

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

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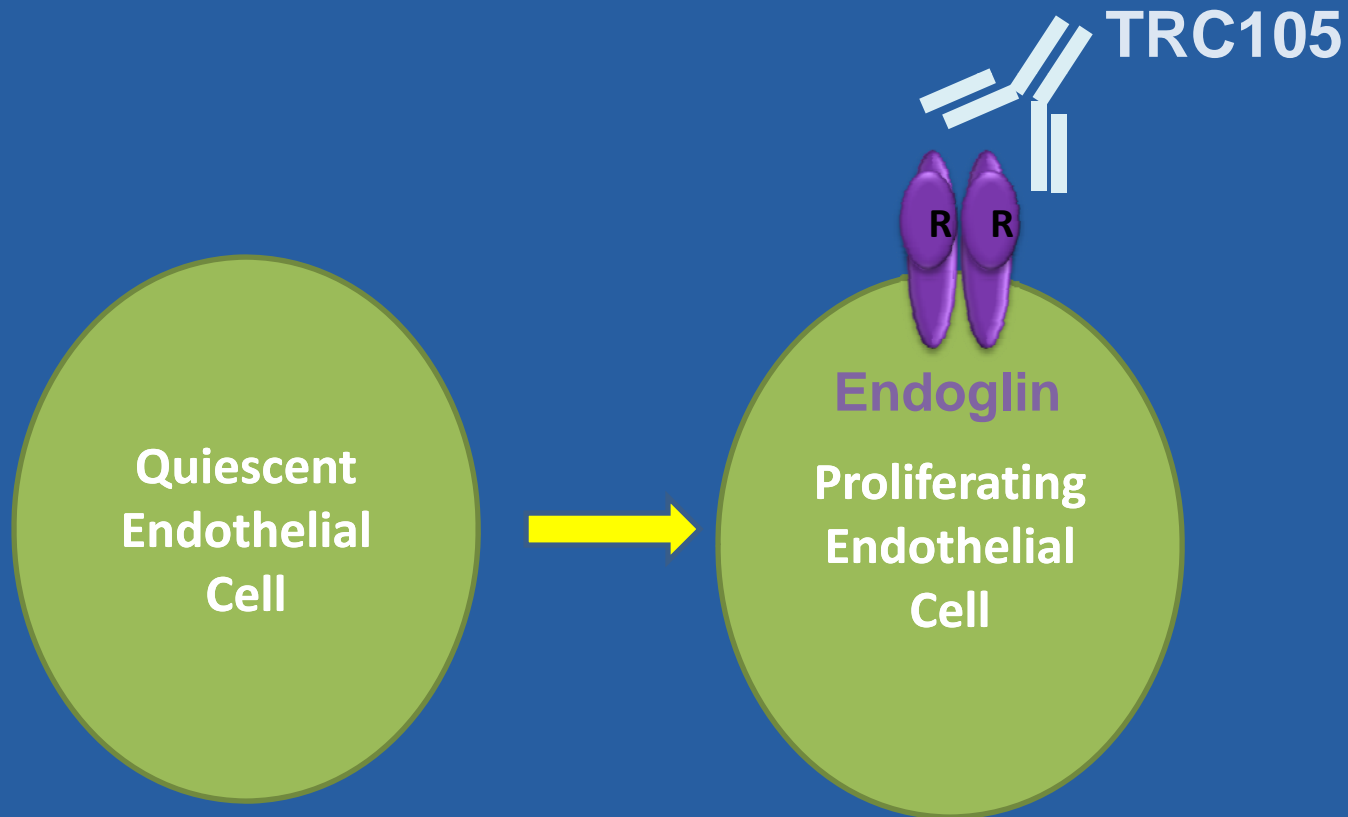
Pinnacle Oncology Hematology, Premiere Oncology, Duke
University Medical Center, Roswell Park Cancer Institute,
TRACON Pharmaceuticals Inc

Disclosures

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 - DS Mendelson, MS Gordon, LS Rosen, H Hurwitz, MKK Wong, BK Seon
- TRACON Employees
 - D Alvarez, BJ Adams, CP Theuer, BR Leigh

TRC105 is a High-Avidity Monoclonal Antibody to Endoglin (CD105)

- Endoglin is abundantly expressed on the surface of proliferating endothelial cells (up to 3×10^6 receptors/cell)



Endoglin Expression is Essential for Angiogenesis

**Endoglin Expressing
Mouse Embryo**



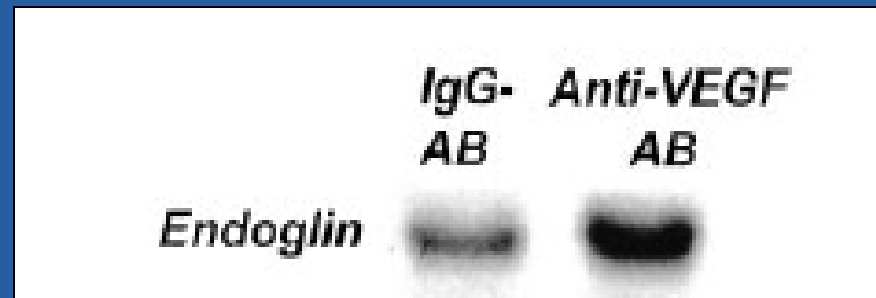
**Endoglin Knockout
Mouse Embryo**



- Endoglin expression is also required for tumor angiogenesis
 - High numbers of endoglin-expressing vessels correlate with poor prognosis across more than 10 solid tumor types including breast, colorectal, prostate, ovarian and lung cancer

Endoglin is a Complementary Target to VEGF for Angiogenesis Inhibition

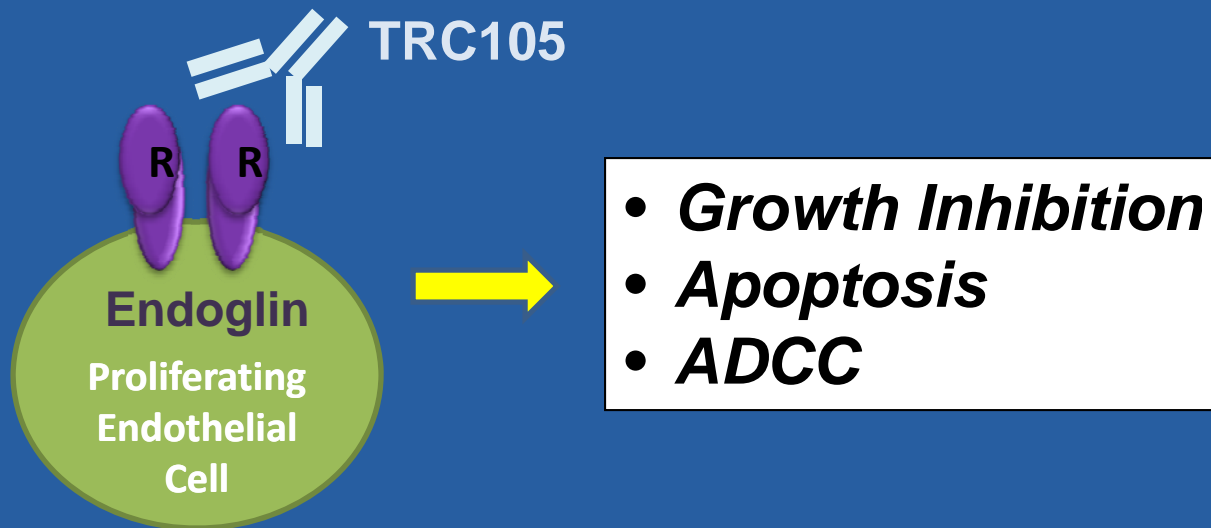
- The Endoglin and VEGF pathways are distinct
 - Endoglin expression is upregulated following VEGF inhibition in human cancer xenografts



- TRC105 enhances the activity of bevacizumab in angiogenesis models

TRC105 Mechanism of Action

- TRC105 binds to endoglin with high avidity ($K_D \sim 1$ ng/mL)
- TRC105 inhibits endothelial cell growth and induces apoptosis
- Antibody dependent cell-mediated cytotoxicity (ADCC) of endothelial cells is achieved at very low TRC105 concentrations (~ 1 ng/mL)



- TRC105 may also have direct antitumor effects, as endoglin is expressed on renal cell cancer stem cells

Study Design & Objectives

DESIGN

- 3 + 3 dose-escalation, first-in-human Phase 1 study conducted at 4 institutions in the United States

OBJECTIVES

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

Study Methods

KEY INCLUSION CRITERIA

- Adults with advanced or metastatic solid tumors 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, unhealed wounds, or bleeding within 4 weeks of study start

Study Results - Demographics

Characteristic	Number of Patients (N=41)	
Age	Median:	65
Gender	Female:	14
	Male:	27
Screening ECOG Performance Status	ECOG 0:	13
	ECOG 1:	28
Number of Prior Regimens	Median:	4
	Range:	1 - 10
Race	Caucasian:	31
	Asian:	2
	African American:	4
	Hispanic/Latino:	3
	Other:	1
Tumor Type	Colorectal:	8
	Prostate:	8
	Lung:	4
	Renal:	3
	Ovarian:	3
	Breast:	2
	Pancreatic:	2
	Sarcoma:	2
	Other:	9

Study Results - Dose Escalation

NS0 Drug Supply

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

CHO Drug Supply

0.3 mg/kg (N=6)
1 mg/kg (N=6)
3 mg/kg (N=3)
10 mg/kg (N=3)
15 mg/kg (N=2)

DLT of Grade 4 hemorrhage from an asymptomatic gastric ulcer; protocol amended

DLT of Grade 3 infusion reaction

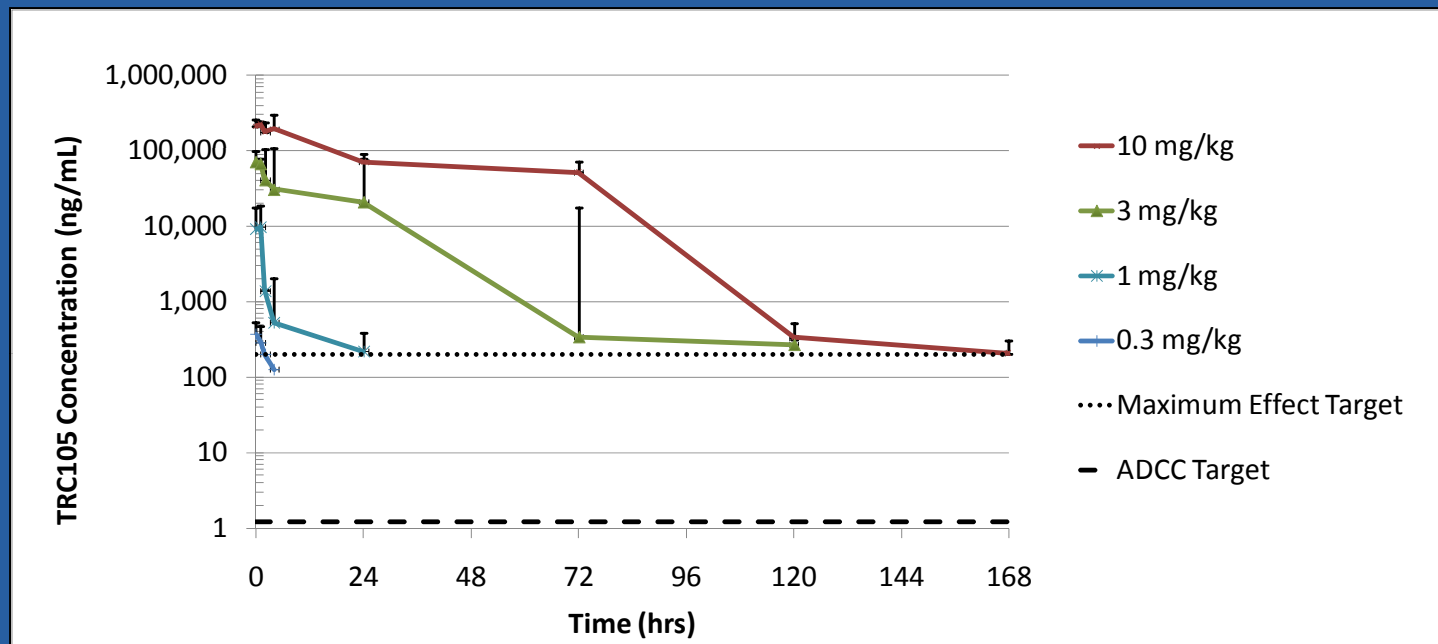
DLT of Grade 3 infusion reaction; protocol amended to mandate premedication

Study Results – Safety

Possibly Related Events (N=41)				
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal hemorrhage				1
Infusion related reaction		5	3	
Fatigue	1	3		
Anemia		1		
Blood bilirubin increased		1		
Proteinuria		1		
Flushing	2			
Arthralgia	1			
Constipation	1			
Diarrhea	1			
Headache	1			
Hyperuricemia	1			
Micturition urgency	1			
Nausea	1			
Vaginal hemorrhage	1			
Vomiting	1			
Diarrhea	1			
Dysgeusia	1			

- Significant hypertension and proteinuria were not observed

Study Results - 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
- The target concentration for maximum effect was maintained for 1 day at 1 mg/kg, 5 days at 3 mg/kg, and 7 days at 10 mg/kg

Study Results - Immunogenicity

TRC105 Source	HAMA +	HACA +
NS0 cells	2 of 21 (9.5%)	7 of 20 (35%)
CHO cells	0 of 15 (0 %)	0 of 13 (0 %)

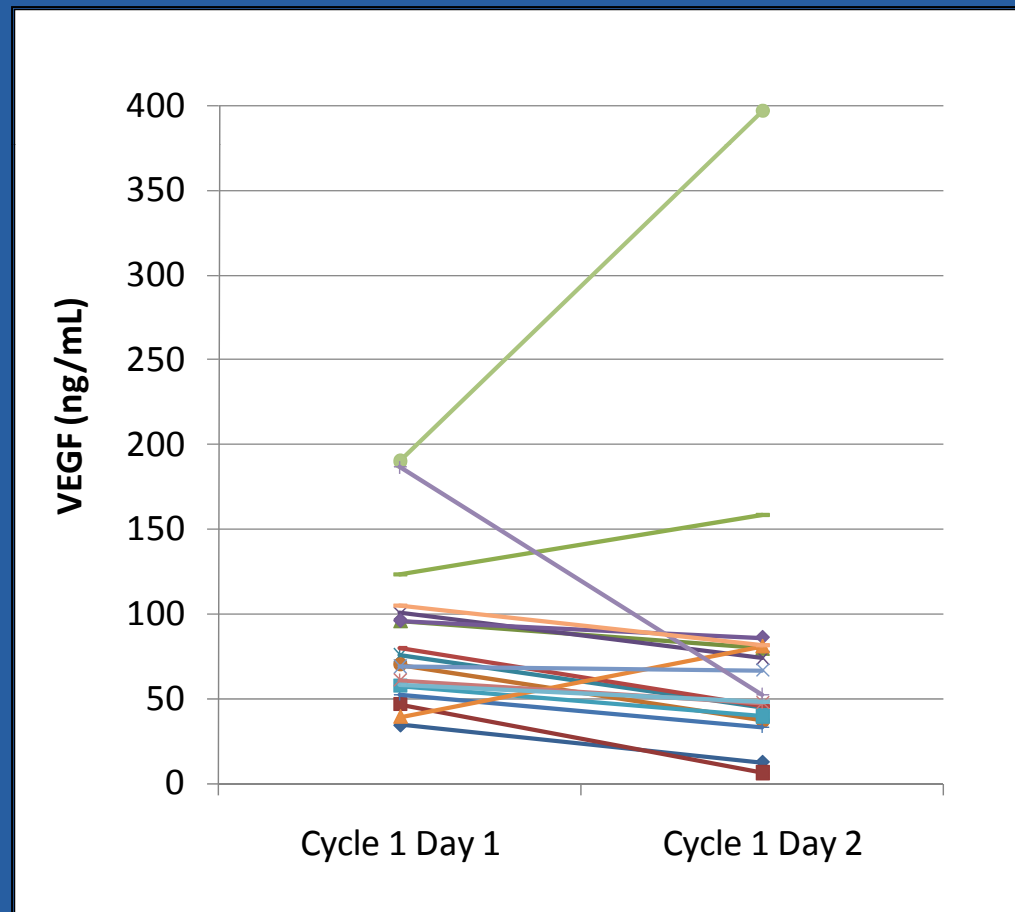
- HAMA (human antimurine antibody) and HACA (human antichimeric antibody) were detected in patients treated with the NS0 supply and did not correlate with adverse events
- Neither HAMA nor HACA were detected in patients dosed with the CHO supply that will be used for future development

Study Results - Efficacy

- Preliminary evidence of clinical activity
 - Decreases in circulating VEGF levels in 15 of 18 patients (83%)
 - Stable disease beyond 2 months in 13 of 35 patients (37%)
 - Stable disease beyond 4 months in 4 of 35 patients (11%)
 - Decreases in circulating tumor markers in 6 of 20 patients (30%)

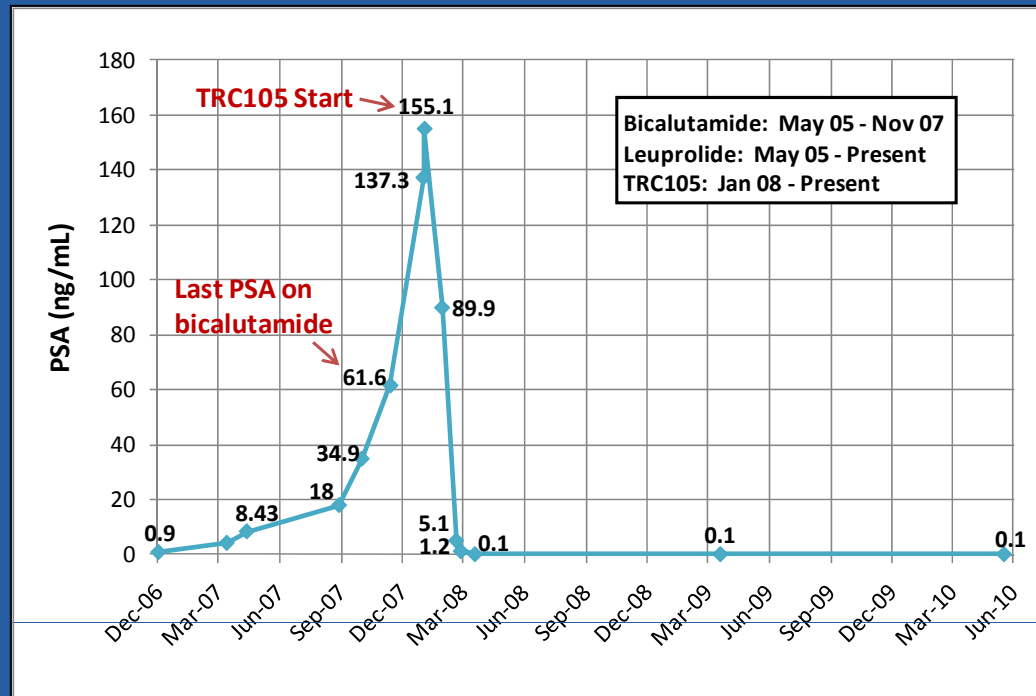
Study Results – Plasma VEGF Reductions

- Plasma VEGF decreased at 24 hours after TRC105 administration in 15 of the first 18 patients (mean decrease from 80 to 50 ng/mL)

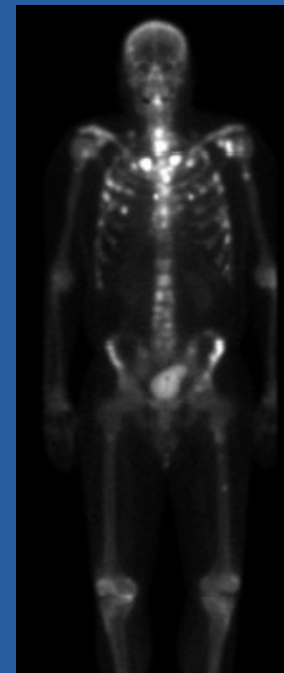


Study Results - Efficacy

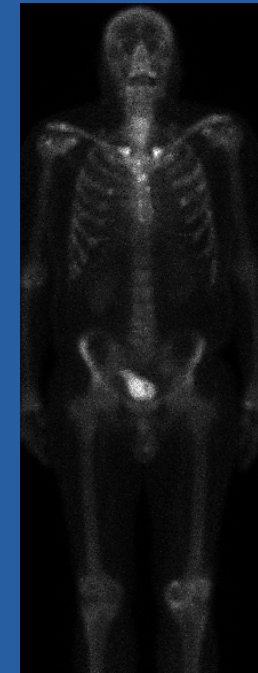
- A patient with castrate-resistant prostate cancer and multiple bone metastases remains on study after 29+ months of treatment with a complete PSA response and improved bone scans



February 2008
3 Doses of TRC105

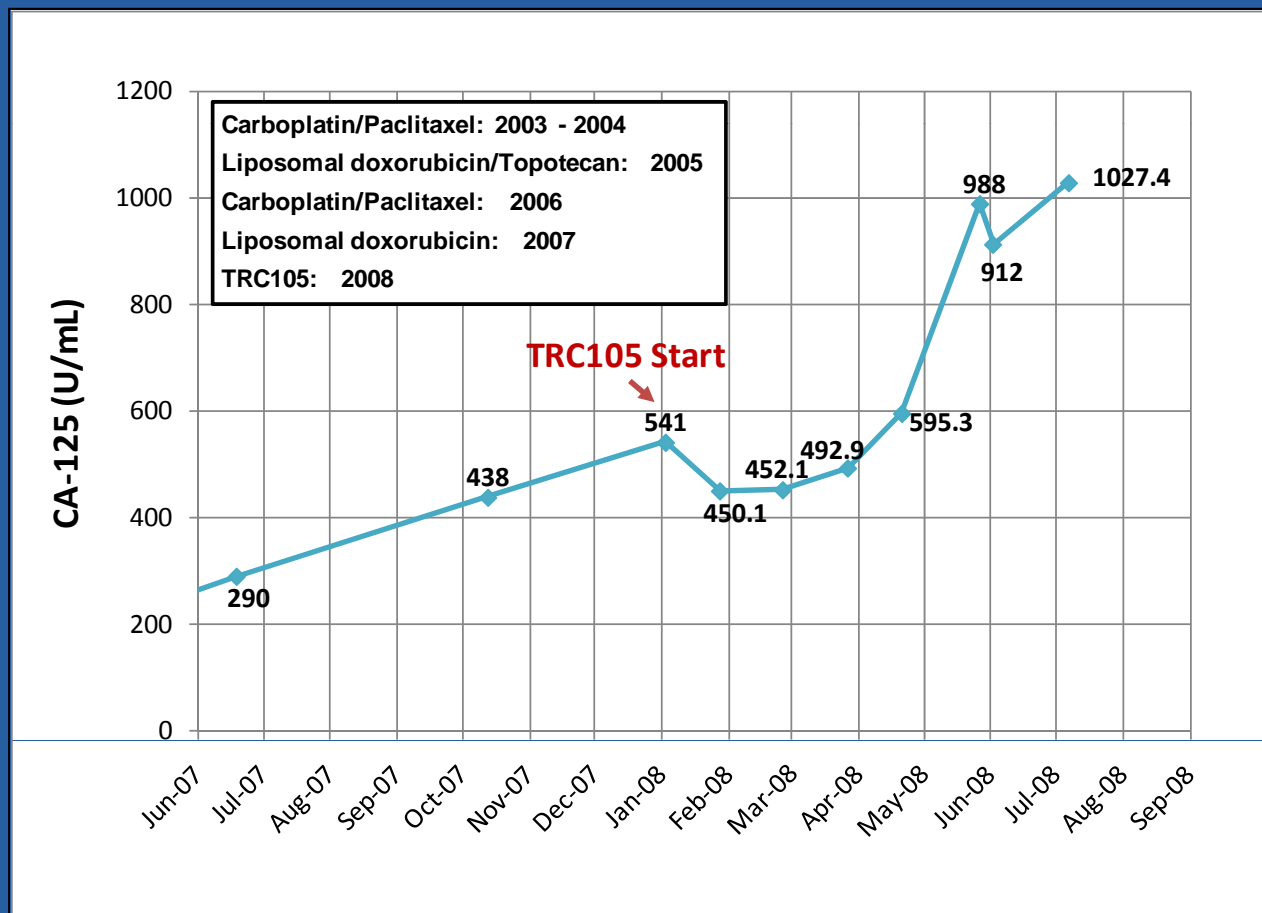


February 2010
55 Doses of TRC105



Study Results - Efficacy

- A patient with platinum-resistant ovarian cancer remained on study for 6 months with radiographically stable disease and a 16% decrease in serum CA-125



Phase 1 Study Summary

- The MTD was not exceeded at 10 mg/kg every 2 weeks
 - Significant hypertension and proteinuria were not observed
 - Dose escalation is ongoing
- Two dose-limiting toxicities were observed
 - Serious bleeding from a gastric ulcer
 - Serious bleeding did not occur in the subsequent 34 patients
 - Grade 3 infusion reactions that required institution of premedication
- Pharmacokinetics
 - Serum TRC105 concentrations above those required for ADCC activity were detected at all dose levels
 - Target concentrations for maximum effect were maintained for 7 days at the 10 mg/kg dose level

Phase 1 Study Summary

- Immunogenicity was not detected in patients treated with CHO-produced TRC105 that will be used for future development
- Individual plasma VEGF levels decreased 24 hours after TRC105 administration in 15 of the first 18 patients
- Decreases in serum tumor markers were noted in 30% of patients with available markers, including patients with colorectal, ovarian and prostate cancer

Next Steps

- Planned and ongoing clinical trials
 - Phase 1/2 trial of single-agent TRC105 in castrate-resistant prostate cancer (ongoing, National Cancer Institute)
 - Phase 2 trial of single-agent TRC105 in recurrent ovarian cancer (Gynecology Oncology Group)
 - Phase 1b trial with capecitabine in metastatic breast cancer (Roswell Park Cancer Institute)
 - Phase 1b/2 trials in combination with VEGF inhibitors

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