A Phase I Study of TRC105 (Anti-CD105 [Endoglin] Antibody) in Metastatic Castration-Resistant Prostate Cancer (mCRPC)

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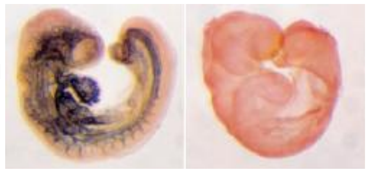
Biology of CD105

- CD105 (endoglin) is a 180 kDa transmembrane protein abundantly expressed on the surface of proliferating vascular endothelial cells
- CD105 expression is required for the formation of new blood vessels

CD105 is essential for angiogenesis

CD105 is expressed in developing blood vessels in mice



CD105 is absent in CD105 knockout mice

8 days gestation

Blood vessels develop normally in mice with CD105

Blood vessels are completely absent in CD105 knock-out mice, causing death in utero

10 days gestation

Li et al. Science 1999; 284: 1534-1537 1999

Tumor MVD assessed with anti-CD105 antibodies correlates with Gleason score, stage, metastasis, proliferative index and survival in prostate cancer

TRC105

- TRC105 is a human/murine chimeric IgG1 kappa monoclonal antibody that binds with high avidity to human CD105 (endoglin) on proliferating endothelial cells
- TRC105 inhibits angiogenesis and tumor growth through inhibition of endothelial cell proliferation, antibody-dependent cellular cytotoxicity and induction of apoptosis

Objectives

- Primary objective is to define the maximum tolerable dose of TRC105
- Secondary objectives include assessment of TRC105 pharmacokinetics, PSA response rate, and overall response rate

Methods

- Eligibility requires ECOG PS ≤ 2 and progressive mCRPC
- Six cohorts of patients receive increasing doses of TRC105 over 1-4 hours, based on the dosing schedule below
- PSA is evaluated prior to each treatment and response is assessed

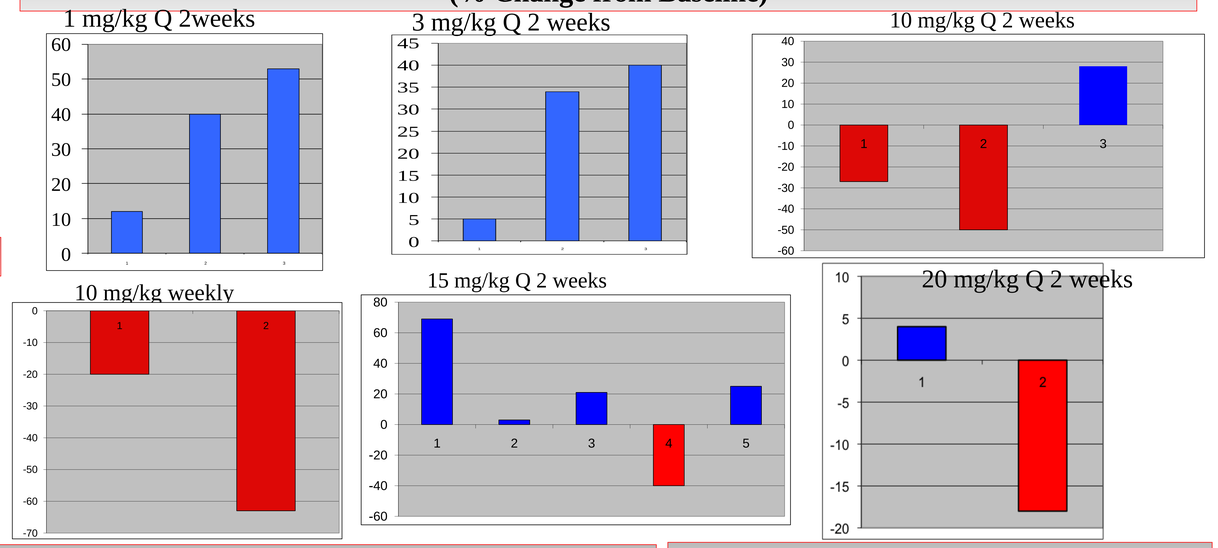
Dose Escalation Schedule

Cohort	Phase I Dose	No. of Patients
1	1 mg/kg Q 2 weeks	3-6
2	3 mg/kg Q 2 weeks	3-6
3	10 mg/kg Q 2 weeks	3-6
4	10 mg/kg weekly	3-6
5	15 mg/kg Q 2 weeks	3-6
6	20 mg/kg Q 2 weeks	3-6

Baseline Characteristics (N=20)

Age	**Median** 63.9 Range (47-71.9)
ECOG	**Median** 1 Range (0-2)
Gleason Score	**Median** 9 Range (6 – 10)
On-Study PSA	**Median** 126.5 Range (0.14 – 2923)
No. of Prior Therapies	**Median** 3 Range (0 – 6)
(+) Soft Tissue Disease	**16**

Best Response in PSA by Cohort (% Change from Baseline)



Possibly Related Adverse Events in Greater Than 1 patient or Grade 3 or 4 Toxicities (N=20)

Preferred CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Infusion Related Reaction	2	2		1
Headache	8	5		
Fever	4	4	1	
Chills	5			
Nausea	3	4		
Vomiting	4	1		
Flushing	7			
Hypotension	2			
Anemia		6	3	
Bone Pain		4		
Sinus Tachycardia	2			
Hypophosphatemia		1		
Epistaxis	7	2		
Fatigue	1	2		
Dyspnea	2			
Cough	2			
Oral hemorrhage	4			
Back pain	2	1		
Anorexia	1	1		
Abdominal pain	2			

Summary of Results

- Accrual has been completed at 20 patients; one patient remains on-study.
- Median time on study is 13 weeks, 5 days (range 5-25).
- PSA declines of 20% and 57% from baseline were seen in two patients in cohort four
- PSA decline of 59% from baseline was seen in one patient in cohort 5
- 10 out of 16 patients with measurable soft tissue disease achieved stable disease after two cycles of treatment

Conclusion

- TRC105 is tolerated at doses up to 20 mg/kg every two weeks with evidence of clinical activity in mCRPC
- The phase II portion of the study will be accruing in the near future.