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TAPPAS: An Adaptive Enrichment Phase 3 Trial of TRC105 And Pazopanib Versus Pazopanib Alone in Patients with Advanced AngioSarcoma

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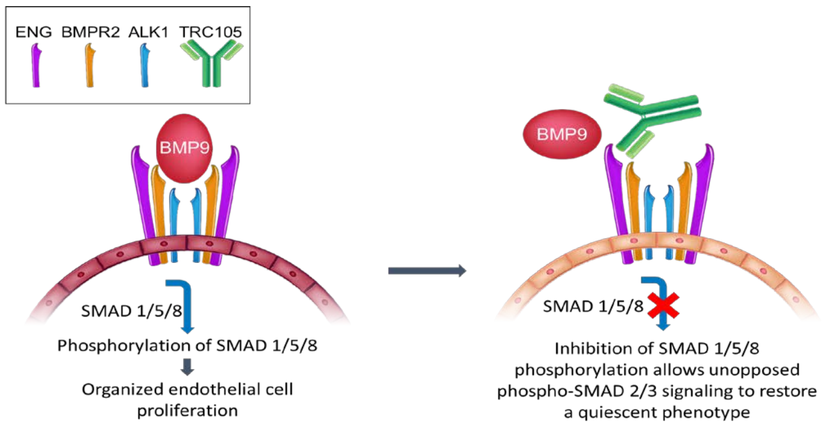
INTRODUCTION

- 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 also expressed on angiosarcoma (AS) (Fritchie 2013).
- Preclinical data demonstrate endoglin is an escape pathway that promotes VEGF resistance (Bockhorn 2003, Davis 2004, Anderberg 2013, Liu 2014).
- 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 (Rosen 2012, Gordon 2014).
- TRC105 combined safely and demonstrated anti-tumor activity with pazopanib, including durable complete responses, in a phase 1/2 study of patients with angiosarcoma (Attia 2016).
- TRC105 received Orphan Drug Designation for soft tissue sarcoma (STS) in the US on January 2016 and EU on April 2016.
- The TAPPAS trial was designed following discussions with the European Medicines Agency (EMA) and US FDA and received Special Protocol Assessment agreement with the FDA in December 2016.
- The TAPPAS trial was the recipient of the 2017 Clinical and Research Excellence (CARE) Award for Most Innovative Trial Design.



STUDY RATIONALE

- Pazopanib is an oral VEGF receptor tyrosine kinase inhibitor (VEGFR TKI) that inhibits multiple receptor tyrosine kinases, including VEGFR-1, VEGFR-2, and VEGFR-3. Pazopanib is approved for the treatment of Soft Tissue Sarcoma with an overall response rate of 4% by RECIST 1.1 and progression free survival (PFS) of 4.6 months following treatment with one prior VEGFR TKI (van der Graaf 2012).
- In a retrospective study of 40 AS patients treated with single agent pazopanib, median PFS was 3.1 months and median OS was 9.9 months with no complete responses (Kollar 2016).
- Endoglin is an essential angiogenic receptor expressed on AS (Fritchie 2013) that is upregulated following VEGF inhibition. TRC105, an endoglin antibody, given with pazopanib produced durable complete responses in AS patients with median PFS of 5.6 months in refractory patients including those who received prior pazopanib (Attia 2016).
- By targeting a non-VEGF pathway that is upregulated following VEGF inhibition and densely expressed in AS, TRC105 has the potential to complement pazopanib in patients with AS.

STUDY OBJECTIVES

Primary

- Compare PFS of TRC105 and pazopanib vs single agent pazopanib in patients with unresectable angiosarcoma

Secondary

- Compare the objective response rate (ORR) of TRC105 and pazopanib vs single agent pazopanib
- Compare overall survival (OS) of TRC105 and pazopanib vs single agent pazopanib
- Assess the overall safety and tolerability of TRC105 and pazopanib vs single agent pazopanib
- Characterize patient reported outcomes between the two arms of the study
- Characterize the PK profile of TRC105 and pazopanib between the two arms of the study
- Assess PFS and ORR by Investigator assessment between the two arms of the study
- Characterize the immunogenicity of TRC105

Exploratory

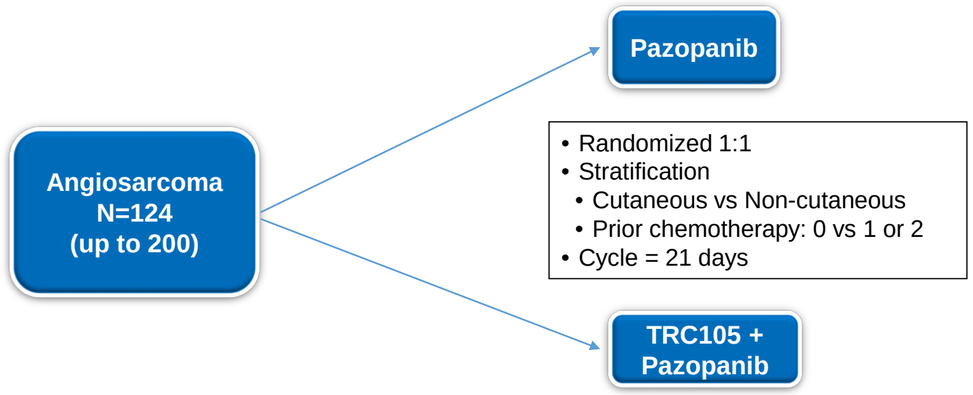
- Correlate efficacy endpoints (e.g., PFS, ORR, and OS) with endoglin expression on angiosarcoma tumor samples
- Correlate efficacy endpoints (e.g., PFS, ORR, and OS) with circulating angiogenic protein biomarkers
- Correlate efficacy endpoints (e.g., PFS, ORR, and OS) with numbers of endoglin expressing circulating tumor cells (CTCs)

ELIGIBILITY

- Advanced cutaneous and non-cutaneous angiosarcoma not amenable to curative intent surgery
- Measurable disease by RECIST 1.1
- No prior treatment with a VEGF inhibitor
- 0, 1, or 2 prior lines of therapy
- ECOG ≤ 1

STUDY DESIGN

TRC105: 10 mg/kg weekly
Pazopanib: 800 mg daily (adults 18+), 600 mg (ages 12-17)



ADAPTIVE DESIGN BASED ON INTERIM ANALYSIS

An interim analysis is planned to determine the conditional power to meet the PFS endpoint. Based on the conditional power, the DMC will recommend continued accrual into 1 of 4 zones.

Favorable Zone: Continue study as planned (N=124) to 95 events

Promising Zone: Increase sample size to 200 patients with cutaneous and non-cutaneous disease and follow to 170 events

Enrichment Zone: Enroll patients with cutaneous disease only (N=170) and follow to 110 events

Unfavorable Zone: Continue study as planned (N=124) and follow to 95 events

COMPARISON OF ADAPTIVE AND FIXED SAMPLE DESIGNS

- The TAPPAS adaptive enrichment design allows for sample size re-estimation to 200 AS patients or enrichment of 100 additional cutaneous AS patients based on conditional power determined at the interim analysis.
- Compared to a fixed sample size design of 200 patients, TAPPAS maintains > 80% power and provides for smaller trial size and shorter duration at the hazard ratio of 0.55 for both cutaneous and non-cutaneous patients.
- Compared to a fixed sample design of 200 patients, TAPPAS provides for greater power, smaller trial size and shorter duration in the case of activity only in cutaneous patients.
- TAPPAS maintains > 80% power in the favorable, promising and enrichment zones at the hazard ratio of 0.55 for the cutaneous subgroup even with larger hazard ratios in the non-cutaneous subgroup.
- Type 1 error (two-tailed alpha of 0.05) is preserved through adaption of the method of Jenkins et al (2011).

SUMMARY

- Based on the results from Phase 1b/2 trial, the combination of TRC105 and pazopanib was well tolerated and was active in patients with AS.
- The pivotal TAPPAS trial is enrolling now and will include approximately 40 sites in the US and Europe.
- In a rare disease, a trial that adapts the sample size and patient population, based on interim data from the trial itself, is preferable to a larger 200 patient fixed sample trial.
- TAPPAS trial design details are at https://clinicaltrials.gov/show/NCT02979899.

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