ASCO 2012
Abstract: 3034

AN OPEN LABEL PHASE 1B DOSE ESCALATION STUDY OF TRC105 COMBINED WITH STANDARD DOSE BEVACIZUMAB FOR ADVANCED SOLID TUMORS

DS Mendelson, LS Rosen, EG Chiorean, F Robert, SD Spencer, BJ Adams, D Alvarez, BK Seon, CP Theuer, MS Gordon;
Pinnacle Oncology Hematology, Scottsdale, AZ; UCLA Health Care Hematology-Oncology, Santa Monica, CA; Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; University of Alabama at Birmingham, AL; Roswell Park Cancer Institute, Buffalo, NY; National Cancer Institute, Bethesda, MD; TRACON Pharmaceuticals, Inc., San Diego, CA

INTRODUCTION

- TRC105 is a chimeric IgG1 anti-CD105 monoclonal antibody with high avidity (K_D = 5 pM)
- CD105, also known as endoglin, is a membrane receptor that is highly expressed by proliferating endothelial cells in solid tumors (Seon 2011). Like VEGF, CD105 is up-regulated by hypoxia and required for angiogenesis; mice that lack CD105 die *in utero* (Li 1999)
- High tumor microvessel density as measured by CD105 immunohistochemistry correlates with poor prognosis in more than 10 solid tumor types
- TRC105 inhibits angiogenesis and tumor growth by inhibiting endothelial cell proliferation and inducing antibody-dependent cellular cytotoxicity and apoptosis
- In mouse models of human cancer, CD105 expression is upregulated by VEGF inhibition (Bockhorn 2003, Davis 2004) and TRC105 potentiates the activity of VEGF inhibitors in preclinical models
- CD105 is expressed on renal cell cancer stem cells (Bussolati 2008) and select solid tumors
- The MTD of TRC105 given as a single agent was 10 mg/kg weekly. Dose escalation was limited by anemia, an on-target effect of TRC105 treatment, without significant hypertension or proteinuria. Telangiectasias, a characteristic finding of CD105 receptor modulation, were observed routinely at the MTD

OBJECTIVES

- Evaluate the safety and tolerability of escalating doses of intravenous TRC105 when added to standard dose bevacizumab in patients with advanced solid tumors
- Evaluate pharmacokinetics, tumor response and immunogenicity

METHODS

Study Design

- Phase 1b, open-label, dose-escalation study conducted at 4 institutions in the United States

Key Inclusion Criteria

- Advanced incurable solid cancer
- ECOG PS of 0 or 1
- Adequate organ function
- Hemoglobin ≥ 9 g/dL

Key Exclusion Criteria

- Lung cancer with central tumor
- CNS disease
- Prior cancer therapy within 3 wks
- Major surgery within 4 wks
- Major bleeding within 6 mo

Dose Escalation Schema

TRC105 Wkly + 15 mg/kg Bev Q3Wks

- 3 mg/kg TRC105 (N=3)
- 6 mg/kg TRC105 (N=5)

↓

TRC105 Wkly + 10 mg/kg Bev Q2Wks
(1st TRC105 dose delayed 1 week)

- 6 mg/kg TRC105 (N=4)
- 8 mg/kg TRC105 (N=4)

↓

TRC105 Wkly + 10 mg/kg Bev Q2Wks
(1st TRC105 dose delayed 1 week and split over 2 days)

- 8 mg/kg TRC105 (N=3)

RESULTS

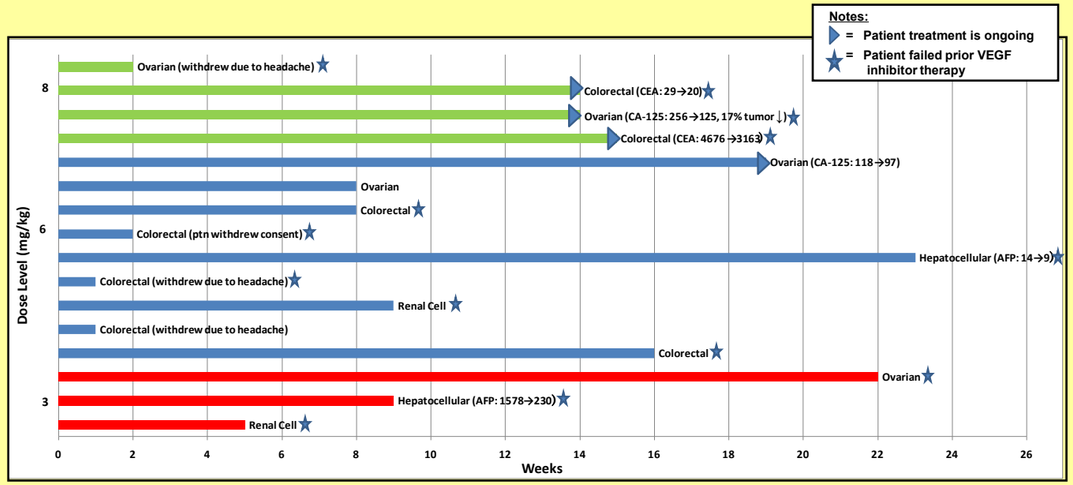
Demographics

Baseline Patient Characteristics (N=16)	
Age	Median: 64 Range: 43-82
Gender	Female: 8 Male: 8
Baseline ECOG Performance Status	ECOG PS 0: 5 ECOG PS 1: 11
Number of Prior Regimens	Median: 5 Range: 2-9
Cancer Type	Colorectal: 7 Ovarian: 5 Hepatocellular: 2 Renal cell: 2

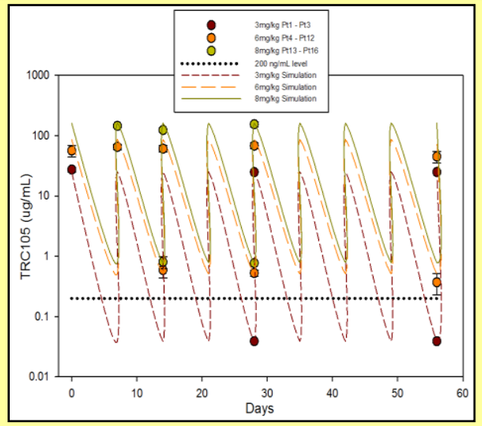
Immunogenicity

HAMA Positive	HACA Positive
1 of 12 (8%)	1 of 12 (8%)

Duration of Participation



Pharmacokinetics



- Continuous TRC105 serum levels above the target concentration of 200 ng/mL were observed at the 6 and 8 mg/kg weekly dose levels

Safety

TRC105 Dosing	Bevacizumab Dosing	Preferred Term	Grade 1	Grade 2	Grade 3
3 mg/kg Wkly (N=3)	15 mg/kg Q3wks	Chills	1		
		Headache	1	1	
		Infusion Related Reaction		1	
6 mg/kg Wkly (N=5)	15 mg/kg Q3wks	Fatigue		1	
		Gingival Bleeding	1		
		Gingivitis	1		
		Headache	1	2	2 (1 DLT)
		Infusion Related Reaction		2	1
		Rash	1		
		Telangiectasia	2		
6 mg/kg Wkly (N=4)	10 mg/kg Q2wks	Epistaxis	3		
		Fatigue		1	
		Flushing	1	1	
		Gingival Bleeding	2		
		Headache	1	3	
		Localized Edema		2	
		Rash	1		
8 mg/kg Wkly (N=4)	10 mg/kg Q2wks	Chills		1	
		Epistaxis	2		
		Flushing	1		
		Gingival Bleeding	1		
		Headache	1	1	1 (DLT)
		Localized Edema		1	
		Rash	1		
		Telangiectasia	1		

- Headaches following the initial dose of TRC105 have been severe in some patients and generally responsive to sumatriptan treatment
- Dose limiting headache occurred following the initial dose of both drugs given concurrently at the 6 mg/kg weekly TRC105 dose level in combination with 15 mg/kg bevacizumab every 3 weeks
- The 6 mg/kg weekly TRC105 dose level was tolerated when the initial TRC105 dose was delayed by 1 week in combination with 10 mg/kg bevacizumab every 2 weeks
- Dose limiting headache recurred when the initial dose of 8 mg/kg TRC105 was administered in combination with 10 mg/kg bevacizumab every 2 weeks, despite delaying the initial TRC105 dose by 1 week
- The 8 mg/kg weekly dose level is being reenrolled with the initial TRC105 dose delayed by 1 week and given over two days during the first week in combination with 10 mg/kg bevacizumab every 2 weeks
- Other common adverse events included fatigue, epistaxis, telangiectasias and gingival bleeding

Efficacy

- 9 of 16 patients (56%) had stable disease ≥ 2 months
- 6 of 14 patients (43%) with measurable soluble tumor markers had at least a 10% decrease in soluble tumor markers from baseline, 5 of whom had failed prior VEGF inhibitor therapy
- Evidence of antitumor activity was observed in all three evaluable VEGF inhibitor refractory patients who received 8 mg/kg TRC105 weekly with 10 mg/kg bevacizumab every 2 weeks.

Ovarian Cancer

- A patient with serous ovarian cancer had a 17% overall reduction in tumor burden after 2 months of treatment at 8 mg/kg TRC105 weekly + 10 mg/kg Q2Wks bevacizumab
- The patient continues on study in month 4 of treatment
- Prior cancer therapy included
  - Carboplatin/paclitaxel
  - Investigational PARP inhibitor
  - Investigational VEGF-R2 multitargeted tyrosine kinase inhibitor
  - Liposomal doxorubicin

SUMMARY & CONCLUSIONS

- Headaches have been dose limiting and have required TRC105 schedule modification, including delaying the initial TRC105 dose until one week following bevacizumab dosing and administering the initial dose over two days.
- The 6 mg/kg and 8 mg/kg weekly TRC105 dose levels achieved continuous serum levels of TRC105 above target concentrations in combination with 10 mg/kg bevacizumab every 2 weeks.
- Dose escalation is planned to the recommended single agent Phase 2 dose and schedule of TRC105 of 10 mg/kg weekly
- Immunogenicity was observed in 1 of 12 patients
- Antitumor activity (radiographic response and tumor marker reductions) was observed in patients who were refractory to VEGF inhibitors.

REFERENCES

- Bockhorn M, Clinical Cancer Research 9:4221-4226, 2003
- Bussolati B, FASEB 22:3696-3705, 2008
- Davis DW, Cancer Research 64:4601-4610, 2004
- Li DY, Science 284:1534-1537, 1999
- Seon BK, Current Drug Delivery 8:135-143, 2011