Pharmacodynamic biomarker studies of TRC105 anti-endoglin (CD105) antibody revealed anti-angiogenic activity associated with CD105 depletion

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Abstract

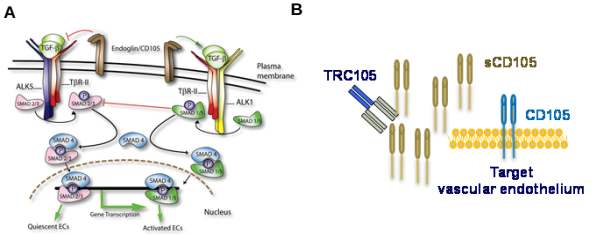
Introduction: Endoglin (CD105) is a component of the transforming growth factor-beta receptor complex and is antagonistic to cellular response to TGF-β1. CD105 is involved in normal vascular development, with its mutation frequently associated with hereditary hemorrhagic telangiectasia. It is over expressed on the surface of proliferating vascular endothelial cells and is implicated in tumor angiogenesis. In hypoxic conditions, CD105 is upregulated through induction of hypoxia-inducible factor 1-α. TRC105 is a chimeric IgG1 antibody specific for CD105 and the agent for this phase I trial.

Methods: 20 patients with metastatic prostate cancer were treated with TRC105 at six dose levels in a phase I trial. Blood samples were analyzed for CD105 antigen depletion, VEGF as a marker for systemic hypoxia, and PSA.

Results: Maximum tolerated dose of 20 mg/kg every two weeks was reached. TRC105 can only be detected at the end of each infusion for the three high dose levels, which significant plasma CD105 reduction was observed at high dose levels. There is a mutual exclusive relationship between plasma TRC105 and CD105, indicating that TRC105 must be in excess top have an effect. The reduction of CD105 was associated with induction of plasma VEGF but not PlGF, suggesting that only VEGFR2 pathway or cells were affected. Ten patients had stable disease, and the reduction of CD105 is associated with PSA stabilization.

Conclusion: A significant induction of VEGF was associated with CD105 reduction at three high dose levels, suggesting the anti-angiogenic activity of TRC105. Exploratory analysis showed a tentative correlation between the reduced CD105 and a decreased PSA velocity, suggestive of potential antitumor activity of TRC105 in metastatic prostate cancer.

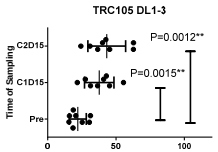
Dose Escalation Schema and CD105/TRC105 Assays



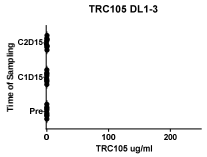
A. Diagram of CD105 function in regulated TGF-b signaling in endothelial cells
B. TRC105 is a therapeutic antibody and potential effects of soluble CD105 (sCD105)

Effective TRC105 at Higher Dose Levels and Plasma TRC105 is Mutually Exclusive with Plasma CD105

A. sCD105 at dose level (DL) 1-3



C. TRC105 at dose level (DL) 1-3

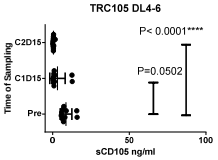


E. Dose levels of TRC105

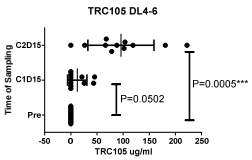
Dose level	TRC105
1	1 mg/kg per 2 wks
2	3 mg/kg per 2 wks
3	10 mg/kg per 2 wks
4	10 mg/kg per wks
5	15 mg/kg per 2 wks
6	20 mg/kg per 2 wks

TRC105 induced sCD105 at low DL, when drug was not detectable

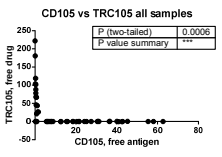
B. sCD105 at dose level (DL) 4-6



D. TRC105 at dose level (DL) 4-6



F. Mutual Exclusivity of CD105 and TRC105

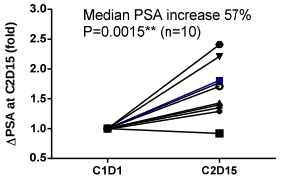


TRC105 depleted sCD105 at high DL, when drug accumulated

TRC105 and sCD105 did not coexist

Potential Clinical Activity of TRC105 in Metastatic Prostate Cancer

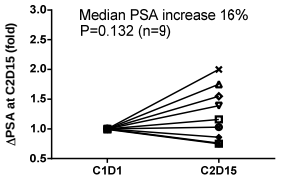
A. When TRC105 drug was absent



Patients without decreased CD105

Rapid raise of PSA

B. When TRC105 drug was present



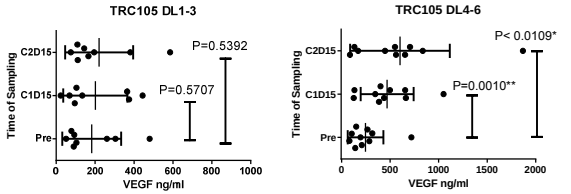
Patients with decreased CD105

Slower raise of PSA

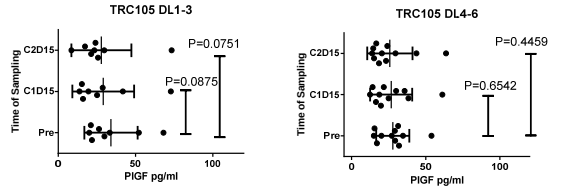
	Pretreatment				C2D15			
Serum PSA (ug/ml)	Median	IQR	No. of Patients	P	Median	IQR	No. of Patients	P
Pts w/ CD105 reduction	1	NA	9	NA	1.16	0.81-1.65	9	0.132
Pts w/o CD105 reduction	1	NA	10	NA	1.57	1.36-1.91	10	0.0015**

Anti-angiogenic Activity of TRC105: Inducing VEGF and bFGF, but not PlGF

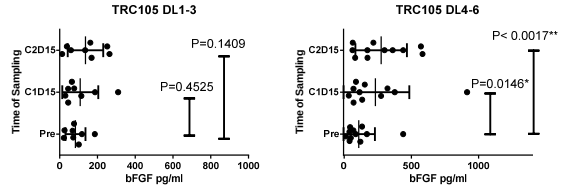
A. High TRC105 dose associated with rise of plasma VEGF



B. TRC105 did not lead to increased PlGF



C. TRC105 led to increased bFGF



Conclusions

1. First evidence of antigenic activity associated with high dose levels
2. High dose levels associated with slowing rise of PSA
3. Removal of sCD105 essential for achieve TRC105 excess
4. Unlike other VEGF or VEGFR targeted agents, no rise in PlGF
5. In contrast, an increase in bFGF