

A PHASE 1 STUDY OF TRC105 (ANTI-CD105 ANTIBODY) IN PATIENTS WITH ADVANCED SOLID TUMORS

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INTRODUCTION

- TRC105 is a chimeric IgG1 anti-CD105 monoclonal antibody with very high avidity (5 pM, 1 ng/mL)
- CD105, also known as endoglin, is a membrane receptor that is essential for angiogenesis and highly expressed by proliferating vascular endothelial cells in solid tumors (Seon 2011)
- TRC105 inhibits angiogenesis and tumor growth by inhibiting endothelial cell proliferation and inducing antibody-dependent cellular cytotoxicity and apoptosis
- Like VEGF, CD105 is upregulated by hypoxia and is knockout lethal; mice that lack CD105 die *in utero* from absent vascular development (Li 1999)
- High tumor microvessel density as measured by CD105 immunohistochemistry correlates with poor prognosis across more than 10 solid tumor types, including breast, colorectal, prostate and lung cancer
- In mouse models of human cancer, CD105 expression is upregulated by VEGF inhibitors (Bockhorn 2003, Davis 2004)
- TRC105 potentiates the activity of VEGF inhibitors in preclinical models
- CD105 is expressed on renal cell cancer stem cells (Bussolati 2008)

RESULTS

Patient Demographics

Baseline Patient Characteristics (N=50)	
Age	Median: 64 Range: 25 - 84
Gender	Female: 15 Male: 35
Baseline ECOG Performance Status	ECOG PS 0: 15 ECOG PS 1: 35
Number of Prior Regimens	Median: 4 Range: 1-13
Cancer Type	Colorectal: 10 Prostate: 9 Renal: 5 Lung: 4 Ovarian: 3 Sarcoma: 3 Breast: 2 Pancreatic: 2 Other: 12

Immunogenicity

TRC105 Source	HAMA Positive	HACA Positive
NS0 cells	2 of 21 (9.5%)	7 of 20 (35%)
CHO cells	0 of 28 (0%)	0 of 26 (0%)

- HAMA and HACA rarely detected in 21 patients treated with NS0-produced TRC105 and did not correlate with infusion reactions or other adverse events
- Neither HAMA nor HACA detected in 29 patients treated with CHO-produced TRC105 to be used for all future clinical trials

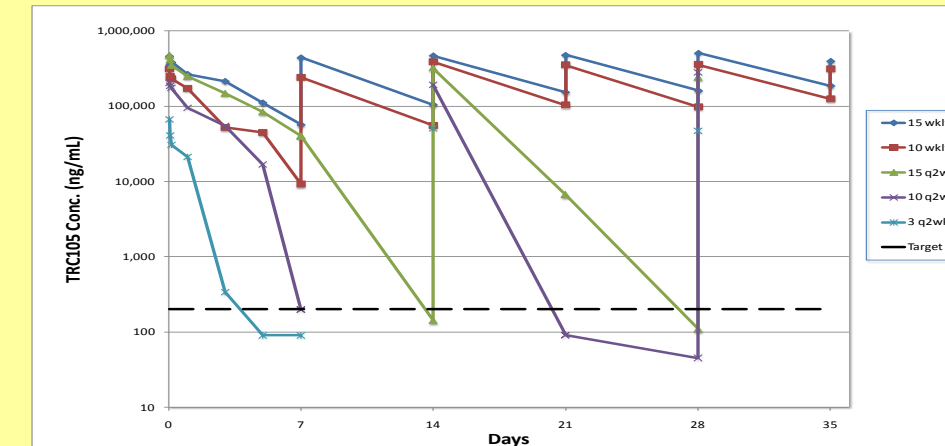
Safety

Possibly Related Adverse Events in >1 Patient or Grade 3/4 (N=50)							
Drug Supply	TRC105 Dose	Schedule	Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4
NS0	0.03 mg/kg	Every 2 Weeks	Fatigue		1		
			Gastrointestinal hemorrhage				1
			Anemia		1		
NS0	0.1 mg/kg	Every 2 Weeks	Diarrhea	1			
			Flushing	1			
			Diarrhea	1			
NS0	0.3 mg/kg	Every 2 Weeks	Infusion related reaction		1	1	
			Fatigue		1		
			Nausea	1			
CHO	0.3 mg/kg	Every 2 Weeks	Vomiting	1			
			Infusion related reaction		2	1	
			Headache	1			
CHO	1 mg/kg	Every 2 Weeks	Infusion related reaction	1		1	
			Constipation	1			
			Flushing	1			
CHO	10 mg/kg	Every 2 Weeks	Infusion related reaction		2		
			Anemia		1		
			Epistaxis	1			
CHO	15 mg/kg	Every 2 Weeks	Fatigue	1	1	1	
			Anemia	1			
			Fatigue	1			
CHO	10 mg/kg	Weekly	Nausea	1			
			Vomiting	1			
			Epistaxis	1	1		
CHO	15 mg/kg	Weekly	Fatigue	1	1		
			Anemia	2	1		
			Headache	2			
CHO	15 mg/kg	Weekly	Pyrexia	2			
			Telangiectasia	1			
			Anemia			2	1
CHO	15 mg/kg	Weekly	Constipation		1		
			Fatigue		1		
			Headache		1		
CHO	15 mg/kg	Weekly	Infusion related reaction		2	1	
			Epistaxis	2	1		
			Telangiectasia	1			

Summary of Grade 3/4 Adverse Events:

- Grade 4 hemorrhage from a gastric ulcer occurred in one patient on Study Day 5 after the initial TRC105 infusion at 0.1 mg/kg
- The bleeding had resolved by the time of upper endoscopy after 2 units PRBCs
- No other Grade 3 or 4 hemorrhage
- Grade 3 infusion reactions in Cycle 1 at 0.3 to 1.0 mg/kg
- Dexamethasone-based premedication regimen allowed dose escalation to 15 mg/kg weekly
- Dexamethasone can be safely tapered and discontinued with weekly TRC105 administration
- Grade 3 anemia during Cycle 2 in 3 of 3 patients at 15 mg/kg weekly, with one patient progressing to Grade 4 by Cycle 3
- Gradually progressive hypoproliferative anemia was associated with TRC105 accumulation to very high levels
- Dose-limiting anemia is likely the result of TRC105 suppression of CD105-positive proerythroblasts (RBC precursors) in marrow
- Anemia is reversible, treatable, and easily monitorable allowing modification of TRC105 dose relative to the degree of anemia

Pharmacokinetics



- TRC105 concentrations that engage ADCC (1 ng/mL) were achieved at all dose levels
- The target concentration for maximum effect (200 ng/mL) was achieved at doses of 0.3 mg/kg and higher
- Serum concentrations expected to saturate CD105 binding sites (>200 ng/mL) were achieved continuously at 15 mg/kg q2 weeks and 10 mg/kg weekly
- TRC105 accumulated with weekly dosing

OBJECTIVES

- Evaluate the safety and tolerability of escalating doses of intravenous TRC105 in patients with advanced solid tumors
- Evaluate pharmacokinetics, tumor response and immunogenicity

METHODS

Study Design

- Phase 1, open-label, dose-escalation, first-in-human study conducted at 4 US institutions

Key Inclusion Criteria

- Advanced incurable solid cancer
- ECOG PS of 0 or 1
- Adequate organ function
- Hemoglobin \geq 10 g/dL

Key Exclusion Criteria

- Lung cancer with central tumor
- CNS disease
- Clinically significant effusions
- Prior cancer therapy within 4 wks
- Major surgery within 4 wks
- Major bleeding within 4 wks

Dose Escalation Schema

NS0-Produced TRC105

0.01 mg/kg q2 wks (N=3)
0.03 mg/kg q2 wks (N=3)
0.1 mg/kg q2 wks (N=6)
0.3 mg/kg q2 wks (N=3)
1 mg/kg q2 wks (N=6)

CHO-Produced TRC105

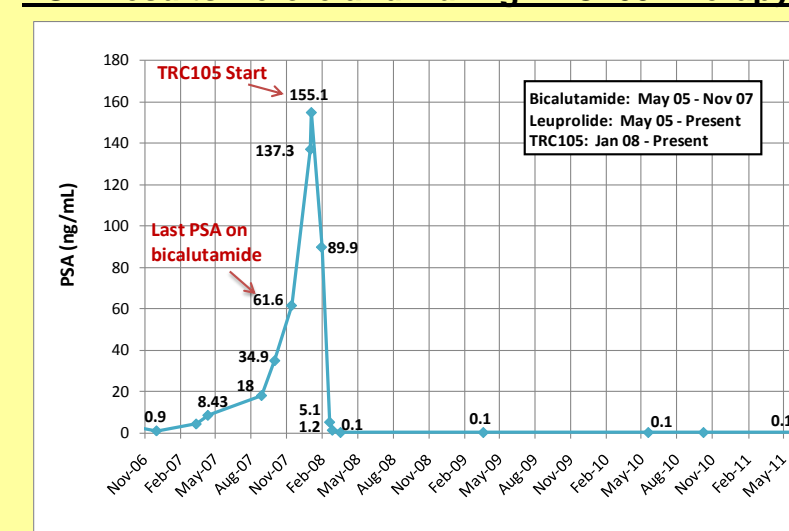
0.3 mg/kg q2 wks (N=6)
1 mg/kg q2 wks (N=6)
3 mg/kg q2 wks (N=3)
10 mg/kg q2 wks (N=3)
15 mg/kg q2 wks (N=4)
10 mg/kg q wk (N=3)
15 mg/kg q wk (N=4)

Efficacy

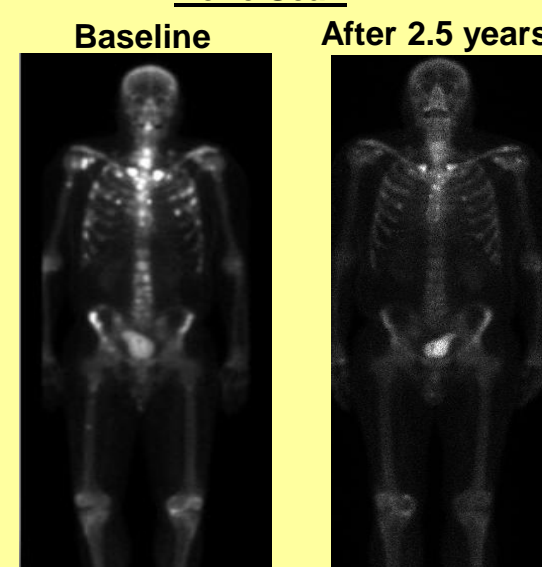
Prostate Cancer

- A patient with metastatic castrate-resistant prostate cancer and multiple painful skeletal metastases has been on TRC105 therapy for over 3 years with:
 - Complete PSA response
 - Resolution of bone pain
 - Bone scan normalization

PSA Results Before and During TRC105 Therapy



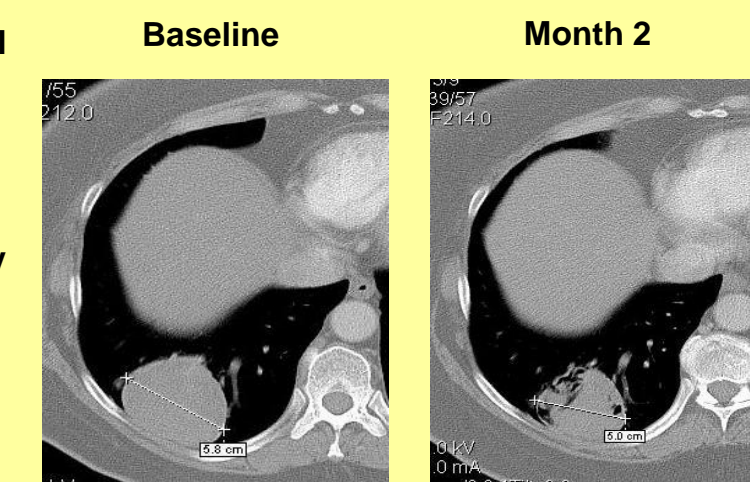
Bone Scan



Endometrial Cancer

- A patient with lung metastases from endometrial cancer remains on study after 10+ months of treatment with a reduction in the maximum dimension of all 8 tumors
- Overall tumor burden reduction was 7%, 9%, 13%, and 8% at Month 2, 4, 6, and 8, respectively
- Progression-free survival on TRC105 exceeds that for all 3 prior systemic regimens including:
 - Carboplatin/paclitaxel (4 months)
 - Anastrozole (8 months)
 - Ifosfamide (2 months)

Chest CT Scan



SUMMARY & CONCLUSIONS

- Safety and Tolerability**
 - Dose-limiting hypoproliferative anemia occurred at 15 mg/kg weekly
 - Grade 3 infusion reactions controlled with premedications
 - Isolated Grade 4 hemorrhage at 0.1 mg/kg every 2 weeks did not recur at higher doses
 - TRC105 was tolerated at doses up to 15 mg/kg every 2 weeks and 10 mg/kg weekly
- Pharmacokinetics and Immunogenicity**
 - Serum concentrations expected to saturate CD105 binding sites (>200 ng/mL) were achieved continuously at 15 mg/kg every 2 weeks and 10 mg/kg weekly
 - HAMA /HACA not detected in patients administered CHO-produced TRC105 to be used in all future studies

Pharmacodynamics and Efficacy

- Global decrease in key angiogenic biomarkers with treatment (ASCO 2011 Poster #10565)
- SD \geq 2 months in 22 of 45 pts (49%), SD \geq 4 months in 6 of 44 pts (14%)
- One patient with castrate-resistant metastatic prostate cancer remains on TRC105 therapy for >3 years with a complete PSA response, bone scan normalization and resolution of bone pain
- One patient with refractory endometrial cancer remains on TRC105 therapy in Month 10 with reduced tumor burden
- Tumor marker decreases (CEA, PSA or CA125) in 8 of 21 pts (38%)

REFERENCES

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