Detection of Endoglin-Expressing CTCs in Patients Enrolled in an Adaptive Enrichment Phase 3 Trial of TRC105 And Pazopanib versus Pazopanib alone in Patients with Advanced AngioSarcoma (TAPPAS)

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INTRODUCTION

- 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 (Rosen 2012, Gordon 2014).
- Endoglin is densely expressed on angiosarcoma (Fritchie 2013), and endoglin expression is associated with poor prognosis (Pardali 2011).
- 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 (Kollar 2016), 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 for the primacy endpoint of progression free survival, 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.
- Circulating tumor cells (CTC) are collected in patients enrolled in TAPPAS at baseline and following six weeks of protocol treatment and will be correlated with efficacy.

METHODS

- CTC were enriched by ApoStream® from 8 mL whole blood samples drawn prior to treatment, with either pazopanib at 800 mg p.o. daily or pazopanib 800 mg p.o. daily + TRC105 at 10 mg/kg weekly at baseline (Cycle 1 Day 1) and 6 weeks following initiation of study treatment, at Cycle 3 Day 1.
- CTCs that expressed endoglin and DAPI (nuclear staining) by immunofluorescence that used a non-competing endoglin antibody were quantified. Endoglin+/DAPI+ CTCs were further characterized as atypical cells using Diff-Kwik staining.

RESULTS

- Paired samples were available for 51 patients (63% of those enrolled with sufficient time to process paired samples)
- Changes were considered significant for a CTC increase or decrease by at least two-fold and by at least 1 cell/mL from baseline
- Changes were also tabulated for cases of a CTC increase or decrease by at least ten-fold and by at least 1 cell/mL from baseline

Table 1: Summary statistics (Endoglin+ DAPI+ cells/mL)

	Mean	Median	Range
C1D1	66.5	1.38	0 - 1172
C3D1	1.30	1.38	0 - 185

Table 2: Summary statistics (Changes in Endoglin+ DAPI+ cells/mL from Baseline)

	≥ 2-fold change	> 10-fold change
Eng+ CTC Increase	19/51 (37%)	13/51 (25%)
Eng+ CTC Decrease	18/51 (35%)	13/51 (25%)

Figure 1: Patients With Increases in Total CD105+, DAPI+ Count per mL Blood

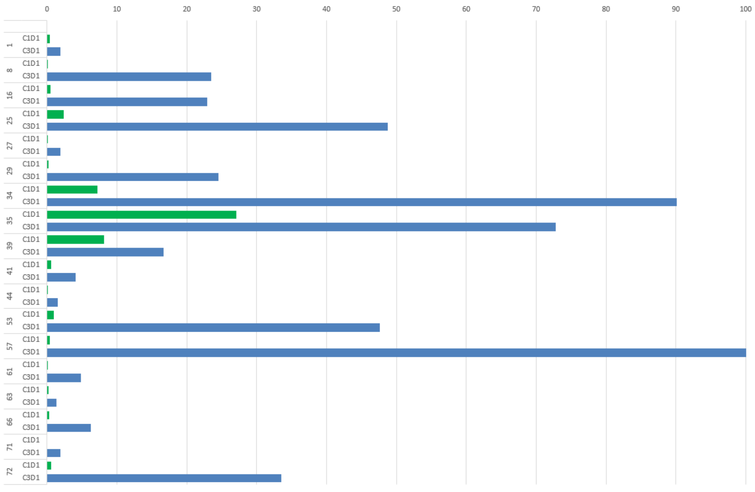


Figure 2: Patients With Decreases in Total CD105+, DAPI+ Count per mL Blood

Figure 3: Representative Patient with Increases in Endoglin+ CTC

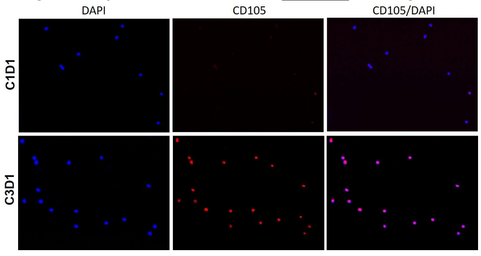
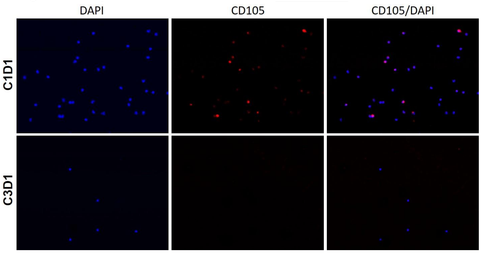
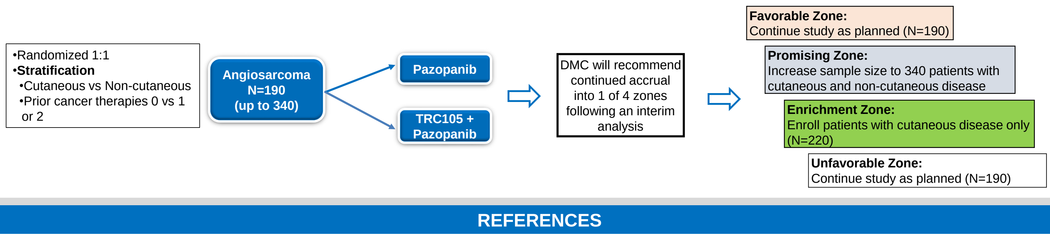


Figure 4: Representative Patient with Decreases in Endoglin+ CTC



CONCLUSIONS

- Significant changes in endoglin+ CTC were observed following treatment with TRC105 + pazopanib and/or single agent pazopanib.
- Baseline endoglin+ CTC and response to treatment will be correlated with efficacy endpoints at the time of final analysis.
- The interim analysis to determine the final sample size and study population of the Phase 3 TAPPAS trial is expected in 1Q 2019.



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