

FINAL RESULTS FROM A PHASE 1 STUDY OF TRC093 (HUMANIZED ANTI-CLEAVED COLLAGEN ANTIBODY) IN PATIENTS WITH SOLID CANCER



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INTRODUCTION

TRC093 is a humanized IgG1 monoclonal antibody to cryptic collagen epitopes that are exposed during angiogenesis and tumor growth. 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 including paclitaxel and bevacizumab.

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+

REFERENCES

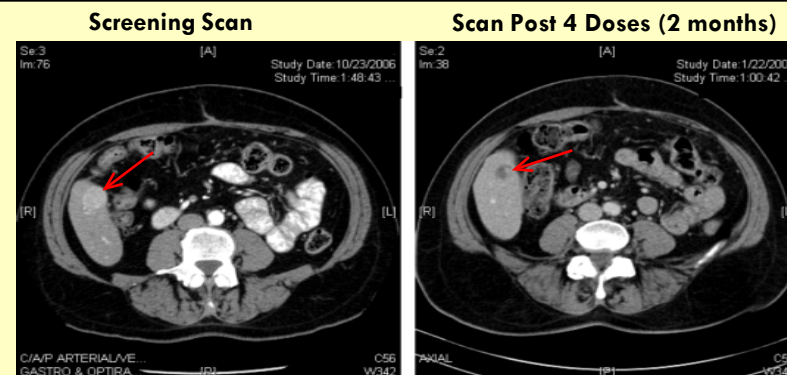
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RESULTS

Baseline Characteristics

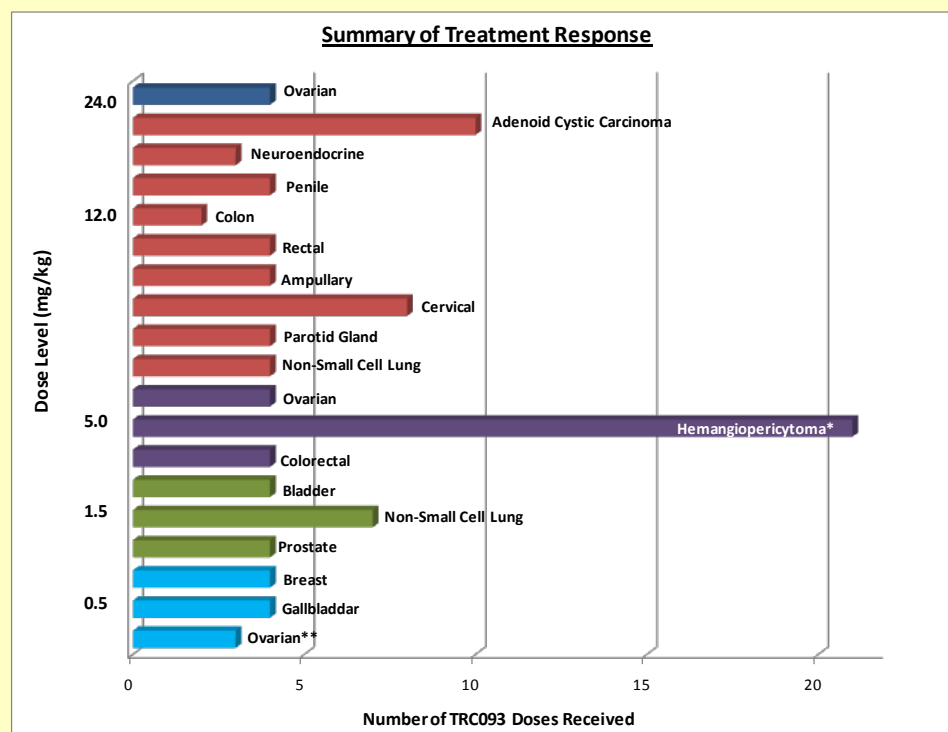
Characteristic	Number of Patients (N=19)
Median Age	59 years
Gender	Female: 8 Male: 11
Screening ECOG Performance Status	ECOG 0: 6 ECOG 1: 13
Prior Chemotherapy	Median Number of Prior Systemic Anticancer Therapies: 5 Range: 2-14
Race	Caucasian: 17 Black/African American: 1 Native Hawaiian/Other Pacific 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 3 doses of TRC093 at 5 mg/kg indicated disease progression overall.

Treatment Response



* A hemangiopericytoma patient treated at 5 mg/kg demonstrated stable disease by CT scan for 9 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 3 doses of TRC093 at 5 mg/kg but demonstrated disease progression overall (see CT scans above).

- TRC093 was administered on Days 1 and 15 of each 28-day cycle
- All patients were treated until progression with efficacy evaluations performed every 4 doses (2 months)
- The 12 mg/kg dose level was determined to be the maximum feasible dose due to limited drug supply and was expanded in order to gain additional safety information in lieu of treating additional patients at 24 mg/kg
- A total of 9 patients were treated at the 12 mg/kg dose
- Only one patient was treated at 24 mg/kg due to limited drug supply

Summary of Safety Data – Related Events

Preferred Term	# Patients Out of 19 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	5
Pain	1	
Drug Hypersensitivity	1	

Preferred Term	# Patients Out of 19 Total Treated	
	Grade 1	Grade 2
Anorexia/Decreased Appetite	1	1
Hyponatremia	1	
Arthralgia		1
Joint Stiffness		1
Muscle Spasms	1	
Musculoskeletal Stiffness	1	1
Pain in Extremity	2	
Dizziness	1	
Dysarthria	1	
Dysgeusia	1	
Rhinorrhea	1	
Pruritus	1	

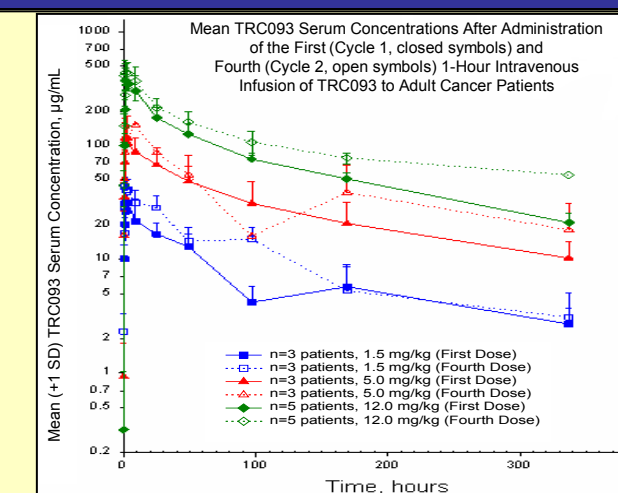
Pharmacokinetics

Summary of Serum TRC093 Exposure Parameters Following Multiple Intravenous Infusions of TRC093¹

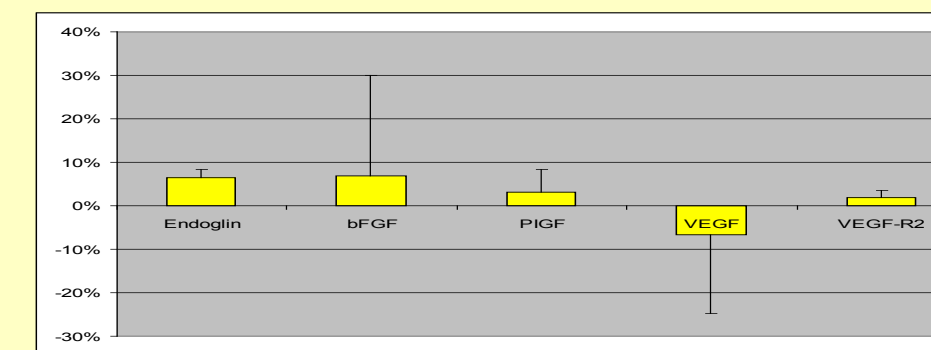
TRC093 Dose (mg/kg)	n	C _{max} (µg/mL)	AUC _{0-n} (hr*µg/mL) ²	Half-life, hr
0.5	2	8.9 (0.4)	1090 ³	369
1.5	3	43.3 (9.5)	3349 (1150)	488 (159)
5.0	3	131 (58.7)	14069 (8354)	302 (123)
12.0	6	467 (111)	35336 (4374)	262 (71)
24.0	1	1475 ³	- ⁴	- ⁵

¹Mean (SD)
²AUC_{0-n} = Serum TRC093 AUC during the fourth dose interval
³S.D. could not be calculated, n=1
⁴Insufficient serum concentration data to calculate AUC_{0-n}
⁵PK parameters could not be reliably estimated using a linear 2-compartment PK model

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



Protein Biomarkers



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

Summary and Conclusions

- TRC093 was well-tolerated at doses up to 24 mg/kg every 2 weeks without dose-limiting toxicity or related adverse events > Grade 2
- Pharmacokinetic evaluation demonstrated linear dose-dependent exposure
- Human antihuman antibody (HAHA) formation was not observed
- Mean circulating VEGF levels declined with treatment
- Early evidence of efficacy included stable disease for up to 9 months and a mixed response at 2 months
- 26% of patients demonstrated stable disease ≥ 2 months
- These results support further development of TRC093 in combination with standard of care agents