A Phase 1/2 Study Of TRC105 In Combination With Sorafenib In Hepatocellular Carcinoma (HCC)

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Introduction

Sorafenib is an oral multi-kinase inhibitor of vascular endothelial growth factor (VEGF) receptor, the platelet-derived growth factor (PDGF) receptor, and Raf and was the first systemic medical therapy to prolong survival in HCC based on the SHARP study which demonstrated a median overall survival benefit compared to placebo(10.7 months v 7.9 months; HR 0.69; P<0.001). Since the SHARP study, attempts to combine agents with sorafenib have been disappointing.

Endoglin (CD105) is a transmembrane receptor overexpressed by proliferating endothelial cells that is required for angiogenesis and upregulated by hypoxia in response to VEGF inhibition. TRC105 is a chimeric IgG1 monoclonal antibody that binds CD105 with high avidity and inhibits binding of its key ligand, bone morphogenic protein. TRC105 inhibits angiogenesis and mediates apoptosis and antibody-dependent cell-mediated cytotoxicity (ADCC) of proliferating endothelium.

Preclinical data:

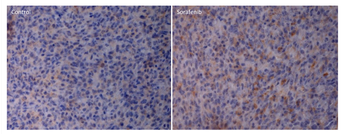

Figure 1: Detection of endoglin expression In BNL hepatocellular tumors growing subcutaneously and treated with sorafenib.

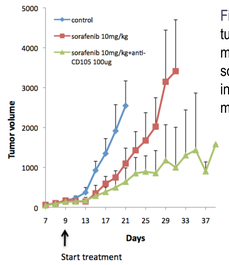

Figure 2: Mice with sc. BNL tumors were treated with anti-mouse endoglin antibody + sorafenib. Results from two individual experiments with n=5 mice are shown

Preclincal data (1): CD105 expression after sorafenib treatment.

BNL tumors in Balb/c mice were treated with Sorafenib (10 mg/kg/d). Tissue was harvested after 3 days and analyzed. As shown in Figure 1, sorafenib treatment induced an increase in endoglin expression compared to control.

Preclincal data (2): Anti-mouse endoglin antibody in combination with sorafenib daily.

Based on the observation that sorafenib causes endoglin expression we tested the combination of anti-mouse endoglin antibody (clone MJ7/18) + sorafenib. As shown in Figure 2 the combination of anti-CD105 + sorafenib was more effective than sorafenib treatment alone.

Clinical trial:

Primary Objectives

✓To establish the MTD for TRC105 when given with sorafenib in HCC.

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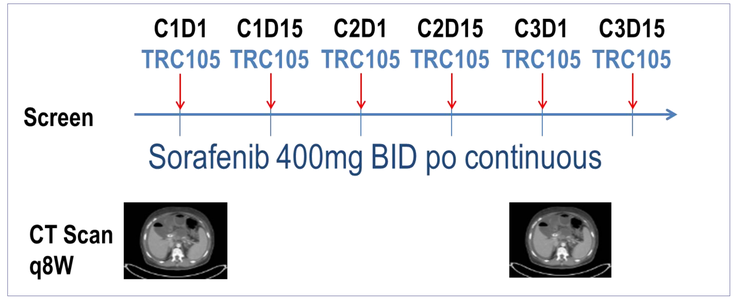
Additional Translational Objectives

✓Pharmacodynamic Biomarkers
- ✓VEGF, PlGF, bFGF, sVEGFR1, soluble CD105
- ✓DCE-MRI

✓Preliminary Evidence of Anti-Tumor Response
- ✓Response rate and PFS

Clinical trial :

Patients with HCC were enrolled in a phase I study of TRC105 given at 3, 6, 10, 15mg/kg every 2 weeks plus sorafenib 400mg po bid.



Select Eligibility Criteria:
- ✓ Compensated liver function (Childs Pugh A/B7)
- ✓ ECOG performance status 0/1
- ✓ No prior sorafenib
- ✓ Metastatic disease and/or not amenable to locoregional therapies (TACE, RFA etc)
- ✓ Absence of 'high-risk' varices confirmed by baseline endoscopy.

Dose Level	Sorafenib dose (mg/d)	TRC-105 dose (mg/kg)
1	800	3
2	800	6
3	800	10
4	800	15

Results :

N=20 pts were enrolled. N=2 were inevaluable for DLT. Baseline characteristics for evaluable patients summarized in Table 1.

DL	N	DLT
1	3	No
2	3	No
3	6	Yes (ALT)
4	6	No

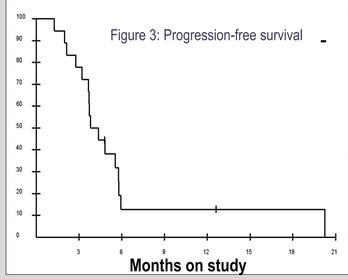


Figure 3: Progression-free survival

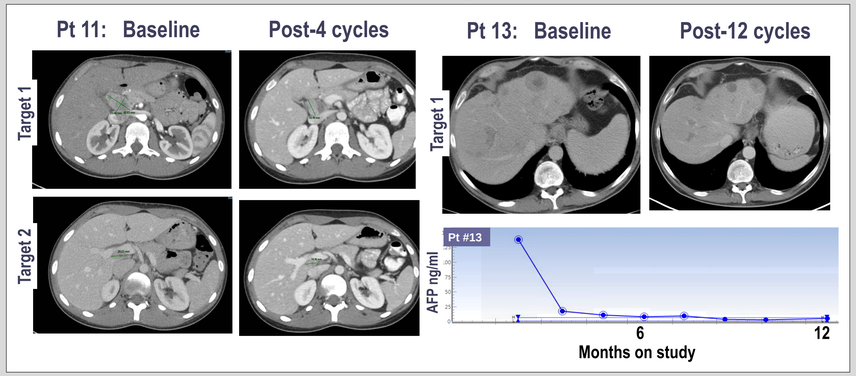
- 1 DLT (increased AST) occurred at Dose Level (DL) 3 (10mg/kg TRC105) which was expanded. Dose escalation continued to DL 4 (15 mg/kg TRC105) without further DLT.
- The most frequent toxicity was epistaxis (G1 or G2). One patient developed G3 cerebral tumor hemorrhage at a site of metastasis and one patient with coronary artery disease developed G5 myocardial infarction
- Efficacy data are shown in Figures 4 (change in AFP) and 5 (RECIST response). Of N=15 pts evaluable for response, N=3 (20%) developed a confirmed PR by RECIST and the majority of patients had tumor reduction. All PR by RECIST occurred at DL 3 or 4 (30% PR rate in DL3 or 4 evaluable patients). As shown in Figure 3, median PFS was 4.1 months. 6-month PFS probability was 12.7%. Median potential follow-up was 17.5 months.

Characteristic	No. of pts
HCC / FLHCC	17/1
Male/Female	12/6
Mean Age (Range)	60 (18 – 76)
Cirrhosis (Yes/No)	11/7
Hepatitis B/C/NA	2/9/7
Administered cycles Mean (Range)	4.75 (2- 22)
Best Response PR SD Not evaluable/clinical progression/PD	3 10(N=1, 22m) 5

Table 1: Patient characteristics

Toxicity (Grade ≥ 3)	Dose levels (N) 1 N=3	2 N=3	3 N=6	4 N=6	T
Anemia			1		1
Hand-foot syndrome	1	1	1		3
Hypophosphatemia	1		1		2
Intracranial hem.		1			1
AST/ALT elevation	1		3	2	6
Diarrhea	1				1
Hepatic failure		1		1	2
Neutropenia					1
Amylase/lipase inc.			1		1
Cardiac ischemia			1(G5)		1
Hypertension			1		1

Table 2: Toxicity data



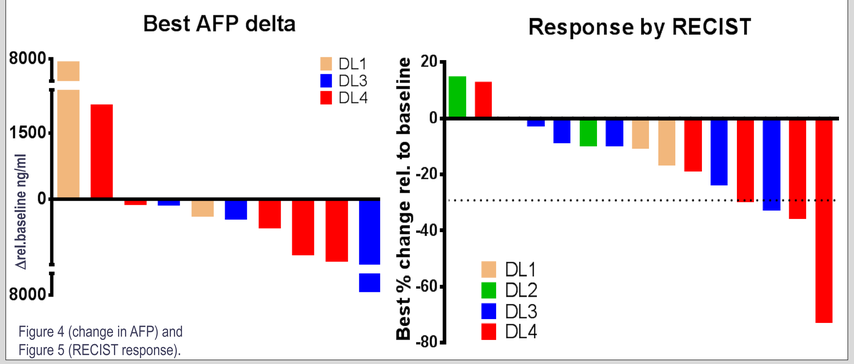


Figure 4 (change in AFP) and Figure 5 (RECIST response).

CONCLUSIONS:

TRC105 combined with sorafenib was well tolerated at the recommended single agent doses of both drugs. Encouraging evidence of activity was observed and the study is proceeding to the phase 2 stage.