

Phase 1 Study of TRC105 [Anti-CD105 (Endoglin) Antibody] Therapy in Patients with Advanced Refractory Cancer

LS Rosen, MS Gordon, HI Hurwitz, M Wong, BJ Adams,
D Alvarez, BK Seon, BR Leigh, CP Theuer;
Premiere Oncology, Santa Monica CA; Premiere
Oncology, Scottsdale AZ; Duke University, Durham NC;
Roswell Park Cancer Institute, Buffalo NY; TRACON
Pharmaceuticals Inc., San Diego CA

Presentation Overview

- TRC105 Background
- Study Objectives
- Study Design
- Study Results
- Summary & Conclusions

TRC105 Mechanism of Action

- 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 knock-out “lethal”; mice that lack CD105 die in utero from absent vascular development (Li et al, 1999)

TRC105 Mechanism of Action

- 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)

Study Objectives

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

Study 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 ≥ 18 years) with advanced or metastatic solid cancer for whom curative therapy is unavailable
- ECOG performance status of 0 or 1
- Adequate organ function

Study Methods

KEY EXCLUSION CRITERIA

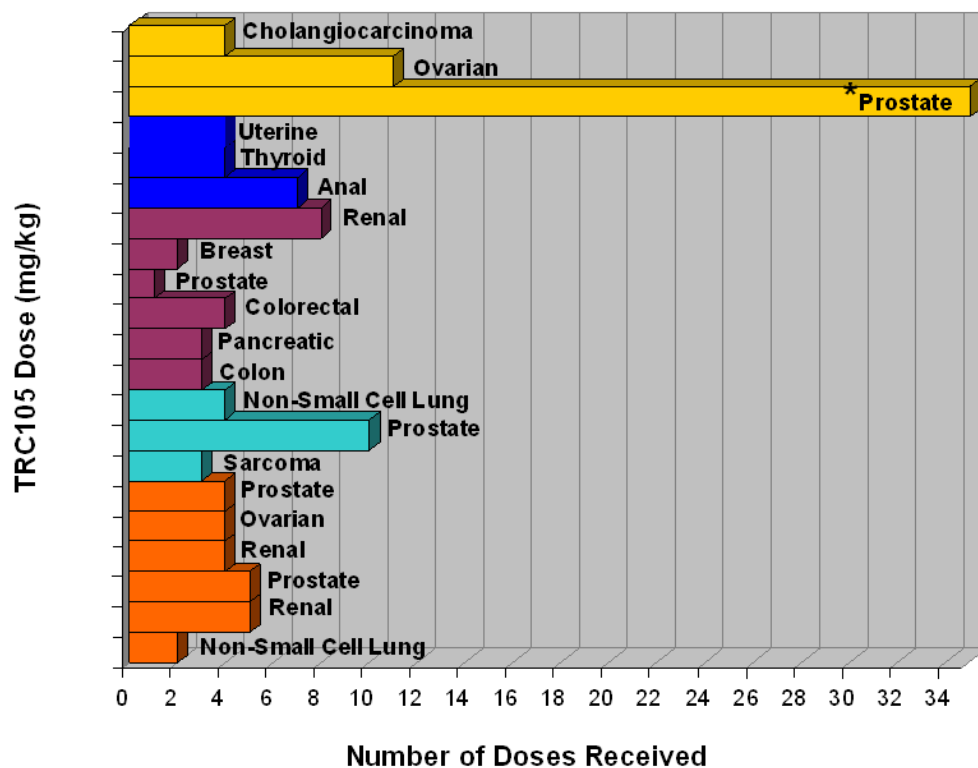
- Receipt of cancer treatment within 4 weeks of study start.
- History of primary or secondary brain tumors.
- Lung cancer with central chest lesions.
- Major surgery within 4 weeks of study start.
- Unhealed wounds or bleeding within 30 days of dosing.
- Significant pericardial, pleural or peritoneal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

Study Results - 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

Study Results – Summary of Treatment Status

105ST101 Phase 1 Summary of Treatment Status



*A prostate cancer patient remains on study after 35 doses of TRC105 (18 28-day cycles)

Study Results - Immunogenicity

- Two patients developed human antimouse antibody one occurred in a patient dosed at 0.03 mg/kg after 6 doses and the second occurred in a patient dosed at 0.3 mg/kg after 10 doses of TRC105, both were undetectable 4 weeks and 12 weeks respectively following discontinuation of TRC105

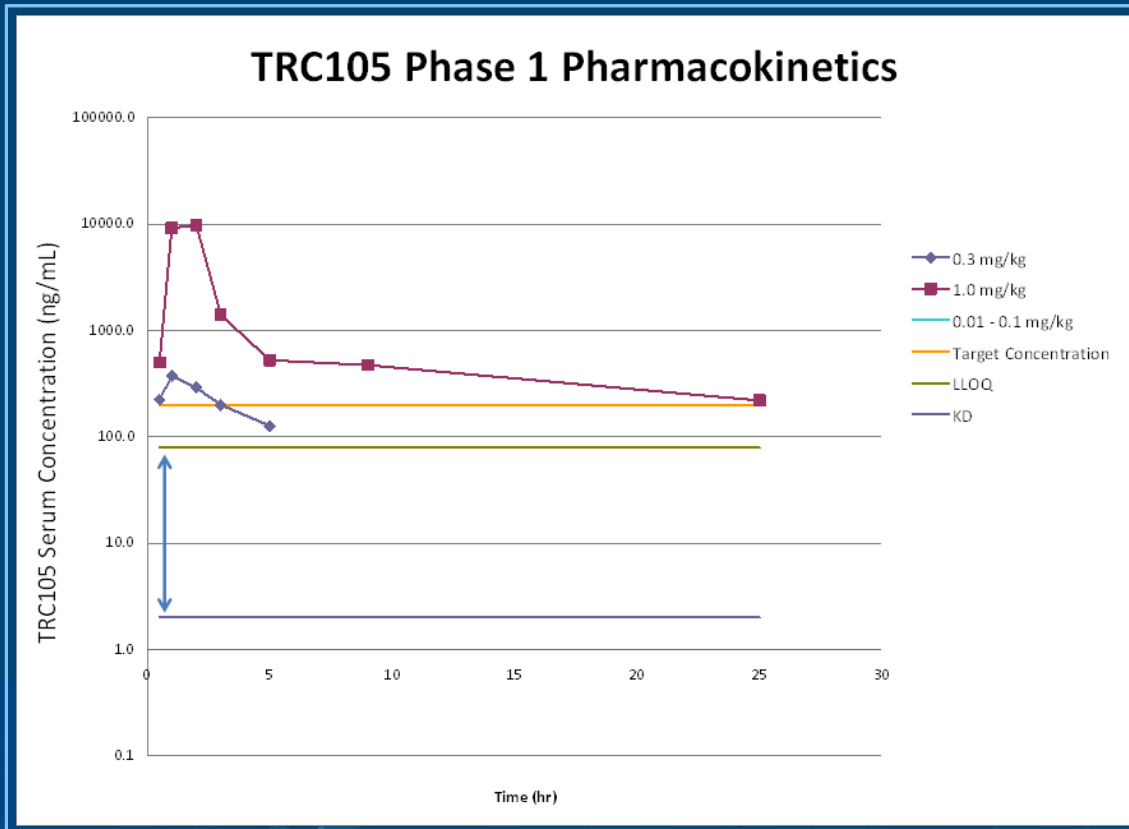
105ST101 Study Results - Safety

TRC105 Possibly Related Adverse Events				
Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4
Anemia		1		
Diarrhea	2			
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			

Study Results - Safety

- Dose limiting toxicity was observed at 0.1 mg/kg due to bleeding from an asymptomatic gastric ulcer within 1 week of the first TRC105 infusion. The bleeding resolved by the time of endoscopy after 2 units of packed red cells. The protocol was amended to exclude peptic ulcer disease and risk factors for peptic ulceration.
- Dose limiting toxicity was observed at 1.0 mg/kg due to hypersensitivity reaction during TRC105 infusion requiring parenteral medication.

Study Results - Pharmacokinetics



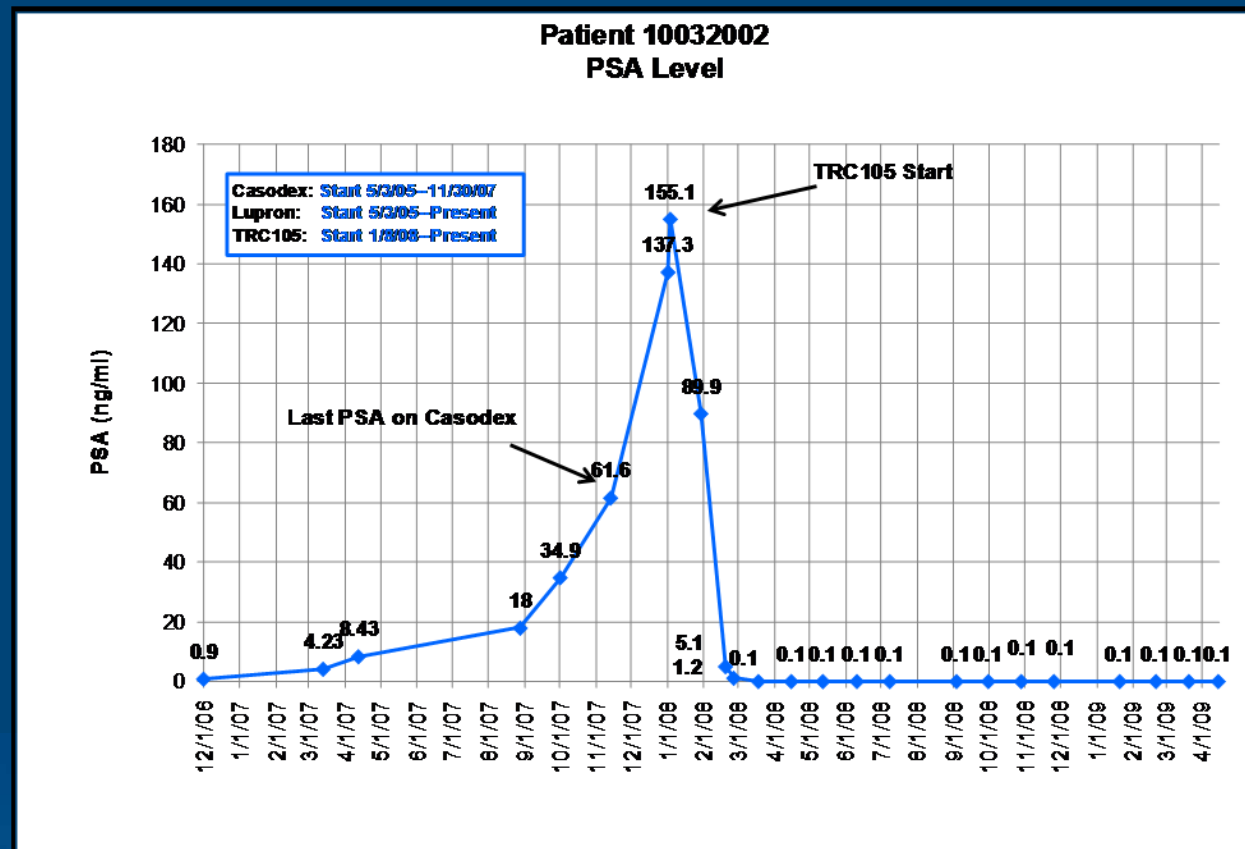
- TRC105 levels were detected in the first three cohorts at concentrations above the KD but below levels shown to saturate CD105 binding sites
- TRC105 levels exceeding concentrations shown to saturate CD105 binding sites for 24 hours were achieved in cohort 5 (1.0 mg/kg), with $C_{max} > 10,000$ ng/mL

Study Results - 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
- 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
- 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 ≥ 2 months

Study Results - Efficacy

Patient 10032002 PSA Trend



Study Results - Efficacy

February 11, 2008

Following 3 Doses of TRC105

June 16, 2008

Following 12 Doses of TRC105

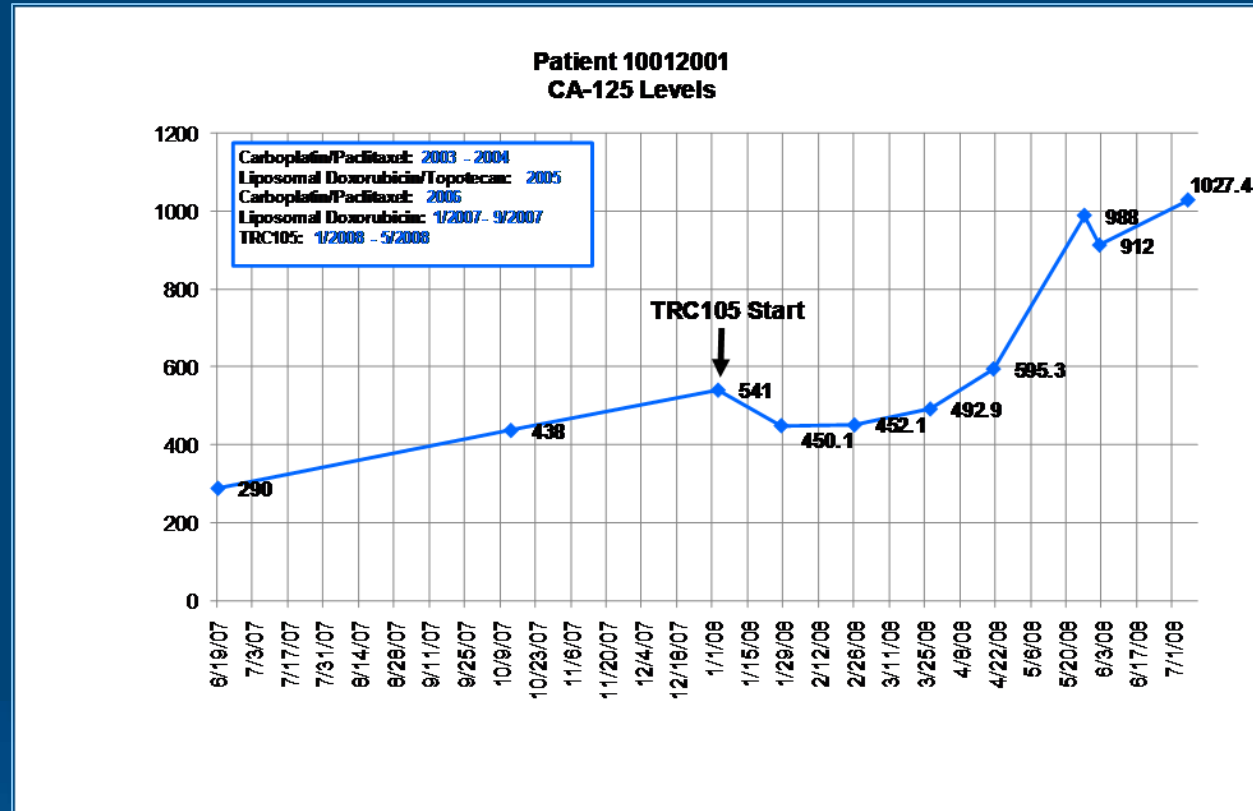
**Patient
10032002**

**Whole body
bone imaging
study**



Study Results - Efficacy

Patient 10012001 CA-125 Trend



Summary & Conclusions

- 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
- One patient with castrate-resistant metastatic prostate cancer remains on study at Cycle 18 (Month 17) with a complete PSA response
- One patient with metastatic ovarian cancer remained on study through Month 6 with stable disease and a 16% decrease in plasma CA125

Summary & Conclusions

- Two of 21 patients (<10%) developed HAMA after 6 & 10 doses of TRC105
- These data suggest that TRC105 is an attractive candidate for development alone and in combination with other agents
- Further dose escalation is planned to saturate CD105 binding sites for the full 2-week dosing interval