Modulation of Angiogenic Factors from Advanced Refractory Cancer Patients in a Phase I Study of TRC105

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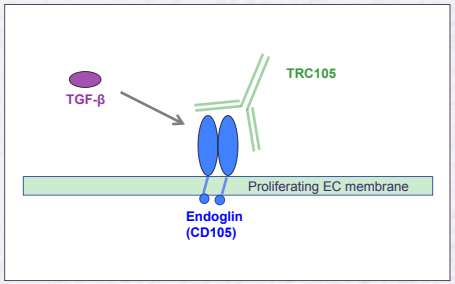
Background

Endoglin (CD105) is a homodimeric transmembrane glycoprotein expressed on proliferating endothelial cells (EC) (1). Endoglin is required for EC proliferation (2) and promotes angiogenesis in more than 10 tumor types (3). TRC105, a chimeric monoclonal antibody, binds endoglin with high avidity and suppresses EC function (Figure 1), inhibits angiogenesis and retards the growth of human tumor xenografts (4-7). TRC105 is currently being studied in Phase 1b and Phase 2 trials of advanced cancer patients.

Methods

Biomarker analyses were done on the initial 21 advanced refractory cancer patients enrolled in a 50-patient Phase 1 study of TRC105. Plasma from patients treated with escalating doses of TRC105 (0.01- 1 mg/kg) every 2 weeks by intravenous infusion was sampled at several time points during the initial two, 4-week cycles (C1D1, C1D2, C1D8, C1D15, C2D1, C2D22) and at the end of study (EOS). 39 candidate biomarkers (Table 2) related to tumor growth, angiogenesis, and inflammation were assayed at baseline (BL), at 1 month (C2D1), and at EOS.

Figure 1. TRC105 function diagram



Results

❖ Baseline and on-treatment samples for biomarker analysis were available from 19 patients (Table 1) .

Table 1. Characteristic of biomarker study population.

Characteristic		Patients (N=19)
TRC105 (mg/kg)	0.01*	3
	0.03	3
	0.1	6
	0.3	3
	1	4
Age	median	59
Gender	female	8
	male	11
Tumor types	prostate	5
	colorectal	2
	ovarian	2
	renal	2
	others	8

* Color align with drug cohorts in Waterfall plots (Figure 2 and 3).

❖ C2D1 was chosen to reflect treatment-related changes after one cycle (2 doses) of TRC105. C2D1 levels were available on 18 patients. Wilcoxon signed rank tests reveal that multiple angiogenic factors were significantly down regulated at C2D1 (Table 3). Representative Waterfall plots were shown for important angiogenic biomarkers (Figure 2).

❖ EOS levels were chosen to reflect potential changes associated with disease progression. EOS levels were available for 13 of the 19 patients with baseline levels. 12 of these patients had disease progression at EOS. Median time to EOS was 74 days (range 56-120 days). Wilcoxon tests reveal that several initially downregulated proteins were significantly re-elevated by EOS (Table 3, Figure 3) .

❖ No dose dependency was observed (data not shown).

❖ Spearman's rank correlation was used to test pair-wise correlations among VEGF family members (VEGF-A, C, D and VEGF-R1, R2); TGF-β family members (TGF-β1, TGF-β2, and TGFβ-R3); and angiopoietin family members (Ang-2 and Tie-2). No strong correlation was observed (data not shown).

Table 2. List of 39 biomarkers evaluated.

soluble angiogenic biomarkers	Matrix-derived angiogenic biomarkers	Coagulation biomarkers	Vascular activation and inflammation biomarkers
Ang-2	MMP-2	CRP	Gro-α
bFGF	MMP-9	D-dimer	IL-6
HGF	OPN	Pai-1 active	IL-8
IGFBP-1, -3	TGF-β R3	Pai-1 total	P-selectin
PDGF-AA, -BB	TGF-β1	Tissue Factor	E-selectin
PEDF	TGF-β2	vWF	SDF-1b
PlGF	TSP-1		ICAM-1
sVEGF-R1, -R2	TSP-2		VCAM-1
sTie-2			MCP-1
VEGF-A, C, D			E-cadherin

Table 3. Change in circulating angiogenic biomarkers.

Baseline to C2D1		C2D1 to EOS	
Biomarker	**p-value**	**Biomarker**	**p-value**
IGFBP-3 ↓	0.0008	E-cadherin ↑	0.0093
VEGF-C ↓	0.0021	sTie-2 ↑	0.0122
VEGF-D ↓	0.0034	IL-6 ↑	0.0269
bFGF ↓	0.0076	VEGF-C ↑	0.0269
PDGF-AA ↓	0.011	VEGF-D ↑	0.0342
PDGF-BB ↓	0.0386	IGFBP-3 ↑	0.0425
CRP ↑	0.0395	VEGF-A ↑	0.3804
PlGF ↓	0.0448	TGF-β1	0.791
TGF-β1 ↓	0.0638		
VEGF-A ↓	0.1324		

Figure 2. Waterfall plots show reduction of angiogenic biomarkers from baseline to the end of cycle 1.

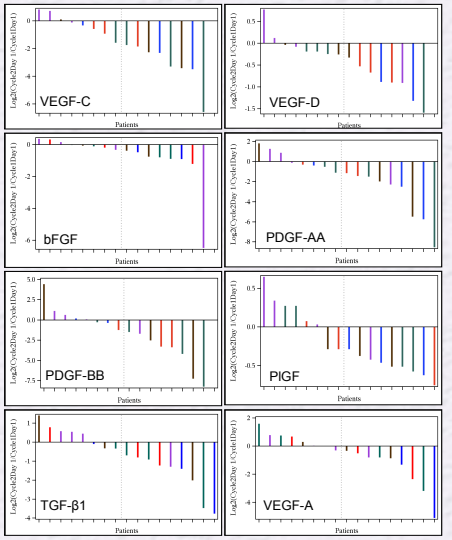
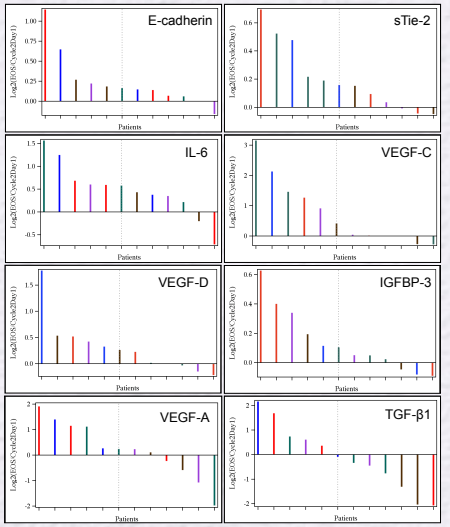


Figure 3. Waterfall plots show elevation of biomarkers from the end of cycle 1 to EOS.



❖ Preliminary data suggest that prostate cancer patients benefit from TRC105. The best responder (patient A) who has castrate-resistant prostate cancer and multiple bone metastases has been on study for over 3 years and exhibited a complete PSA response and improved bone scans (ASCO presentation, 2011; poster #3073).

❖ Figure 4 illustrates a longitudinal view of VEGF-A levels in patient A over the course of treatment. Patient A had robust reduction of VEGF-A levels compared to average of the four other prostate cancer patients. The same pattern was observed for VEGF-C (data not shown).

❖ Similarly, patient A exhibited a reduction in TGF-β1 levels. This observation is intriguing since endoglin is a type III receptor for TGF-β.

Figure 4. Longitudinal change of VEGF-A for the best responder (red) vs. average of the other prostate cancer patients (blue).

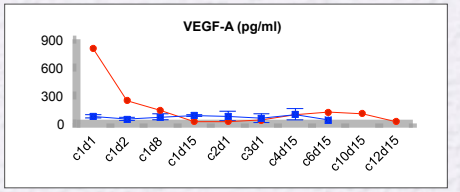
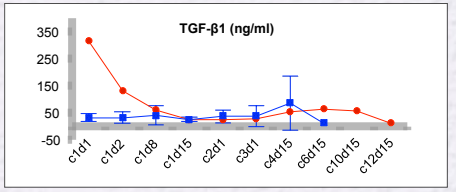


Figure 5. Longitudinal change of TGF-β1 for the best responder (red) vs. average of the other prostate cancer patients (blue).



Conclusions

❖ This is the first angiomic profile of TRC105 in cancer patients. QA/QC analysis revealed this approach was technically robust.

❖ TRC105 treatment was associated with reductions of several key angiogenic factors, including VEGF-A, VEGF-C, VEGF-D, PlGF, PDGF-AA, PDGF–BB, and bFGF.

❖ Disease progression was associated with an increase in several angiogenic factors, including VEGF-C, VEGF-D.

❖ There is a potential inverse relationship between the changes associated with treatment and with disease progression; this finding may suggest candidate mechanisms of sensitivity and resistance to TRC105.

References

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