-limiting toxicity was observed at 0.1 mg/kg due to bleeding from an untreated asymptomatic gastric ulcer within 1 week of the first TRC105 infusion. The bleeding had resolved by the time of endoscopy after 2 units of packed red blood cells, and the patient was removed from study. The protocol was amended to exclude peptic ulcer disease and those with risk factors for peptic ulceration.

**Grade 1 intermittent postcoital vaginal bleeding occurred in a premenopausal woman treated at 0.01 mg/kg with locally recurrent ovarian cancer. The same postcoital bleeding was also noted in this patient prior to enrollment.

PK/PD Summary

- TRC105 binds human CD105 on umbilical vein endothelial cells (HUVECs) with high avidity (K_D of ~ 2 ng/mL).
- TRC105 saturates human CD105 binding sites at concentrations of ~ 200 ng/mL *in vitro*, and 200 ng/mL is considered the target concentration for human PK studies.
- 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 were achieved in cohort 4 (0.3 mg/kg), with $C_{MAX} = 160-2600$ ng/mL.
- HAMA data is available for the first 12 treated patients. One patient was positive at 0.03 mg/kg on Cycle 4 Day 1 (prior to dose 7).

Conclusions

- TRC105 is tolerated at doses up to 1.0 mg/kg every 2 weeks with evidence of clinical activity.
- A single dose-limiting toxicity has been observed: Grade 4 bleeding from a gastric ulcer after the first dose of TRC105.
- One of 12 patients treated in the first 3 cohorts developed HAMA after 3 months of treatment.
- One castrate-refractory metastatic prostate cancer patient remains on study at 11 months with a complete PSA response to TRC105 therapy.
- One metastatic ovarian cancer patient was treated for 6 months with radiographically stable disease and a 16% decrease in plasma CA125.
- Three additional patients (with anal, renal cell and prostate cancer) had stable disease after ≥ 2 months of TRC105.
- These data suggest that TRC105 is an attractive candidate for development alone and in combination with other agents.

References:

Li C, Sorenson LK, Brooke BS et al. Defective angiogenesis in mice lacking endoglin. Science 284:1534-7, 1999.
Bockhorn M, Tsuzuki Y, Zu L et al. Differential vascular and transcriptional responses to anti-VEGF antibody in orthotopic human pancreatic cancer xenografts. Clin Can Res 9:4221-6, 2003.
Davis DW, Inoue K, Dimery CPN et al. Regional effects of an anti-VEGF receptor monoclonal antibody on receptor phosphorylation and apoptosis in human 253J B-V bladder cancer xenografts. Canc Res 64:4601-10, 2004

