

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 expression is increased during hypoxia and protects hypoxic endothelial cells from apoptosis
- CD105 expression releases endothelial cells from the inhibitory effects of TGF- β signaling

CD105 is essential for angiogenesis

CD105 is expressed in developing blood vessels in mice



CD105 is absent in CD105 knockout mice

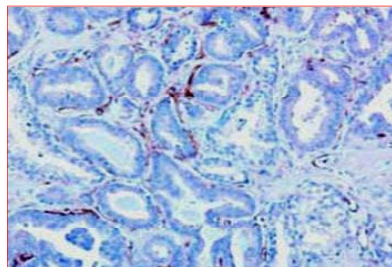
Blood vessels develop normally in mice with CD105



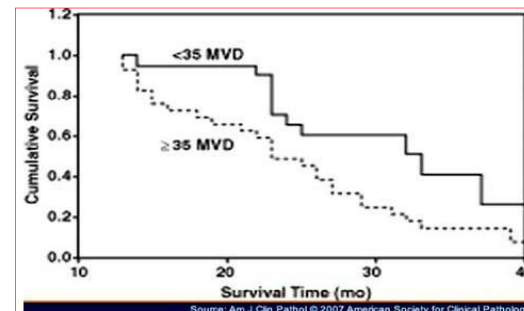
Blood vessels are completely absent in CD105 knockout mice, causing death in utero

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



Anti-CD105 antibody staining of a prostate cancer specimen. CD105 is strongly expressed in the blood vessels of prostate cancer



El-Gohary et al. Am J Clin Pathol 2007;127:572-579

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 \leq 2 and progressive mCRPC
- Three cohorts of 3-6 patients receive increasing doses of TRC105 over 1-4 hours, based on the dosing schedule below
- Premedications include dexamethasone, acetaminophen, famotidine and diphenhydramine
- PSA is evaluated prior to each treatment and response is assessed every two cycles with imaging studies

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 weekly	3-6

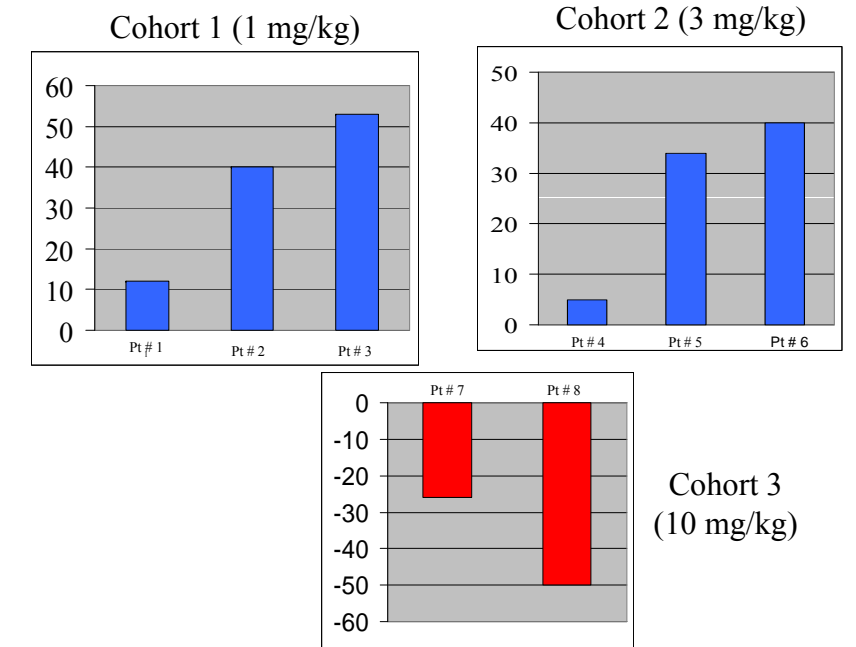
Baseline Characteristics

Age	Median 65 Range (47 – 84)
ECOG	0 = 0 1 = 7 2 = 1
Gleason Score	Median 8 Range (6 – 10)
On-Study PSA	Median 210 Range (0.10 – 3373)
No. of Prior Therapies	Median 2.5 Range (0 – 6)

Possibly Related Adverse Events in > 1 Patient or Grade 3 or 4 (N =8)

Preferred CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Infusion Related Reaction	2	3		
Headache	4	2		
Fever	2	2		
Chills	3			
Nausea	2	1		
Vomiting	3			
Flushing	2			
Hypotension	1	1		
Anemia		2		
Pain		2		
Sinus Tachycardia	2			

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



Summary of Results

- 8 out of 30 total patients have enrolled (3 pts in cohort 1, 3 in cohort 2 and 2 in cohort 3)
- Median time on study is 14 weeks (range 7-16)
- No DLTs in any of the dosing cohorts to date
- No related grade 3 or 4 toxicities
- PSA declines of 26% and 51% from baseline were seen in two patients in cohort three (both had progressed on docetaxel and at least one 2nd-line agent)
- 5 out of 6 patients with measurable soft tissue disease achieved stable disease (two in cohort 1, two in cohort 2 and one in cohort 3); the latter 3 patients in cohorts 2 and 3 remain on study

Conclusion

- TRC105 is tolerated at doses up to 10 mg/kg every two weeks with early evidence of clinical activity in mCRPC
- Accrual is ongoing to evaluate higher doses and more frequent dosing, ORR, PFS and OS