ASCO 2011
Abstract Number: 3073

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

J. W. Goldman, M. S. Gordon, H. Hurwitz, R. Pili, D. S. Mendelson, B. J. Adams, D. Alvarez, B. K. Seon, C. P. Theuer, B. R. Leigh, L. S. Rosen;

Premiere Oncology, Santa Monica, CA; Pinnacle Oncology Hematology, Scottsdale, AZ; Duke University Medical Center, Durham, NC; Roswell Park Cancer Institute, Buffalo, NY; TRACON Pharmaceuticals, Inc., San Diego, CA

ASCO Annual '11 Meeting

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)

Introduction

- 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)

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

Methods

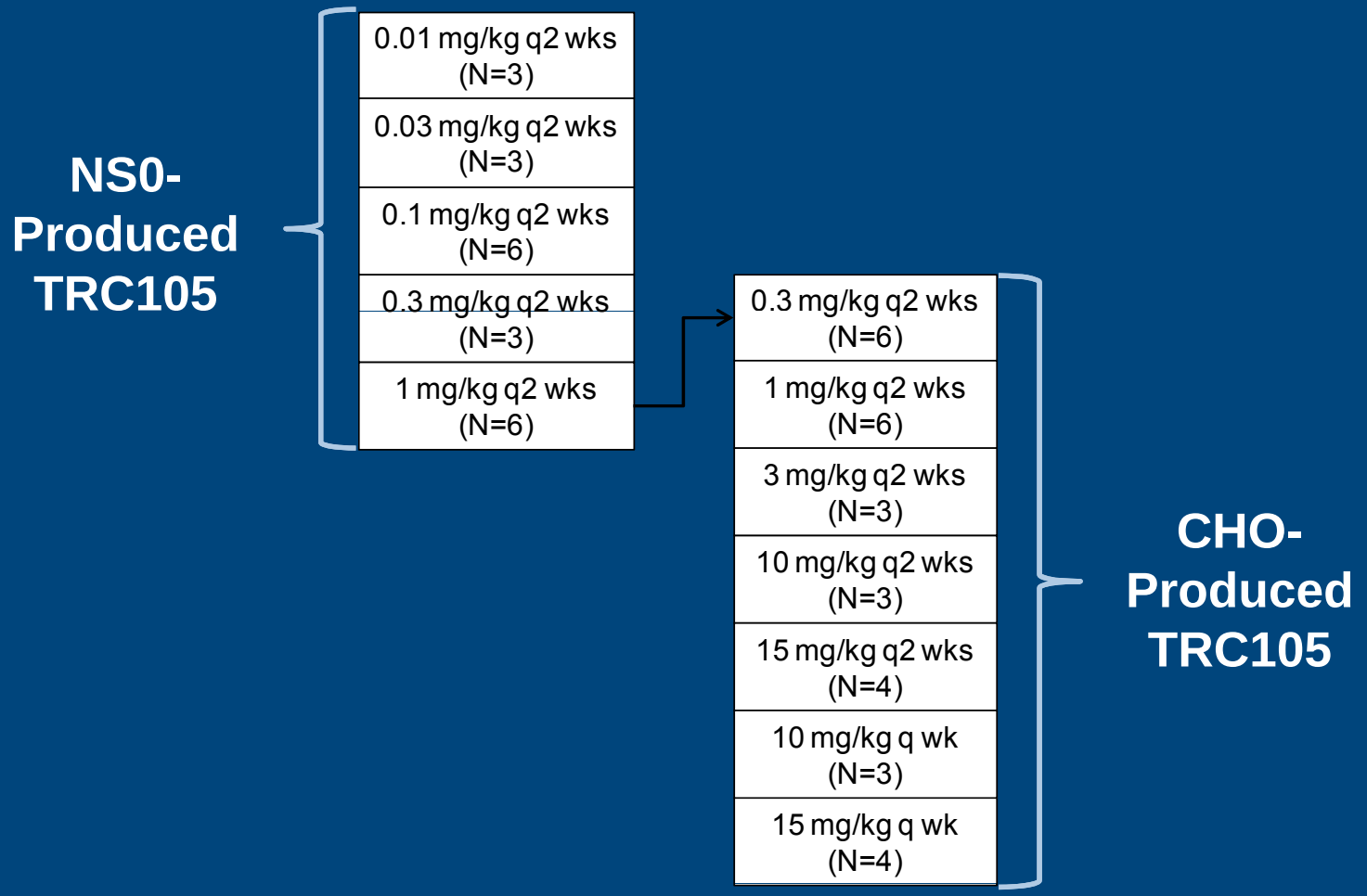
Key Inclusion Criteria

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

Methods: Dose Escalation Schema



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

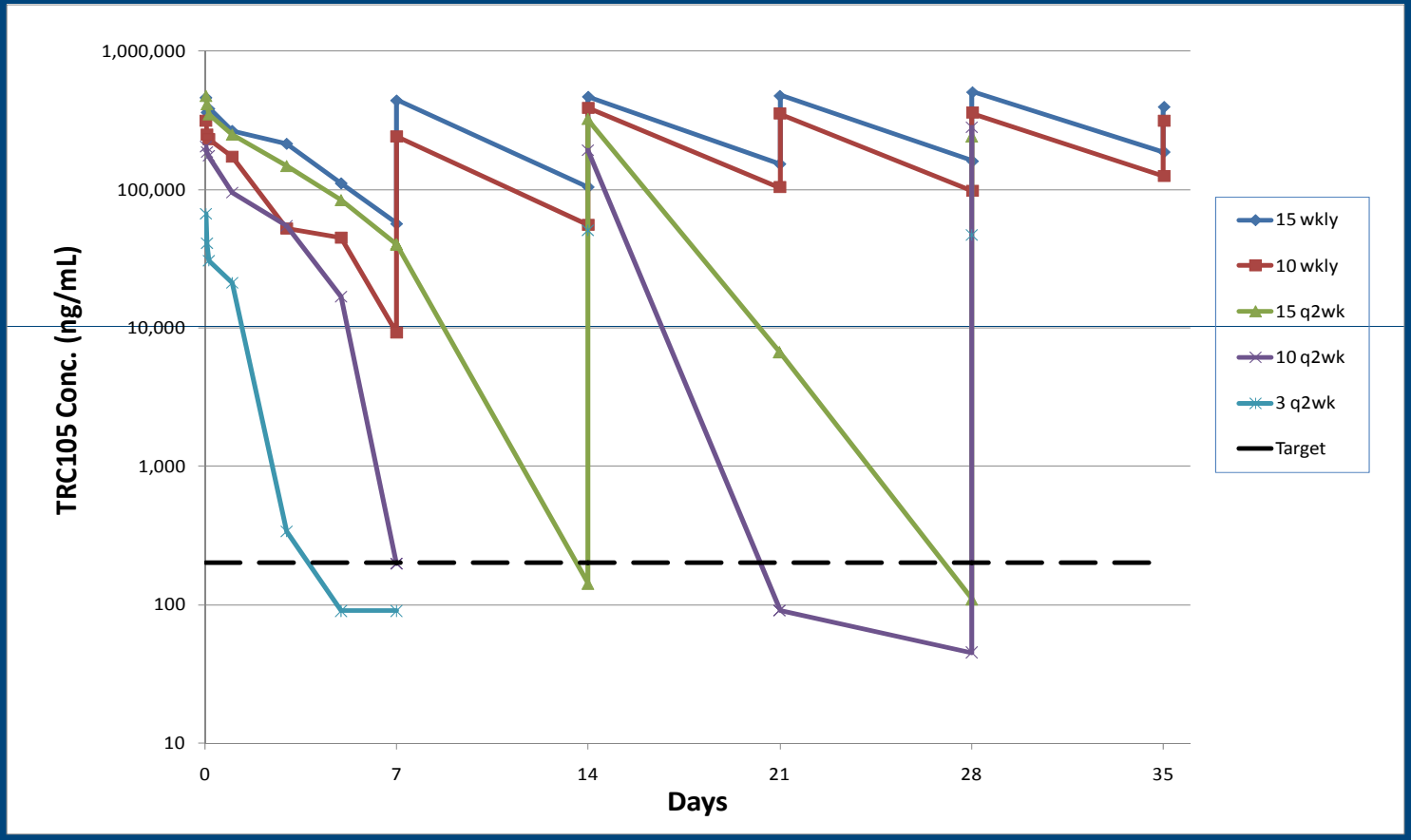
TRC105 Source	HAMA Positive	HACA Positive
NS0 cells	2 of 21 (9.5%)	7 of 20 (35%)
CHO cells	0 of 28 (0 %)	0 of 26 (0 %)

- 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

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.

Pharmacokinetics



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		
NS0	0.1 mg/kg	Every 2 Weeks	Gastrointestinal hemorrhage				1
			Anemia		1		
			Diarrhea	1			
			Flushing	1			
NS0	0.3 mg/kg	Every 2 Weeks	Diarrhea	1			
NS0	1 mg/kg	Every 2 Weeks	Infusion related reaction		1	1	
			Fatigue		1		
			Nausea	1			
			Vomiting	1			
CHO	0.3 mg/kg	Every 2 Weeks	Infusion related reaction		2	1	
			Headache	1			
CHO	1 mg/kg	Every 2 Weeks	Infusion related reaction			1	
			Constipation	1			
			Flushing	1			
CHO	10 mg/kg	Every 2 Weeks	Infusion related reaction		2		
			Anemia		1		
			Epistaxis	1			
			Fatigue	1			
CHO	15 mg/kg	Every 2 Weeks	Anemia		1	1	
			Fatigue	1			
			Nausea	1			
			Vomiting	1			
CHO	10 mg/kg	Weekly	Epistaxis	1	1		
			Fatigue	1	1		
			Anemia		1		
			Headache	2			
			Pyrexia	2			
			Telangiectasia	1			
CHO	15 mg/kg	Weekly	Anemia			2	1
			Constipation		1		
			Fatigue		1		
			Headache		1		
			Infusion related reaction		1		
			Epistaxis	2			
			Telangiectasia	1			

Safety: 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

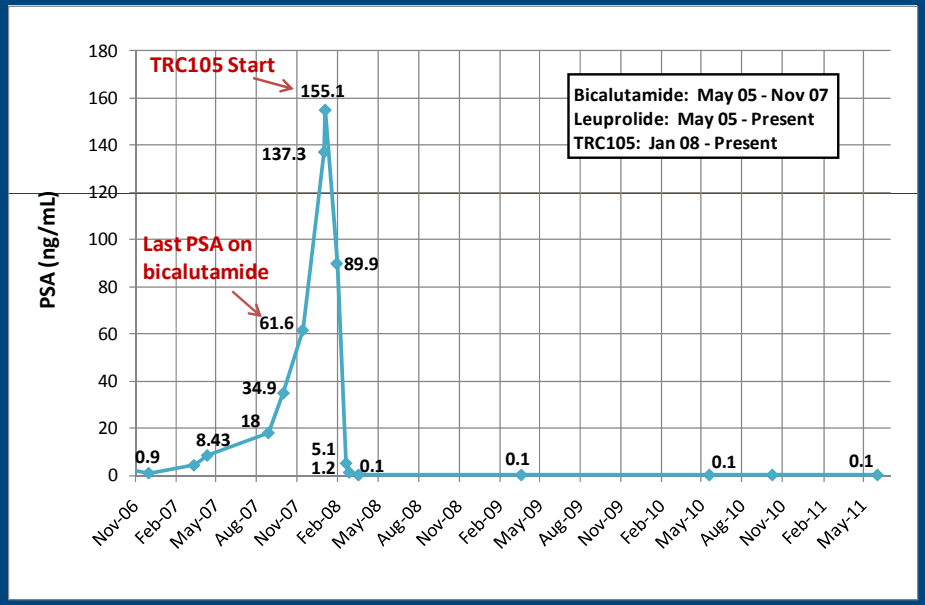
Safety: Summary of Grade 3 & 4 Adverse Events

- **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 hypoproductive 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**

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
- Complete PSA response
- Resolution of bone pain
- Bone scan normalization

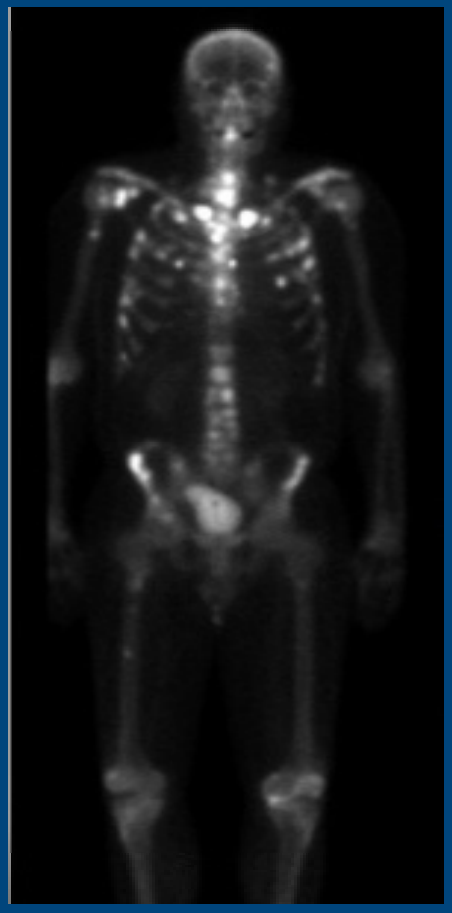
PSA Results Before and During TRC105 Therapy



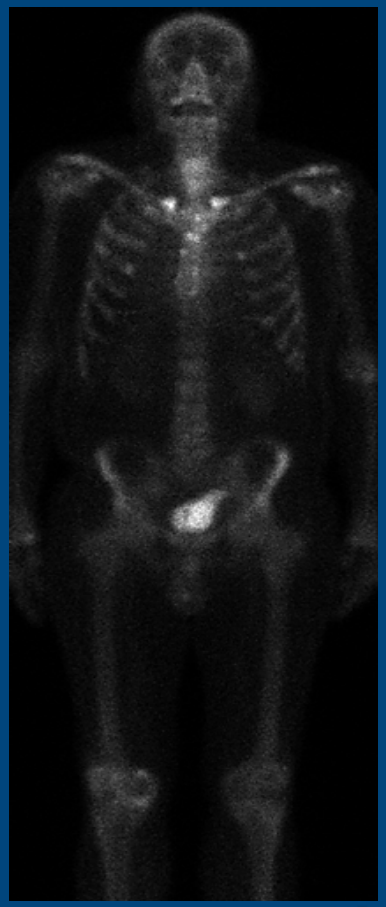
Efficacy: Prostate Cancer

Bone Scan

Baseline



After 2.5 years



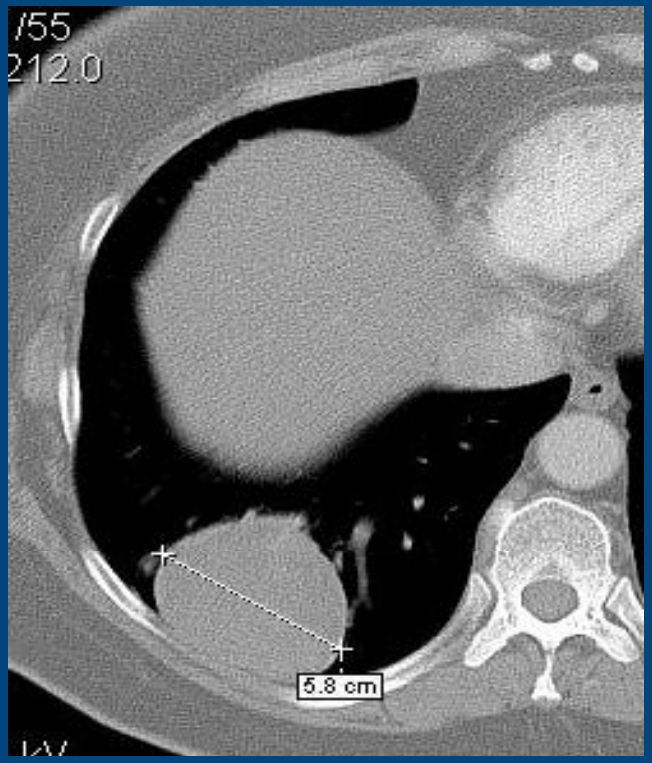
Efficacy: Endometrial Cancer

- 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 including this 5.8 cm tumor
- 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)

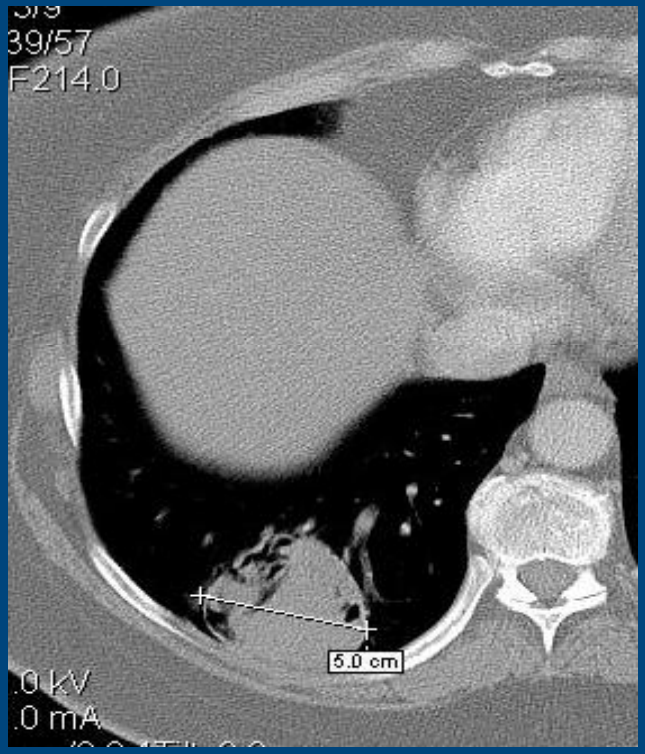
Efficacy: Endometrial Cancer

Chest CT Scan

Baseline



Month 2



Summary and Conclusions

- Safety and Tolerability
  - Dose-limiting hypoproductive 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

Summary and Conclusions

- Pharmacodynamics and Efficacy
  - Global decrease in key angiogenic biomarkers with treatment (ASCO 2011 Poster #10565)
  - SD ≥ 2 months in 22 of 45 pts (49%), SD ≥ 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

- 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