A PHASE 1, OPEN-LABEL, DOSE ESCALATION STUDY OF THE HUMANIZED MONOCLONAL ANTIBODY (HuMAb) TRC093, AN INHIBITOR OF ANGIOGENESIS THAT BINDS TO CLEAVED COLLAGEN, IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS

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UPDATED ABSTRACT

Background: TRC093 is a humanized monoclonal antibody that binds cleaved collagen to inhibit angiogenesis and tumor growth. Preclinical studies confirm the safety and antitumor activity of the agent in multiple solid tumors as monotherapy and in combination with cytotoxic and targeted agents. We performed a Phase 1 trial to evaluate the safety and tolerability of TRC093 in patients with solid tumors.

Methods: Patients were required to have advanced refractory cancer, ECOG ≤ 2, and adequate organ function including proteinuria and hematuria ≤ 1+. TRC093 was administered by 90 minute IV infusion on days 1 and 15 of each 28-day cycle until progression. Cohorts of 3 patients were planned at doses of 0.5, 1.5, 5, 12 and 24 mg/kg.

Results: A total of 16 patients have been treated to date, 3 at each of the 0.5, 1.5, and 5 mg/kg dose levels, 6 at the 12 mg/kg and 1 at the 24 mg/kg dose levels without the development of dose-limiting toxicity. The 12 mg/kg dose level was expanded and considered the maximal feasible dose (rather than the top dose level of 24 mg/kg) due to limited drug supply. The most common adverse event (all grade 1 or 2) felt to be possibly drug-related was fatigue. Infusion reactions and related grade > 2 AEs have not been observed. One patient with non-small-cell lung cancer treated at the 1.5 mg/kg dose, a patient with malignant hemangiopericytoma treated at the 5.0 mg/kg dose and a patient with metastatic cervical cancer treated at the 12.0 mg/kg dose had stable disease for 2 months, 10 months and 2 months respectively. In addition, one patient with granulosa cell carcinoma of the ovary with progressive disease had a mixed response in the liver after 2 months of treatment. Biomarker data showed an average increase in endoglin (CD105), FGF, PIGF, VEGF R2 and an average decrease in VEGF across all patients. TRC093 demonstrated linear dose-dependent PK typical of a humanized antibody and there was no evidence of human antihuman antibody (HAHA) development in any of the 16 treated patients.

Conclusion: TRC093 is well-tolerated when administered by 90 minute IV infusion every 2 weeks. Phase 1b and 2 trials based on preclinical studies will evaluate TRC093 in combination with other targeted and standard cytotoxic therapies.

INTRODUCTION

TRC093 is a humanized IgG1 monoclonal antibody to cleaved collagen types I through V. Cleaved collagen epitopes are selectively expressed on proliferating vasculature, including tumor vasculature and developing retinal vasculature [1, 2, 3]. TRC093 has been shown to inhibit angiogenesis and tumor growth in mouse models of cancer [4,5] and has also been shown to inhibit choroidal neovascularization in mouse models of age-related macular degeneration. Studies also indicate TRC093 potentiates the activity of approved anticancer therapies in preclinical xenograft models.

OBJECTIVES

- Evaluate the safety and tolerability of TRC093 when administered intravenously every two weeks to patients with solid tumors.
- Evaluate the pharmacokinetics, tumor response, and human antihuman antibody (HAHA) formation following administration of TRC093.

METHODS

STUDY DESIGN
- Phase 1, non-randomized, open-label, dose-finding, first-in-human study conducted at 3 institutions in the U.S.

KEY INCLUSION CRITERIA
- Adults (age ≥ 18 years) with advanced or metastatic solid tumors refractory to standard treatment or for which no effective treatment exists.
- ECOG performance status 0, 1 or 2.
- Adequate organ function.

KEY EXCLUSION CRITERIA
- Receipt of cancer treatment within 4 weeks.
- CNS malignancy.
- Major surgery within 4 weeks.
- Unhealed wounds, ulcers or bone fractures.
- Screening proteinuria or hematuria > 1+.

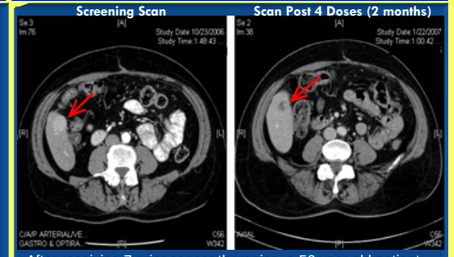
RESULTS

This is an interim analysis of an ongoing study; data presented have not been audited. A total of 16 patients have been enrolled and have been evaluated as part of this presentation.

Baseline Characteristics

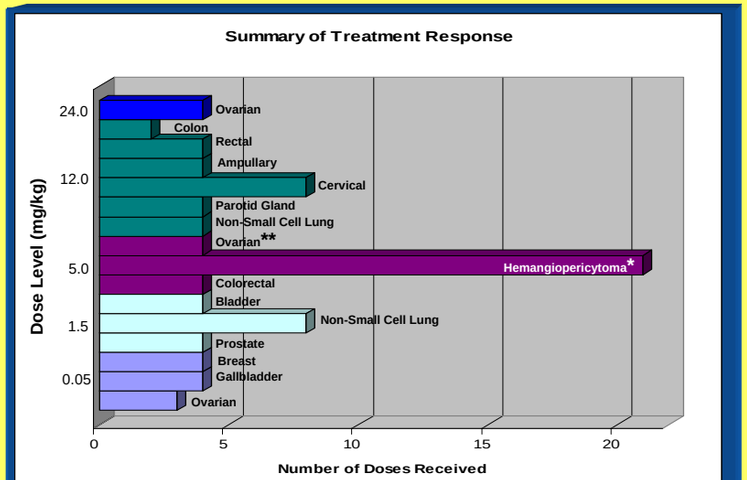
Characteristic	Number of Patients (N=16)
Median Age	58
Gender	Female - 7 Male - 9
Screening ECOG Performance Status	ECOG 0 - 6 ECOG 1 - 10
Prior Chemotherapy	Median Number of Prior Therapies - 6 Range: 2 - 14
Race	Caucasian - 14 Black/African American - 1 Native Hawaiian/Other Pacific Islander - 1

CT Scan Results



After receiving 7 prior cancer therapies, a 56 year old patient with granulosa cell ovarian cancer demonstrated a mixed response in her liver (two lesions regressed, including the right lobar lesion indicated above) although the presence of a new lesion after 4 doses of TRC093 at 5.0 mg/kg indicated disease progression overall.

Summary of Treatment Status



All patients were treated until progression with efficacy evaluations performed every 4 doses (2 months). Only one patient was treated at 24 mg/kg due to limited drug supply. The 12 mg/kg cohort was expanded in order to gain additional safety information in lieu of treating additional patients at 24 mg/kg.
No dose-limiting toxicities were observed at any dose levels. Human antihuman antibody formation was not observed in any of the 16 treated patients.

*A hemangiopericytoma patient treated at 5 mg/kg demonstrated stable disease by CT scan for 10 months prior to progressing at Month 11. Sites of disease included the chest wall, malignant pleural effusion, malignant ascites, lymph nodes and pancreas.

**An ovarian cancer patient demonstrated a mixed response in her liver after 4 doses of TRC093 at 5 mg/kg but demonstrated disease progression overall (see CT scans above).

Summary of Safety Data – Related Events

Preferred Term	# Patients Out of 16 Total Treated: Grade 1	Grade 2
Anemia		1
Palpitations	1	
Lacrimation Increased	1	
Photophobia	1	
Abdominal Discomfort	1	
Gastritis	1	
Nausea	2	
Asthenia	1	
Fatigue	2	4
Pain	1	

Preferred Term	# Patients Out of 16 Total Treated: Grade 1	Grade 2
Anorexia/Decreased Appetite	1	1
Hyponatremia	1	
Arthralgia		1
Muscle Spasms	1	
Musculoskeletal Stiffness		2
Pain in Extremity	2	
Dizziness	1	
Dysarthria	1	
Dysgeusia	1	
Rhinorrhea	1	
Pruritus	1	

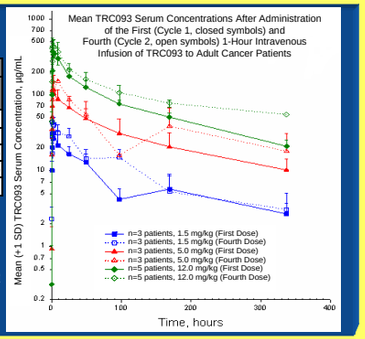
Pharmacokinetics

Summary of Serum TRC093 Exposure Parameters Following Multiple Intravenous Infusions of TRC093[1]

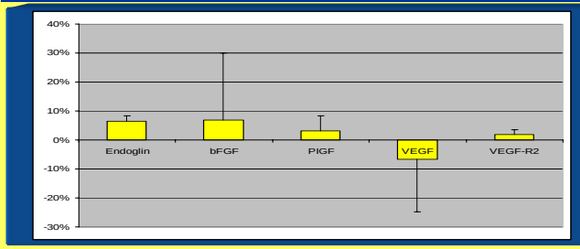
TRC093 Dose (mg/kg)	n	1st Dose (Cycle 1) Cmax (µg/mL)	1st Dose (Cycle 1) AUCO-n (hr*µg/mL)[2]	4th Dose (Cycle 2) Cmax (µg/mL)	4th Dose (Cycle 2) AUCO-n (hr*µg/mL)[2]
0.5	2	9.9 (3.0)	505 (430)	8.9 (0.4)	1090[3]
1.5	3	32.0 (4.0)	2469 (912)	43.3 (9.5)	3349 (1150)
5.0	3	117 (43)	9914 (4120)	131 (58.7)	14069 (8354)
12.0	6	379 (92)	26432 (4184)	467 (111)	35336 (4374)
24.0	1	1006[3]	75635[3]	1475[3]	-[4]

[1] Mean (SD).
[2] AUC_{0-t}= Serum TRC093 AUC during a dose interval.
[3] S.D. could not be calculated, n=1.

Pharmacokinetic evaluation demonstrated linear dose-dependent exposures characteristic of a humanized monoclonal antibody.



Protein Biomarkers



This figure presents the average change in protein biomarker values between Cycle 1 Day 1 and Cycle 1 Day 22 for the 16 treated patients across all dose levels. Results are expressed as mean percent change +/- standard error.

SUMMARY AND CONCLUSIONS

- TRC093 is well-tolerated at doses up to 24 mg/kg every 2 weeks without the development of dose-limiting toxicity or related adverse events > Grade 2.
- Pharmacokinetic evaluation demonstrated linear dose-dependent exposure.
- There was no evidence of HAHA formation in any of the 16 treated patients.
- One patient with hemangiopericytoma treated at 5 mg/kg demonstrated stable disease by CT scan for 10 months and received 21 doses of TRC093.
- An ovarian patient treated at 5 mg/kg demonstrated a mixed response in the liver after 4 doses of TRC093.
- These data suggest that TRC093 is an attractive candidate for further clinical development.

References:
1. Petitclerc E, Boutaud A, Prestayko A, et al. New functions for non-collagenous domains of human collagen type IV. J Bio Chem, 2000. 275:8051-61.
2. Hangai M, Kitaya N, Xu J et al. Matrix metalloproteinase-9-dependent exposure of a cryptic migratory control site in collagen is required before retinal angiogenesis. Am J Pathol, 2002. 161:1429-37.
3. Xu J, Rodriguez D, Petitclerc E, et al. Proteolytic exposure of a cryptic site within collagen type IV is required for angiogenesis and tumor growth in vivo. J Cell Bio, 2001. 154:1069-79.
4. Freimark B, Clark D, Persaventi F et al. Targeting of humanized antibody D93 to sites of angiogenesis and tumor growth by binding to multiple epitopes on denatured collagen: Mol Immunol, 2007. 44:2741-50.
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