

Preclinical Pharmacokinetic & Pharmacodynamic Data for TRC105 (Anti-Endoglin Antibody) are Consistent with Clinical Activity Observed at Low Doses in Patients with Advanced Cancer



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ABSTRACT

BACKGROUND: TRC105 is a human/murine chimeric IgG1 monoclonal antibody that inhibits angiogenesis and tumor growth. TRC105 binds human endoglin (CD105), an intravascular target required for angiogenesis that is highly overexpressed in the surface of proliferating vascular endothelial cells. During a Phase 1 study of TRC105 monotherapy for patients with advanced solid cancer, clinical activity was observed at doses as low as 0.01 mg/kg i.v. every 2 weeks. We present nonclinical PK and PD data that provide a rationale for the expectation of clinical anticancer activity at low doses of TRC105.

METHODS: TRC105 avidity to purified human CD105 was quantified by Biacore® and binding to CD105 on human umbilical vein endothelial cells (HUVECs) was determined by FACS. ADCC was assayed using natural killer effector cells and HUVEC target cells at a 10:1 ratio. Human PK was estimated using TRC105 PK parameters from Cynomolgus monkeys.

RESULTS: TRC105 binds to human CD105 with a K_D of 31 pM (4.6 ng/mL), reflecting a k_a of $8.25 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ and k_d of $2.51 \times 10^{-6} \text{ s}^{-1}$. Once bound, Biacore® studies predict that more than half of TRC105 remains bound to its target after 19 days. FACS binding studies on proliferating HUVECs indicate a K_D of 2.3 ng/mL with saturation at 200 ng/mL. TRC105 produced dose-dependent increases in ADCC at concentrations between 16 and 2000 ng/mL. The volume of distribution in Cynomolgus monkeys was similar to serum volume and the terminal half-life was 6.2 days. PK modeling predicted that a TRC105 dose of 0.01 mg/kg would generate human serum concentrations above the antibody K_D and within a concentration range expected to bind CD105 and induce ADCC on proliferating endothelial cells.

CONCLUSION: TRC105 is a high avidity monoclonal antibody ($K_D = 2.3 - 4.5 \text{ ng/mL}$) to CD105, an intravascular target. The clinical anticancer activity observed at 0.01 mg/kg is consistent with preclinical pharmacodynamic properties and predicted intravascular exposures.

Endoglin (CD105) Characteristics

- CD105 is transmembrane protein expressed by proliferating vascular endothelial cells (Seon et al, 1997)
- CD105 is knockout lethal in mice by gestational day 11 (Li et al, 1999)
- High CD105 expression levels correlate with poor prognosis in more than 10 solid cancers (Dallas et al 2008)
- CD105 is upregulated by VEGF inhibition and hypoxia through HIF-1 α (Bockhorn et al 2003; Davis et al 2004)
- CD105 is expressed by cancer stem cells (Bussolati et al 2008)



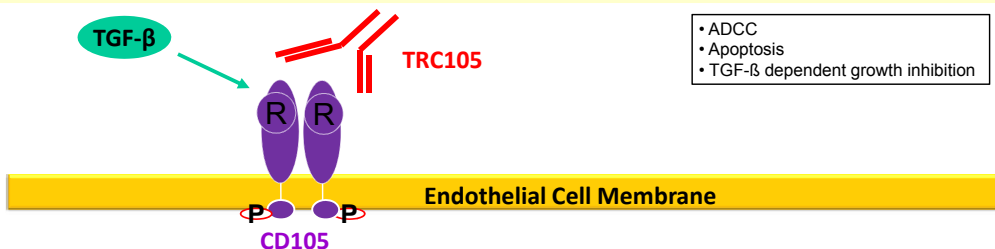
Normal mouse blood vessels *in utero*

CD105 knockout mouse with absent blood vessels and death *in utero*

TRC105 Overview & Mechanism of Action

TRC105 is a chimeric IgG1 antibody that inhibits angiogenesis by binding human CD105 (endoglin) on proliferating endothelium. The murine parent antibody of TRC105 has been shown to induce apoptosis of human endothelial cells (Tsujie et al, 2008), mediate TGF- β dependent inhibition of human endothelium (She et al, 2004), and inhibit the growth of syngeneic murine tumor grafts (Tsujie et al, 2006).

The current studies were designed to quantify TRC105 binding to CD105 and human endothelial cells, assess ADCC, and determine PK in Cynomolgus monkeys to determine a first-in-human dose expected to have pharmacologic activity.

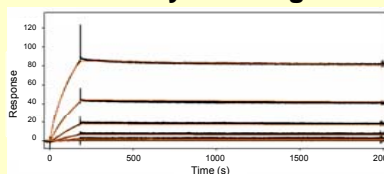


- ADCC
- Apoptosis
- TGF- β dependent growth inhibition

RESULTS

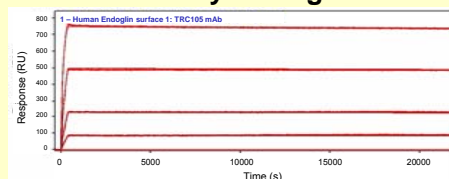
Avidity & ADCC

TRC105 Binds to CD105 with an Affinity of 4.6 ng/mL



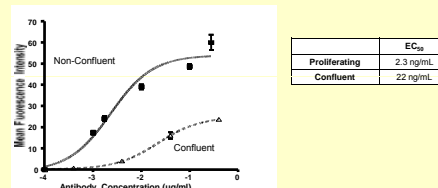
BioRad ProteOn® Method	On Rate (k_a)	Off Rate (k_d)	Affinity (K_D)
TRC105 fixed on GLC sensor chip	$8.2 \times 10^5 \text{ M}^{-1} \text{ S}^{-1}$	$2.5 \times 10^{-6} \text{ S}^{-1}$	31 pM (4.6 ng/mL)

TRC105 Binds to CD105 with an Avidity of 1 ng/mL

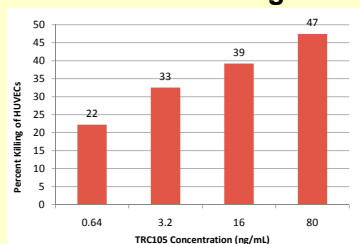


BioRad ProteOn® Method	On Rate (k_a)	Off Rate (k_d)	Avidity (K_D)
CD105 fixed on GLC sensor chip	$8.9 \times 10^5 \text{ M}^{-1} \text{ S}^{-1}$	$0.5 \times 10^{-6} \text{ S}^{-1}$	5 pM (1 ng/mL)

TRC105 Binds Proliferating HUVECs with a EC_{50} of 2.3 ng/mL

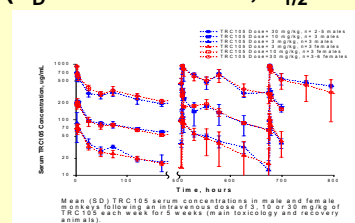


TRC105 Induces ADCC of HUVECs at < 1 ng/mL



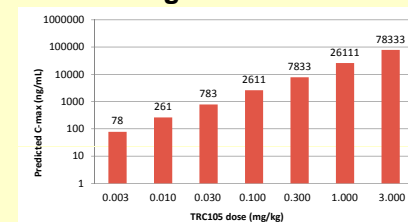
Pharmacokinetics

TRC105 PK in Macaques (V_D =serum volume, $T_{1/2}$ =6.2 d)



Monkeys were dosed i.v. weekly for 5 doses with TRC105 at 3, 10 or 30 mg/kg, and serum levels were determined following the 1st and 4th doses.

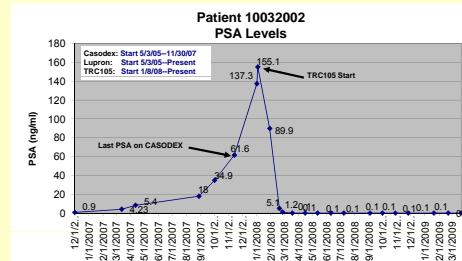
TRC105 at 0.01 mg/kg is Predicted to Produce a C_{max} of 261 ng/mL in humans



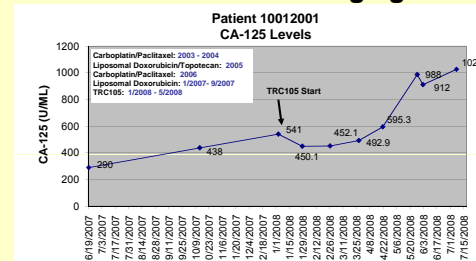
Human TRC105 serum concentrations were estimated by interspecies scaling of monkeys dosed with TRC105.

Clinical Activity

PSA Response in a Patient with Prostate Cancer Treated with TRC105 at 0.01 mg/kg



CA-125 Response in a Patient with Ovarian Cancer Treated with TRC105 at 0.01 mg/kg



Summary & Conclusions

Endoglin (CD105) is an attractive target for angiogenesis inhibition:

- Expressed selectively on proliferating endothelium
- Essential for angiogenesis
- Correlated with poor prognosis
- Immediately available in the vascular space
- Complements inhibitors of the VEGF pathway

TRC105 clinical activity at low doses results from high avidity and potency:

- Binds human CD105 on proliferating endothelium with a K_D of 1 - 2 ng/mL
- Engages ADCC at low concentrations
- A TRC105 dose of 0.01 mg/kg is expected to result in concentrations with pharmacodynamic activity

References

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