INTRODUCTION

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

• Endoglin is a membrane receptor required for angiogenesis (Li 1999) that is highly expressed by proliferating endothelial cells in solid tumors (Saini 2011), and is upregulated following VEGF inhibition.
• Endoglin expression allows continued angiogenesis despite VEGF inhibition (Bochorn 2013). VEGF inhibition results in telangiectasia and is associated with improved cancer survival (Duarte 2014).

• TRC105 is a chimeric IgG1 endoglin monoclonal antibody with high affinity (K_d = 3 µM) that inhibits angiogenesis (Nolan-Reese 2012), potentiates the activity of VEGF inhibitors in preclinical models, and causes telangiectasia and increased serum VEGF concentrations at its recommended phase 2 dose (Kasael 2015, Rosen 2014).

• TRC105 is dosed combined with pazopanib, a multitargeted tyrosine kinase inhibitor (TKI) with activity, in combination with pazopanib, 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.

• 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.

• Adverse events characteristic of each individual drug were not increased in frequency or severity when the two drugs were administrated concurrently.

• A randomized phase 3 study with TRC105 in combination with pazopanib is planned to definitively establish the role of TRC105 in combination with pazopanib in treating advanced angiosarcoma.

STUDY RATIONALE

VEGF Inhibitors Have Limited Activity in Angiosarcoma

• Pazopanib is an inhibitor of multiple kinases including VEGF receptors that is approved for the treatment of soft tissue sarcoma (STS) (Maki 2009) and angiosarcoma (Agulnik 2013) • ORR = 9% (No CRs) in a retrospective analysis of 30 pts.

• Sorafenib is an inhibitor of VEGF receptors that is approved for the treatment of hepatocellular carcinoma (HCC) (Higashi 2007) • ORR = 14% (1/37 CR) in a single agent study.

• Bevacizumab is an antibody that neutralizes VEGF • ORR = 15% (2/26 CR) in a phase 2 study with pazopanib (Kollar 2015).

• Axitinib is an inhibitor of VEGF receptors that is approved for the treatment of renal cell carcinoma (RCC) (Agus 2009) • ORR = 15% (1/7 CR) in a single agent study (Kollar 2015).

• A randomized phase 3 study with pazopanib (n = 200) did not meet its primary endpoint of mPFS in patients with advanced angiosarcoma treated with pazopanib versus placebo (Kollar 2015).

RESULTS

• PFS = 3.0 months (French sarcoma group) Angiosarcoma (n = 41) • ORR = 9% (No CRs)

• PFS = 3.8 months (Agulnik 2013) Angiosarcoma (n = 23) • ORR = 11% (1 CR)

• PFS = 3.0 months (ASCO 2014) Angiosarcoma (n = 37) • ORR = 14% (1/37 CR)

• TRC105 treatment in advanced angiosarcoma patients is well tolerated and has demonstrated encouraging activity, with a median PFS of 16.6 months in patients treated with TRC105 plus pazopanib.

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 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 designed as an adaptive design that allows for sample size re-estimation or enrichment of cutaneous disease based on interim analysis, with a 80% power to detect a hazard ratio of 0.55, using a two-tailed alpha of 0.05.