DOSE-SPECIFIC CLEARANCE OF TRC105 (ANTI-CD105 ANTIBODY) IN ADVANCED SOLID TUMOR PATIENTS

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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)
- 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 pharmacokinetic behavior of escalating doses of intravenous TRC105 in patients with advanced solid tumors

METHODS

Study Design

- Phase 1, open-label, dose-escalation, first-in-human study conducted at 4 US institutions

Pharmacokinetic Data

- Serum samples were collected on days of the first and fourth dose at 0,0.5,1, 2, 4,24, 72 and 120 hours following infusion doses of 3, 10 and 15mg/kg/wk and 10 and 15 mg/kg/2wk Sparse samples were also collected prior to dosing and immediately after dosing during additional dosing days .TRC105 concentration was determined using a validated ELISA with a LOQ of 78 ng/mL

Dose Escalation Schema

3 mg/kg q2 wks (N=3)
10 mg/kg q2 wks (N=3)
15 mg/kg q2 wks (N=4)
10 mg/kg q wk (N=3)
15 mg/kg q wk (N=4)

Pharmacokinetic Analysis

- Two-stage population model of naïve-pooled data for 16 patients on C1D1 using a 2-compartment target-mediated disposition model in WinNonlin software

RESULTS

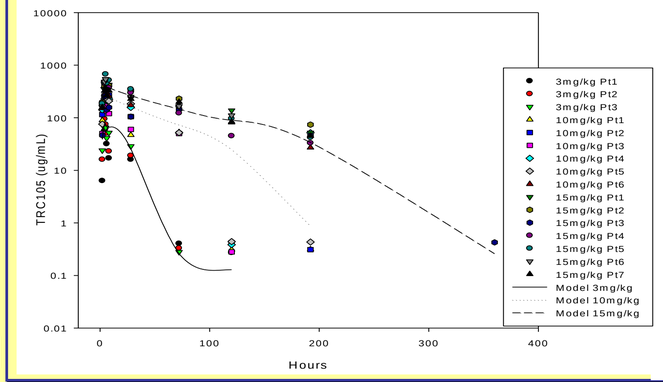
Patient Demographics

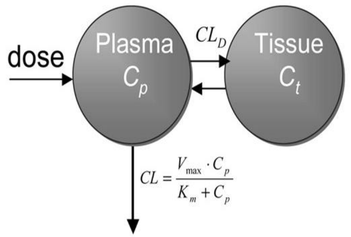
Baseline Patient Characteristics (N=50)	
Age	Median: 64 Range: 25 - 84
Gender	Female: 15 Male: 35
Baseline ECOG Performance Status	ECOG PS 0: 15 ECOG PS 1: 35
Number of Prior Regimens	Median: 4 Range: 1-13
Cancer Type	Colorectal: 10 Prostate: 9 Renal: 5 Lung: 4 Ovarian: 3 Sarcoma: 3 Breast: 2 Pancreatic: 2 Other: 12

Safety

- TRC105 was tolerated at 10 mg/kg weekly and 15 mg/kg every 2 weeks
- 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

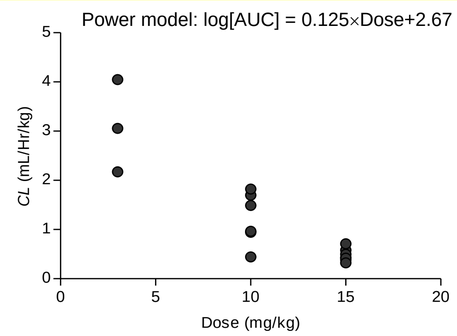
Pharmacokinetic Model





Schematic representation of pharmacokinetic model

Dose-Specific Clearance



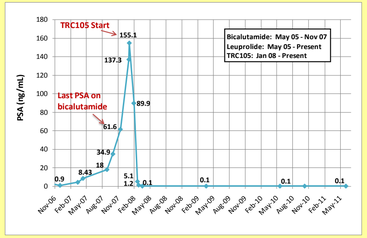
The AUC-single dose relationship of TRC105 revealed supra-proportionality in serum exposure at 15 mg/kg compared to 3 and 10 mg/kg.

Efficacy

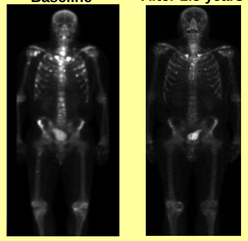
Prostate Cancer

- A patient with metastatic castrate-resistant prostate cancer and multiple painful skeletal metastases has been on TRC105 therapy for over 4 years with:
  - Complete PSA response,
  - Resolution of bone pain
  - Bone scan normalization

PSA Results Before and During TRC105 Therapy



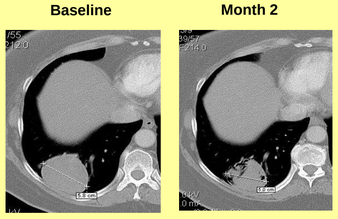
Bone Scan



Uterine Carcinosarcoma

- A patient with lung and intraabdominal metastases from uterine carcinosarcoma had a minor radiographic response for 18 months evidenced by an overall reduction in the sum of tumor diameters of between 7% and 13% during treatment
- Progression-free survival on TRC105 exceeds that for all 3 prior systemic regimens including:
  - Carboplatin/paclitaxel (4 months)
  - Anastrozole (8 months)
  - Ifosfamide (2 months)

Chest CT Scan



Pharmacokinetic Parameters

- The post-infusion Cmax was linearly related to dose (r = 0.85) which suggested the nonlinearity in clearance was attributed to target-mediated disposition.
- The steady state volume of distribution was low (≈ 5.40 L/70kg) indicating TRC105 was confined to the vasculature with a low capacity target (i.e., low relative abundance) making it susceptible to saturation.
- Accumulation factor at 56 days was 1.77-fold over single doses on C1D1.
- TRC105 was tolerated at doses up to 15 mg/kg every 2 weeks and 10 mg/kg weekly
- 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.

SUMMARY & CONCLUSIONS

- Pharmacokinetics & Safety
  - TRC105 exposure increases disproportionately at 15 mg/kg due to saturating target-mediated disposition.
  - Dose-specific clearance may contribute to reduced tolerability with weekly dosing at 15mg/kg.
- Phase I Study
  - 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 uterine carcinosarcoma had minor radiographic response lasting 18 months
  - Tumor marker decreases (CEA, PSA or CA-125) were seen in 7 of 21 patients (33%)
  - SD > 2 months in 21 of 45 patients (47%) and SD > 4 months in 6 of 44 patients (14%)

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