Poster #110

TRC105 (Endoglin Antibody) in Combination with Pazopanib in Patients with Advanced Angiosarcoma

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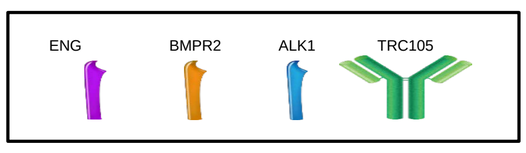
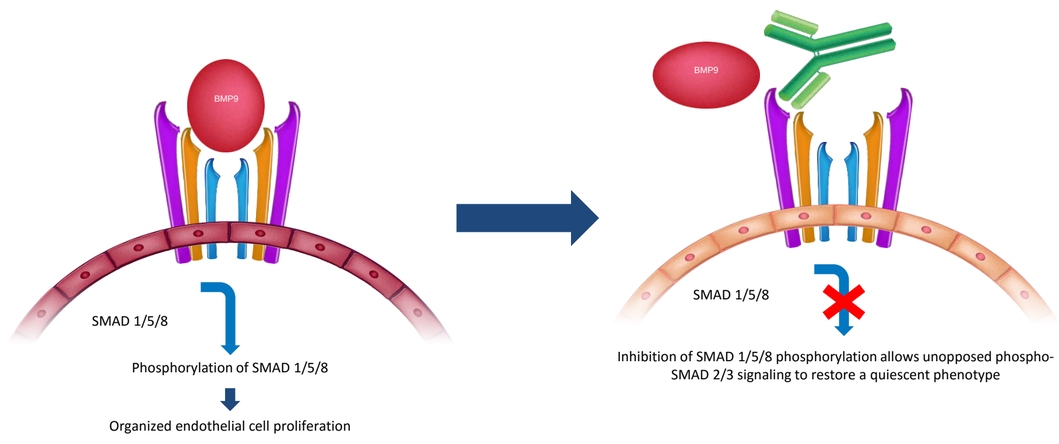
INTRODUCTION

- Endoglin is a membrane receptor required for angiogenesis (Li 1999) that is highly expressed by proliferating endothelial cells in solid tumors (Seon 2011), and is upregulated following VEGF inhibition.
- Endoglin expression allows continued angiogenesis despite VEGF inhibition (Bockhorn 2003, Davis 2004, Anderberg 2013).
- Endoglin heterozygosity is associated with the Osler-Weber-Rendu syndrome that results in 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 (Nolan-Stevaux 2012), potentiates the activity of VEGF inhibitors in preclinical models, and causes telangiectasia and increased serum VEGF concentrations at its recommended phase 2 dose (Karzai 2015, Rosen 2012, Gordon 2014).
- TRC105 combined safely and demonstrated anti-tumor activity with bevacizumab, sorafenib and axitinib in separate phase 1/2 studies (Gordon 2014, Duffy 2015, Choueiri 2015).
- TRC105 received Orphan Drug Designation for soft tissue sarcoma (STS) in the US on Jan 21, 2016 and EU on Apr 28, 2016.





STUDY RATIONALE

- Pazopanib is an inhibitor of multiple kinases including VEGF receptors that is approved for the treatment of STS and demonstrated a partial response rate of 4% and progression free survival (PFS) of 4.6 months by RECIST 1.0 following treatment with chemotherapy in the pivotal PALETTE study.
- Angiosarcoma is a rare and aggressive form of STS of endothelial cell origin associated with poor PFS and overall survival.
- VEGF inhibitors have limited activity in angiosarcoma; no complete responses (CRs) were reported in a retrospective analysis of 30 angiosarcoma patients treated with single agent pazopanib, and median PFS was 3.02 months (**Table 1**; Kollar 2015).
- 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 inhibition and is expressed directly on malignant cells, TRC105 may complement pazopanib in angiosarcoma.

Table 1: VEGF Inhibitors Have Limited Activity in Angiosarcoma

VEGF Inhibitor	Study	Patient Population	Activity
Pazopanib	***Retrospective analysis (EORTC 2015)***	***Angiosarcoma (n = 30)***	• ***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)	Cutaneous angiosarcoma • ORR = 15% (2/26 CR) • PFS = 1.8 months Visceral angiosarcoma • 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 DESIGN

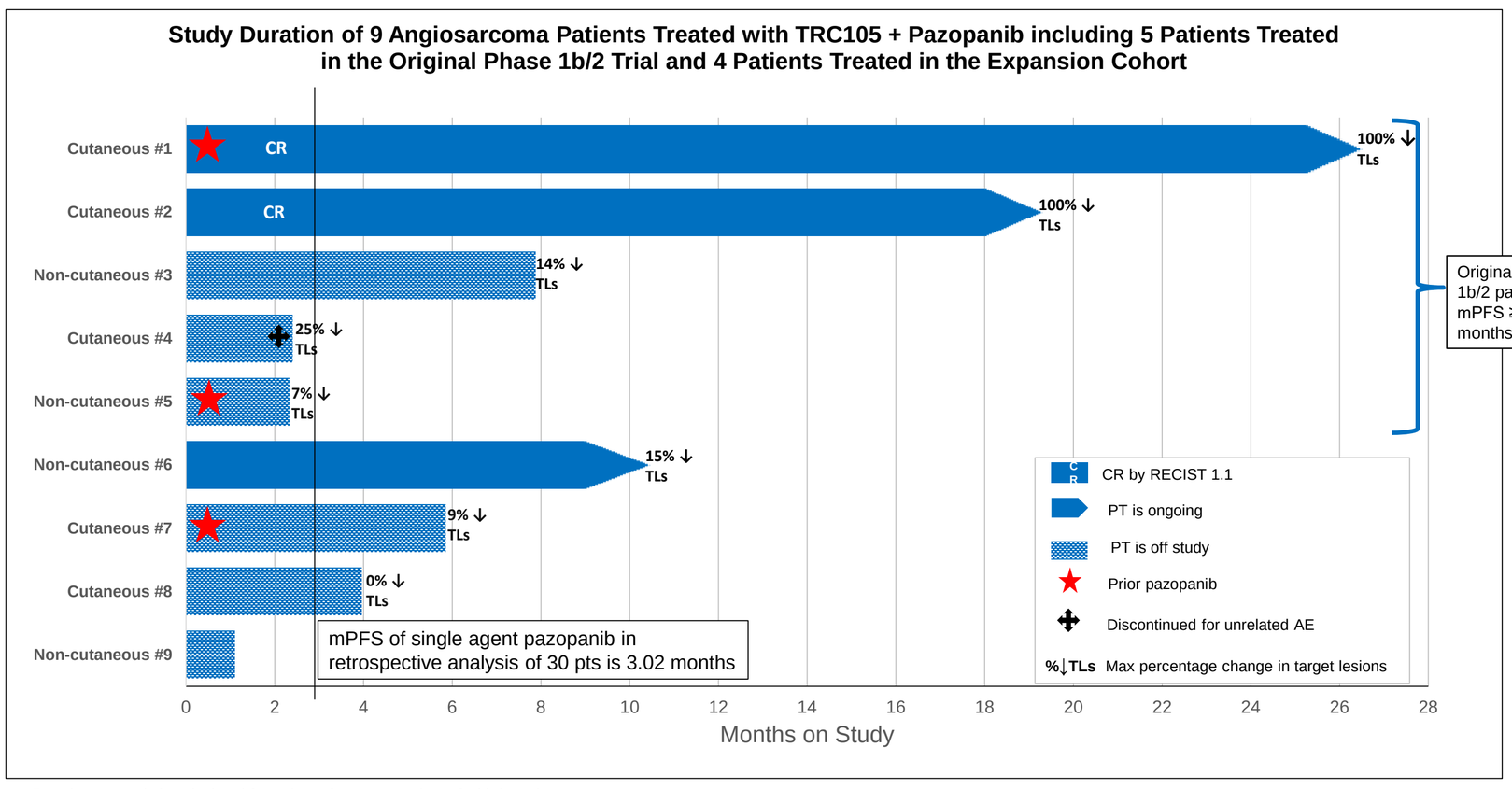
Original Phase 1B/2 Trial Enrolled 5 Angiosarcoma Patients Treated with TRC105 + Pazopanib
- Progression following anthracycline chemotherapy required
- Up to four prior lines of systemic therapy allowed for Phase 2 patients
- Prior pazopanib allowed for Phase 1B patients

Expansion Cohort Enrolled 4 Additional Angiosarcoma Patients Treated with TRC105 + Pazopanib
- Progression following anthracycline chemotherapy required
- Up to four prior lines of systemic therapy allowed
- Prior pazopanib allowed

9 Additional Angiosarcoma Patients were Treated with Single Agent TRC105, with Pazopanib Added at Progression
- Progression following chemotherapy required
- Up to four prior lines of systemic therapy allowed
- Prior pazopanib allowed

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

RESULTS



- Duration on study is calculated from date of consent to date of withdrawal
- Last response assessment used as date of progression for ongoing pts with CR to calculate mPFS

Original Phase 1b/2 patients (n=5) mPFS ≥ 16.6 months*

Original Phase 1b/2 & Expansion Cohort patients (n=9) mPFS = 5.59 months

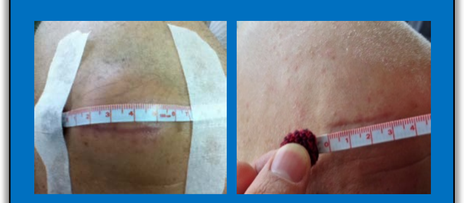
Patient #1 ongoing at month 26 with a CR

- The patient progressed within 15 weeks of treatment with docetaxel combined with pazopanib.

Patient #2 ongoing at month 19 with a CR

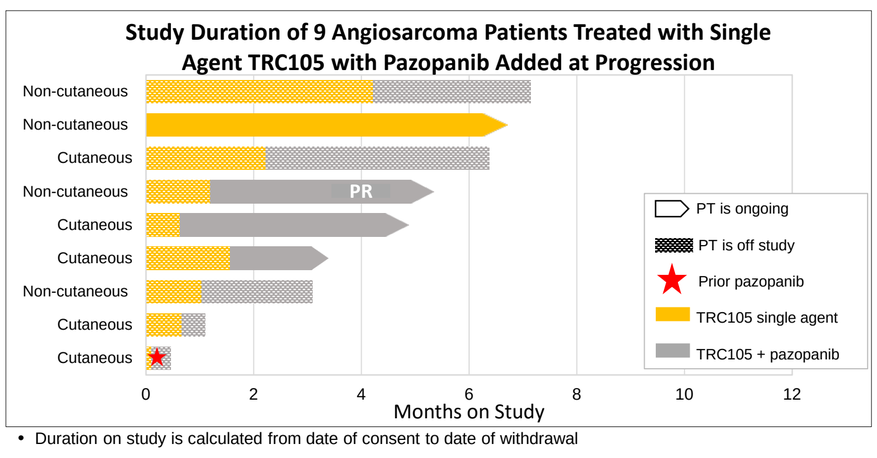
- The patient progressed within 4 weeks of treatment with doxorubicin.

Patient #6 ongoing at month 10 with significant tumor reduction



- The patient progressed within 4 weeks of treatment with gemcitabine, doxorubicin, and docetaxel.

Baseline Patient Characteristics (N=18)	
Age (years)	• Median: 59 • Range: 29 – 90
Gender	• Male: 12 • Female: 6
ECOG	• ECOG 0: 3 • ECOG 1: 15
Number of Lines of Previous Systemic Therapies	• Median: 1 • Range: 1-5



- Duration on study is calculated from date of consent to date of withdrawal

- TRC105 at its RP2D of 10 mg/kg weekly was well tolerated with pazopanib at its approved dose in angiosarcoma patients.
- Adverse events characteristic of each individual drug were not increased in frequency or severity when the two drugs were administrated concurrently.
- TRC105 target concentrations shown to saturate endoglin receptors were achieved continuously at a TRC105 dose of 10 mg/kg weekly.
- Pazopanib steady state PK when dosed with TRC105 was similar to that reported following dosing as a single agent.
- Tumor reductions or clinical improvement were observed in 8 of 9 (89%) angiosarcoma patients treated with the combination of TRC105 and pazopanib in the original phase 1b/2 trial (n=5) or the angiosarcoma expansion cohort (n=4), including two ongoing CRs.
- Median PFS ≥16.6 months in the 5 angiosarcoma patients enrolled in the original Phase 1b/2 trial.
- Median PFS = 5.59 months in the 9 angiosarcoma patients treated with the combination of TRC105 and pazopanib in the original phase 1b/2 trial (n=5) or the angiosarcoma expansion cohort (n=4), of whom 3 had progressed following prior pazopanib. mPFS compares favorably to the mPFS of 3.0 months in a retrospective study of single agent pazopanib (hazard ratio = 0.54).
- Median PFS (< 2 months) in 9 angiosarcoma patients initially treated with single agent TRC105 was similar to mPFS reported in trials of single agent VEGF inhibitors; 4 of these patients remain on study with either single agent TRC105 or TRC105 + pazopanib, including 1 patient with a partial response.

CONCLUSION

- TRC105 combined with pazopanib demonstrated encouraging activity in angiosarcoma patients, including durable CRs by RECIST 1.1 and improved PFS compared to prior studies of single agent VEGF inhibitors (see Table 1) or to single agent TRC105.
- Clinical safety profile of the combination was tolerable and allowed for prolonged dosing.
- A randomized phase 3 study with TRC105 in combination with pazopanib compared to single agent pazopanib in patients with angiosarcoma is planned to confirm the activity seen in this study.
- The trial is planned as an adaptive design that allows for sample size re-estimation or enrichment of cutaneous disease based on an interim analysis, with > 80% power to detect a hazard ratio of 0.55, using a two-tailed alpha of 0.05

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