An Open Label Phase 1b/2 Trial of TRC105 and Sorafenib in Patients with Advanced/Metastatic Hepatocellular Carcinoma (HCC)

Abstract #203107

Kanwal Raghav[1], Kabir Mody[2], Tim Greten[3], Ravi Paluri[4], Richard Lee[5], Brian E. Simpson[6], Bonne J. Adams[6], Charles P. Theuer[6]; Ahmed Kaseb[1]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Mayo Clinic, Jacksonville, FL; [3]National Cancer Institute, Bethesda, MD; [4]University of Alabama Comprehensive Cancer Center, Birmingham, AL; [5]University Hospitals Cleveland Medical Center, Cleveland, OH; [6]TRACON Pharmaceuticals, Inc., San Diego, CA

INTRODUCTION

- Endoglin is a membrane receptor required for angiogenesis (Li 1999) that is densely expressed by proliferating endothelial cells in solid tumors (Seon 2011), and is upregulated following vascular endothelial growth factor (VEGF) inhibition.
- Preclinical data demonstrate endoglin is an escape pathway that promotes VEGF resistance (Bockhorn 2003, Davis 2004, Anderberg 2013, Liu 2014,Tian 2018)
- TRC105 is a chimeric IgG1 monoclonal antibody that binds endoglin with high avidity (K_D= 5 pM), competitively inhibits binding of BMP-9, inhibits angiogenesis (Nolan-Stevaux 2012), potentiates the activity of VEGF inhibitors in preclinical models (Duffy 2017, Tian 2018) and causes telangiectasia and increased serum VEGF concentrations at its recommended Phase 2 dose (Rosen 2012, Gordon 2014, Karzai 2015).
- Endoglin heterozygosity is associated with the Osler-Weber-Rendu syndrome that results in mucocutaneous telangiectasia and is associated with improved cancer survival (Duarte 2014).

PRIOR COMPLETED TRIAL OF TRC105 AND SORAFENIB IN HCC

- In a study performed at the Clinical Center of the National Cancer Institute, the combination of TRC105 and sorafenib was tolerable and the study proceeded per protocol to the maximum planned dose level of TRC105 (15mg/kg every 2 weeks) in combination with 400 mg BID of sorafenib.
- TRC105 and sorafenib demonstrated encouraging evidence of activity, including a 33% partial response rate (5/15 pts) by RECIST, at RP2D doses of TRC105 (Duffy 2017). Median overall survival (OS) of 15.5 months (95% CI, 8.5-26.3 months) exceeded the median OS of sorafenib of 10.7 months reported in the pivotal Phase 3 SHARP trial (Llovet 2008).

STUDY RATIONALE

- Sorafenib is an oral multikinase inhibitor targeting several receptor tyrosine kinases, including the VEGF receptor (VEGFR), implicated in pathologic angiogenesis, tumor growth, and cancer progression.
- TRC105 combined safely and demonstrated anti-tumor activity with sorafenib in a Phase 1/2 study using every other week dosing, but was associated with trough TRC105 serum levels below target concentrations (Duffy 2017).
- The use of TRC105 administered using a hybrid dosing scheme of TRC105 at 10 mg/kg IV weekly for four weeks and 15 mg/kg IV biweekly thereafter with sorafenib may result in improved efficacy over that seen with single agent sorafenib.

STUDY DESIGN

Phase 1b Overview

- Multi Center, Open-Label, Nonrandomized, Dose-Finding study (N = 6 - 12)
- 1° Endpoint: RP2D
- Advanced/Metastatic HCC
- 400 mg sorafenib BID beginning Cycle 1 Day 1 in combination with TRC105 at 10 mg/kg IV weekly for four weeks in Cycle 1 and 15 mg/kg IV biweekly beginning in Cycle 2 and thereafter

Key Inclusion Criteria

- Confirmed hepatocellular carcinoma (HCC) by either histopathology or radiography
- Child-Pugh A or B (7 points)
- Disease not amenable to potentially curative resection or ablative techniques or that has recurred following ablative techniques

Key Exclusion Criteria

- Prior anticancer systemic therapy
- Radiation therapy within 28 days of starting the study treatment
- Patients with cirrhosis must have had esophagogastric endoscopy within the past 6 months prior to study entry for the assessment of varices

RESULTS

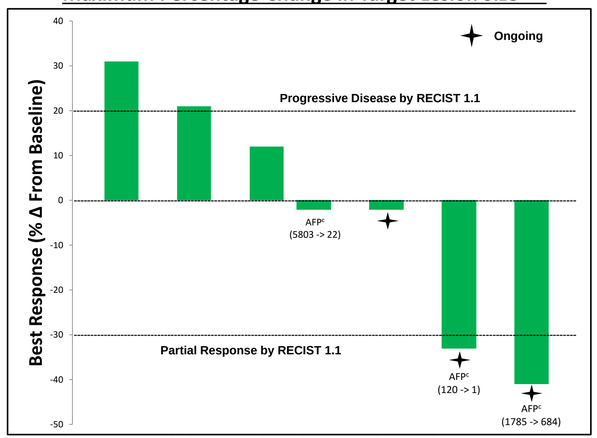
Baseline Patient Characteristics (N=13)

Age	• Median: 65 • Range: 33-82
Gender	• Male: 13 • Female: 0
ECOG	• ECOG 0: 6 • ECOG 1: 7

Mean Serum TRC105 Trough Concentration and Standard Deviation

Weekly Dosing	Mean TRC105 Concentration (ug/mL)	StdDev
C1D8 (N=8)	45.4	9.8
C1D15 (N=7)	43.6	17
C1D22 (N=5)	35.3	22
C2D1 (N=6)	41.3	19
Biweekly Dosing	**Mean TRC105 Concentration (ug/mL)**	**StdDev**
C2D15 (N=4)	23.2	7.5

Maximum Percentage Change in Target Lesion Size[a,b,c]



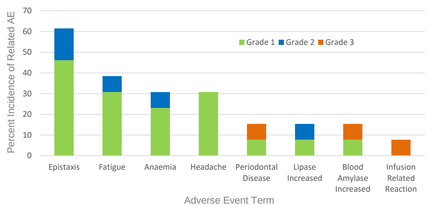
[a]Four patients were not evaluable as they did not have on study scans due to: an unrelated SAE of Grade 3 Nausea, withdrawal of consent, inclement weather (Hurricane Harvey), and need for anticoagulation.
[b]Tumor measurements are currently pending for two ongoing evaluable patients, one of whom has stable disease.
[c]AFP units are ng/mL

SUMMARY OF SAFETY AND EFFICACY

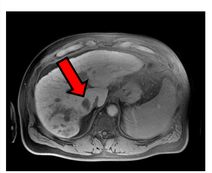
- TRC105 was tolerable when given at 10 mg/kg weekly IV for four doses (cycle 1) and 15 mg/kg biweekly IV beginning in cycle two and thereafter with 400 mg sorafenib twice daily.
- One patient experienced DLT of grade 3 infusion related reaction from which he recovered without sequelae.
- Most common TRC105 related adverse events were expected events of epistaxis, fatigue, anemia, and headache.
- Most common adverse events unrelated to TRC105 were palmar plantar erythrodysesthesia, hyperamylasemia, hyperlipasemia, and increased ALT.
- Partial response by RECIST 1.1 was observed in 2 of 8 evaluable patients (25%) both of whom remain on treatment (month 4 and month 8). An additional patient continued on therapy for over 10 months with stable disease and a minor tumor reduction and > 50% reduction in AFP. In total, 3 of 8 patients had > 50% reduction in AFP.
- TRC105 trough concentrations were sustained with 10 mg/kg weekly for four doses (cycle 1) and 15 mg/kg biweekly in cycle two and thereafter.

RESULTS

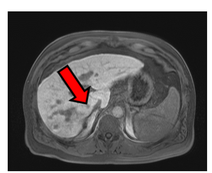
Most Common (n > 1) and all Grade 3 and above TRC105 Possibly Related Adverse Events



MRI at BASELINE and at WEEK 8 in a PATIENT with PARTIAL RESPONSE (41% TUMOR REDUCTION) and DECREASE in AFP from 1785 to 684 ng/mL

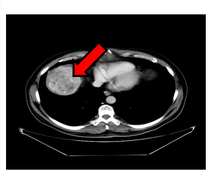


Baseline MRI Hepatic Mass

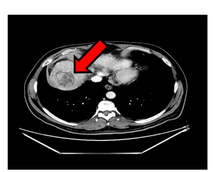


8 Week MRI Hepatic Mass

CT at BASELINE and at WEEK 8 IN PATIENT with PARTIAL RESPONSE (33% TUMOR REDUCTION) and DECREASE in AFP from 120 to 1 ng/mL



Baseline CT Hepatic Mass



8 Week CT Hepatic Mass

CONCLUSION

- TRC105 at 10 mg/kg weekly IV for four weeks and 15 mg/kg biweekly thereafter was tolerable with sorafenib in patients with HCC.
- The combination of TRC105 and sorafenib demonstrated encouraging preliminary signs of activity including a partial response rate of 25% by RECIST, which is consistent with the 33% response rate reported from the NCI single site study, as well as > 50% reduction in alpha fetoprotein (AFP) in three of eight (38%) patients.
- Adverse events characteristic of each drug were not increased in frequency or severity when the two drugs were administered concurrently. The most common TRC105 related events were the expected events of epistaxis, fatigue, anemia and headache.
- Study design details are at https://clinicaltrials.gov/ct2/show/NCT01306058

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