Abstract #268

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

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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 in NCI study (NCT01306058) 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).
- TRC105 administered weekly at its RP2D of 10 mg/kg weekly or administered using a hybrid dosing scheme 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.
- Demonstration of a 20% response rate would justify a randomized trial.

STUDY DESIGN

Phase 1b/2 Overview

Multi Center, Open-Label, Nonrandomized, Dose-Finding study

Phase 1b (N=6-12)

Hybrid Dosing: 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

Phase 2 (N=21)

Primary Endpoint: ORR by RECIST 1.1

Weekly Dosing: 400 mg sorafenib BID beginning Cycle 1 Day 1 in combination with TRC105 at 10 mg/kg IV weekly

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

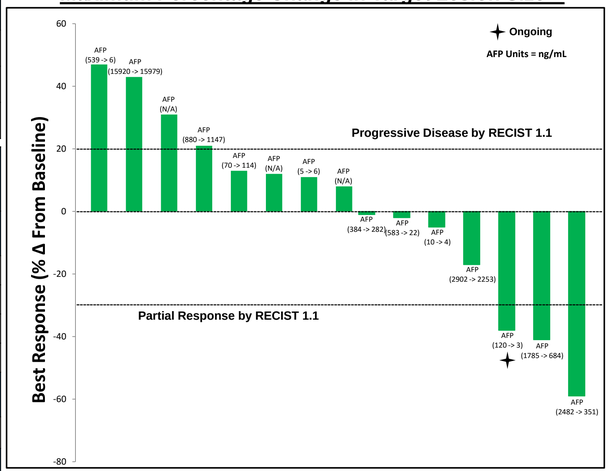
Baseline Patient Characteristics (N=21)

Age	• Median: 65 • Range: 33-82
Gender	• Male: 18 • Female: 3
ECOG	• ECOG 0: 10 • ECOG 1: 11

Mean Serum TRC105 Trough Concentration and Standard Deviation

Weekly Dosing	Mean TRC105 Concentration (ug/mL)	Standard Deviation
Week 1 (N=16)	60.3	84.9
Week 2 (N=14)	33.6	19.5
Week 3 (N=14)	31.1	28.2
Week 4 (N=13)	35.8	28.4
Biweekly Dosing	**Mean TRC105 Concentration (ug/mL)**	**Standard Deviation**
Week 6 (N=8)	14.2	12.1
Weekly Dosing	**Mean TRC105 Concentration (ug/mL)**	**Standard Deviation**
Week 6 (N=3)	44.7	9.0

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



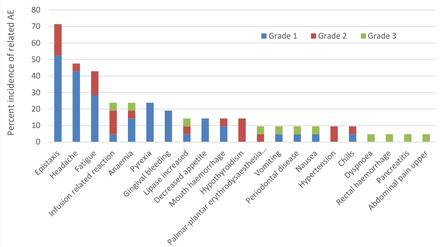
[a]Four patients were not evaluable as they did not have on study scans due to: an unrelated SAE of Grade 3 Nausea, withdrawal of consent, inclement weather (Hurricane Harvey), and need for anticoagulation.
[b]Tumor measurements are currently pending for two ongoing patients.

SUMMARY OF SAFETY AND EFFICACY

- Mean serum levels of TRC105 exceeded the target concentration following weekly dosing of TRC105 at 10 mg/kg (44.7 ug/ml at 6 weeks). Mean trough concentrations decreased following every other week dosing resulting in infusion reactions or a continued requirement for premedication. Therefore, weekly dosing of TRC105 at 10 mg/kg was selected as RP2D.
- One P1b 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, headache and fatigue.
- Most common adverse events regardless of relationship were epistaxis, fatigue, headache, palmar plantar erythrodysesthesia, anaemia and constipation.
- Partial response by RECIST 1.1 was observed in 3 of 15 evaluable patients (20%), with duration of response ranging from 15.7 to 55+ weeks.
- Six of 12 patients (50%) had > 50% reduction in AFP.
- Low titer treatment emergent anti-drug antibody (ADA) was detected in 8/17 patients and high titer ADA were seen in 5/17 patients.

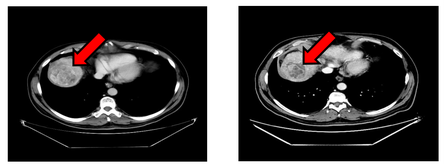
RESULTS

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



Phase 1b:

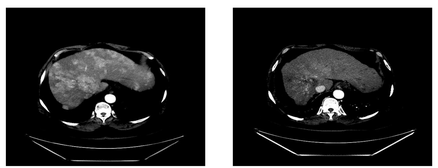
CT at BASELINE and at WEEK 8 in a PATIENT with PARTIAL RESPONSE (38% TUMOR REDUCTION) and DECREASE in AFP from 120 to 3 ng/mL



Baseline | Week 8

Phase 2:

CT at BASELINE and at WEEK 16 in a PATIENT with PARTIAL RESPONSE (59% TUMOR REDUCTION) and DECREASE in AFP from 2482 to 351 ng/mL



Baseline | Week 16

CONCLUSION

- Adverse events characteristic of each drug were not increased in frequency or severity when the two drugs were administered concurrently.
- Mean serum concentrations of TRC105 at 10 mg/kg weekly IV exceeded target concentrations. However, TRC105 trough concentrations were lower in HCC patients compared with prior TRC105 studies in RCC and sarcoma, where hybrid dosing achieved target concentrations. This may reflect increased target mediated clearance in HCC patients via fibrotic/cirrhotic liver disease.
- Treatment emergent ADA was observed more frequently in patients with HCC (76%) compared with studies of TRC105 in other tumor types (e.g., RCC, sarcoma, and lung where ADA has been 7%) and may have influenced PK in individual patients.
- The combination of TRC105 and sorafenib continued to demonstrate encouraging signs of activity including a durable partial response rate of 20% by RECIST, which is consistent with the response rate reported from the NCI single site study, as well as > 50% reduction in alpha fetoprotein (AFP) in half of the patients.
- Study design details are at https://clinicaltrials.gov/ct2/show/NCT01306058

REFERENCES

- Anderberg C, J Exp Medicine 210:563-79, 2013
- Bockhorn M, Clin Cancer Res 9:4221-4226, 2003
- Davis DW, Cancer Research 64:4601-4610, 2004
- Duarte CW, Can Epi Bio & Prev 23:117-25, 2014
- Duffy AG, Clin Cancer Res 23; 4633-4641, 2017
- Gordon MS, Clin Cancer Res 20:5918-5926, 2014
- Karzai FH, BJU Int 116:546-555, 2015
- Li DY, Science 284:1534-1537, 1999
- Liu Y, Inv New Drugs 32: 851-859, 2014
- Llovet JM, NEJM 359:378-90, 2008.
- Nolan-Stevaux O, PLOS One e50920, 7:1-12, 2012
- Rosen L, Clin Cancer Res 18:4820-9, 2012
- Seon BK, Current Drug Delivery 8:135-143, 2011
- Tian H, FASEB Journal doi: 10.1096/fj.201700867RR, 2018