Every Other Week Dosing of TRC105 (Endoglin Antibody) in Combination with Pazopanib in Patients with Advanced Soft Tissue Sarcoma

K.K. Sankhala[1,11], R.F. Riedel[2], R.M. Conry[3], A. Grand'Maison[4], S.I. Robinson[5] , M.A. Barve[6], J.H. Ward[7], P. Friedlander[8], R.G. Maki[8,12] , S. Chawla[1], B.K. Seon[4], D. Alvarez[9], B.J. Adams[9], C.P. Theuer[9], S. Attia[10],

[1]Sarcoma Oncology Center, Santa Monica, CA; [2]Duke University Medical Center, Durham, NC; [3]The University of Alabama at Birmingham, Birmingham, AL; [4]Roswell Park Cancer Institute, Buffalo, NY; [5]Mayo Clinic, Rochester, MN; [6]Mary Crowley Cancer Research Centers, Dallas , TX; [7]University of Utah, Salt Lake City, UT; [8]Icahn School of Medicine at Mount Sinai, New York, NY; [9]TRACON Pharmaceuticals, Inc., San Diego, CA; [10]Mayo Clinic, Jacksonville, FL; [11] Current address: Cedars-Sinai Medical Center, Los Angeles, CA; [12]Current address: Northwell Health, Lake Success, NY

INTRODUCTION

- Endoglin is a membrane receptor required for angiogenesis (Li 1999) that is highly expressed by proliferating endothelial cells in solid tumors (Seon 2011), is upregulated following VEGF inhibition, and allows continued angiogenesis despite VEGF inhibition (Bockhorn 2003, Davis 2004, Anderberg 2013).
- Endoglin heterozygosity is associated with the Osler-Weber-Rendu syndrome that is characterized by mucocutaneous telangiectasia and is associated with improved cancer survival (Duarte 2014).
- TRC105 is a chimeric IgG1 endoglin monoclonal antibody with high avidity (K_D = 5 pM) that inhibits angiogenesis (Seon 2011, Nolan-Stevaux 2012), potentiates the activity of VEGF inhibitors in preclinical models, and causes mucocutaneous telangiectasia at its recommended phase 2 dose (Rosen 2012, Gordon 2014).
- VEGF pathway inhibitors have limited activity in angiosarcoma; no complete responses (CRs) were reported in a retrospective analysis of 40 angiosarcoma patients treated with single agent pazopanib, and median PFS was 3.0 months (Table 1; Kollar 2016).
- Endoglin is densely expressed on angiosarcoma (Fritchie 2013), and endoglin expression is associated with poor prognosis (Pardali 2011).
- By targeting a non-VEGF pathway that is upregulated following VEGF pathway inhibition and is expressed directly on malignant cells, TRC105 may complement pazopanib in angiosarcoma, and TRC105 in combination with pazopanib is being compared to single agent pazopanib in patients with angiosarcoma in the randomized phase 3 TAPPAS trial at multiple sites in the US and EU.

Table 1: VEGF Pathway Inhibitors Have Limited Activity in Angiosarcoma

VEGF Inhibitor	Study	Patient Population	Activity
Pazopanib	***Retrospective analysis (CTOS 2016)***	***Angiosarcoma (n = 40)***	***•ORR = 20% (No CRs) •PFS = 3.0 months •OS = 9.9 months***
Pazopanib	Retrospective analysis (ASCO 2014)	Soft tissue sarcoma, including 6 angiosarcoma patients	•No CR's
Sorafenib	Single agent study (Maki 2009)	Angiosarcoma (n = 37)	•ORR = 14% (1/37 CR) •PFS = 3.8 months
Sorafenib	Single agent study (French sarcoma group)	Angiosarcoma (n = 41)	<u>Cutaneous angiosarcoma</u> •ORR = 15% (2/26 CR) •PFS = 1.8 months <u>Visceral angiosarcoma</u> •ORR = 13% (No CRs) •PFS = 3.8 months
Bevacizumab	Single agent study (Agulnik 2013)	Angiosarcoma (n = 23)	•ORR = 9% (No CRs) •PFS = 3.0 months

STUDY RATIONALE AND METHODS

- TRC105 at its RP2D of 10 mg/kg weekly was well tolerated with standard dose pazopanib in soft tissue sarcoma (STS) patients treated in a Phase 1B/2 study, including patients with angiosarcoma.
- Every other week dosing with TRC105 has been proposed to decrease the frequency of infusions.
- Additional patients with advanced STS and angiosarcoma were therefore treated with a hybrid dosing scheme of TRC105 10 mg/kg weekly for four doses (Cycle 1) followed by every other week dosing at 15 mg/kg starting on Cycle 2 Day 1 of recurring 4 week cycles.
- TRC105 serum concentrations were assessed at steady state following weekly and every other week dosing using the hybrid scheme.
- Treatment duration on TRC105 and pazopanib was compared to the duration of the most recent prior therapy.
- Median PFS was assessed in 18 angiosarcoma patients who received TRC105 and pazopanib.

STUDY DESIGN

Phase 1B/2 Trial Enrolled 9 Angiosarcoma Patients Treated with TRC105 weekly dosing + Pazopanib
- •Progression following anthracycline chemotherapy
- •Up to four prior lines of systemic therapy allowed for Phase 2 patients
- •Prior pazopanib allowed for Phase 1B patients

⇨

Expansion Cohort Enrolled 6 STS Patients Treated with TRC105 hybrid dosing + Pazopanib
- •Progression following anthracycline chemotherapy
- •Up to four prior lines of systemic therapy allowed
- •Prior pazopanib allowed

⇨

9 Additional Angiosarcoma Patients were Treated with TRC105 hybrid dosing + Pazopanib
- •Progression following chemotherapy
- •Up to four prior lines of systemic therapy allowed
- •Prior pazopanib allowed

KEY ENROLLMENT CRITERIA: Measurable disease by RECIST 1.1, ECOG ≤ 1

RESULTS

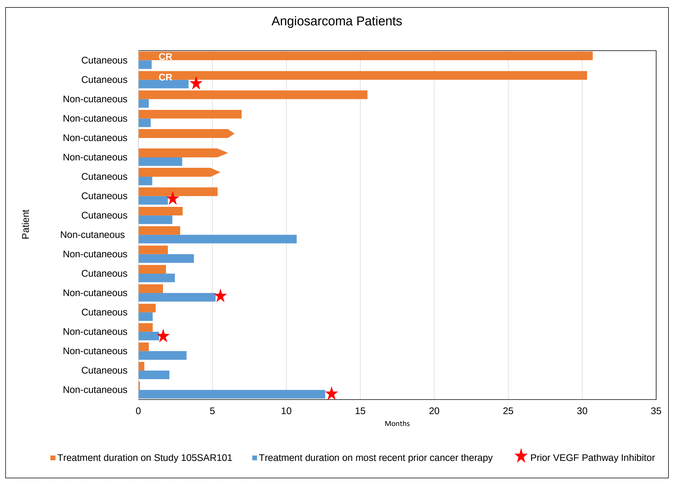
- TRC105 target concentrations shown to saturate endoglin receptors were achieved continuously using a TRC105 hybrid dose of 10 mg/kg weekly followed by 15 mg/kg every other week in 6 patients with STS (Table 2).
- Most common TRC105 related adverse events were epistaxis, headache, fatigue, anemia and gingival bleeding.
- Most common pazopanib related adverse events were diarrhea, fatigue, headache, nausea, dysgeusia, anorexia, oral pain, increased TSH and hypertension.
- Adverse events characteristic of each individual drug were not increased in frequency or severity when the two drugs were administered concurrently.
- Median PFS was 7.8 months in 13 patients without prior VEGF inhibitor treatment and 5.6 months in all 18 angiosarcoma patients treated with the combination of TRC105 and pazopanib using 10 mg/kg weekly dosing or hybrid dosing.
- Treatment duration on TRC105 and pazopanib exceeded treatment duration on the most recent prior therapy in 7 of 12 VEGF naïve angiosarcoma patients, and 2 of 5 patients who received a VEGF inhibitor as part of their most recent prior therapy.
- Treatment duration on TRC105 and pazopanib exceeded treatment duration on the most recent prior therapy in 4 of 5 STS patients.

Table 2: TRC105 Steady State Trough Serum Concentrations

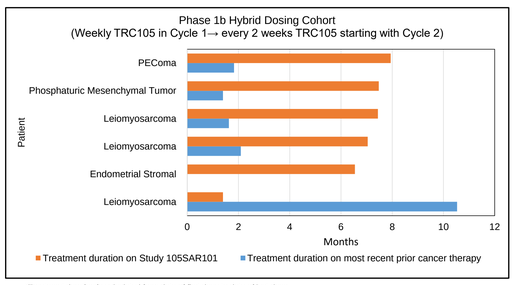
Study Day	N	Mean (µg/ml)	Range (µg/ml)
Cycle 2 Day 1	6	124	80-174
Cycle 2 Day 15	6	86	62-144
Cycle 3 Day 1	5	91	73-121
Cycle 3 Day 15	4	80	63-100

Angiosarcoma Patient Baseline Characteristics (N=18)	
Age (years)	• Mean: 60.8 • Range: 39 - 90
Gender	• Male: 8 • Female: 10
ECOG	• ECOG 0: 3 • ECOG 1: 15
Number of Lines of Previous Systemic Therapies	• Median: 1 • Range: 0-5

STS Patient Baseline Characteristics (N=6)	
Age (years)	• Mean: 64.5 • Range: 58 - 73
Gender	• Male: 2 • Female: 4
ECOG	• ECOG 0: 0 • ECOG 1: 6
Number of Lines of Previous Systemic Therapies	• Median: 3.5 • Range: 1-5



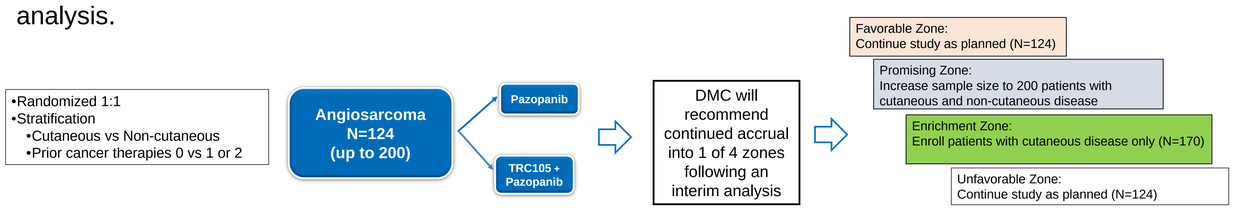
*Treatment duration is calculated from date of first dose to date of last dose



*Treatment duration is calculated from date of first dose to date of last dose

CONCLUSIONS

- TRC105 was well tolerated and achieved steady state target concentrations when combined with pazopanib using a hybrid dosing scheme of 10 mg/kg weekly for four doses followed by every other weekly dosing at 15 mg/kg.
- The safety profile of the combination was tolerable and allowed for prolonged dosing.
- TRC105 combined with pazopanib demonstrated encouraging activity in angiosarcoma patients, including durable CRs by RECIST 1.1, improved PFS compared to prior studies of single agent VEGF pathway inhibitors (see Table 1), and superior disease control compared to prior treatment.
- The randomized phase 3 TAPPAS study of TRC105 in combination with pazopanib compared to single agent pazopanib in patients with angiosarcoma is designed to detect a hazard ratio of 0.55, using a two-tailed alpha of 0.05, with > 80% power as the baseline statistical assumption. However, the trial includes an adaptive design that allows for sample size re-estimation or enrichment of cutaneous disease based on an interim analysis.



REFERENCES

- Anderberg C, J Exp Med 210:563-79, 2013
- Bockhorn M, Clin Cancer Res 9:4221-26, 2003
- Choueiri T, GU ASCO 2015
- Davis DW, Cancer Res 64:4601-10, 2004
- Duarte CW, Can Epi Bio & Prev 23:117-25, 2014
- Duffy AG, GI ASCO 2015
- Fritchie K, EORTC-AACR-NCI 2013
- Gordon MS, Clin Cancer Res 20:5918-26, 2014
- Kollar A, CTOS 2016
- Li DY, Science 284:1534-37, 1999
- Nolan-Stevaux O, PLOS One 7:1-12, 2012
- Pardali E, Oncogene 30:334-45, 2011
- Rosen L, Clin Cancer Res 18:4820-9, 2012
- Seon BK, Current Drug Del 8:135-43, 2011