TRAXAR Study: A Randomized Phase 2 Trial of Axitinib and TRC105 versus AXitinib Alone in Patients with Advanced or Metastatic Renal Cell Carcinoma (mRCC)

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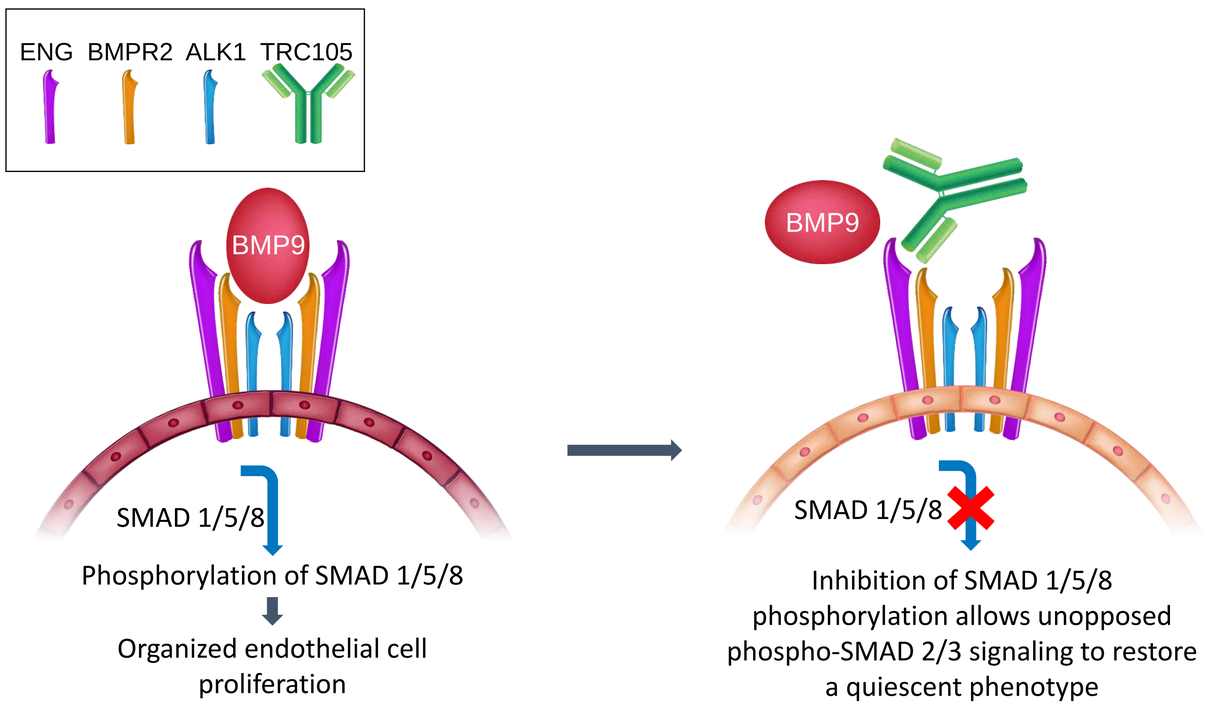
INTRODUCTION

- Endoglin is a membrane receptor required for angiogenesis (Li 1999) that is highly expressed by proliferating endothelial cells in solid tumors (Seon 2011), and also expressed on renal carcinoma stem cells (Bussolati 2008)
- 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 (KD = 5 pM) that inhibits angiogenesis (Nolan-Stevaux 2012) and potentiates the activity of VEGF inhibitors in preclinical models, and causes telangiectasia and increased serum VEGF concentrations at its recommended Phase 2 dose (RP2D) (Rosen 2012, Gordon 2014)
- Telangiectasia, a characteristic finding of the Osler-Weber-Rendu syndrome, is observed routinely at the recommended Phase 2 dose and immunogenicity is rare (Rosen 2012, Gordon 2014)



STUDY RATIONALE

- Axitinib is an oral VEGF receptor tyrosine kinase inhibitor (VEGFR TKI) that inhibits multiple receptor tyrosine kinases including VEGFR-1, VEGFR-2, and VEGFR-3. Axitinib is approved for the treatment of RCC with an overall response rate of 11% by RECIST 1.1 and progression free survival (PFS) of 4.8 months following treatment with one prior VEGFR TKI
- TRC105 combined safely with bevacizumab, sorafenib, and pazopanib in separate Phase 1/2 studies and demonstrated anti tumor activity (Gordon 2014, Duffy 2015, Attia 2015)
- By targeting a non-VEGF pathway that is upregulated following VEGF inhibition, TRC105 has the potential to complement axitinib in patients with RCC

PHASE 1b CONCLUSIONS

- Phase 1b enrolled 18 patients and assessed the safety and tolerability of TRC105 + axitinib in advanced RCC
- TRC105 dose escalation proceeded from 8 mg/kg (n=3) to 10 mg/kg (n=15) without dose limiting toxicity
- TRC105 at its RP2D of 10 mg/kg was well tolerated with axitinib in renal cell carcinoma patients
- Adverse events characteristic of each drug were not increased in frequency or severity when the two drugs were administered concurrently, and most commonly included epistaxis, headache, fatigue, diarrhea, and gingival bleeding
- Partial response (PR) by RECIST 1.1 occurred in 5 of 17 (29%) patients who progressed on prior VEGFR TKI, 4 of which were in the fourth line setting. None of the RECIST responders had a PR to prior VEGFR TKI treatment. PR by modified Choi criteria occurred in 10 of 17 (59%) patients
- Improved activity was seen in clear cell (8 of 12 patients with modified Choi responses, including 4 partial responses by RECIST 1.1)
- Median PFS (mPFS) overall was 11.3 months in all patients and also 11.3 months in patients with clear cell RCC by Kaplan-Meier
- Axitinib dose-escalation occurred to 7 mg BID in 22.2% of patients and to 10 mg BID in 11.1% of patients

PHASE 2 METHODS

- Randomized (1:1), multicenter study in patients with advanced or metastatic clear cell renal cell carcinoma
- Approximately 150 patients will be enrolled at approximately 50 sites
- Patients receive axitinib at a starting dose of 5 mg BID on a 28 day cycle with or without TRC105 at 10 mg/kg weekly
- Titration of axitinib is permitted after cycle 1
- Primary Objective: To estimate PFS by RECIST 1.1
- Secondary Objectives: To evaluate overall response, disease control rate, PK, immunogenicity, and circulating angiogenic biomarkers

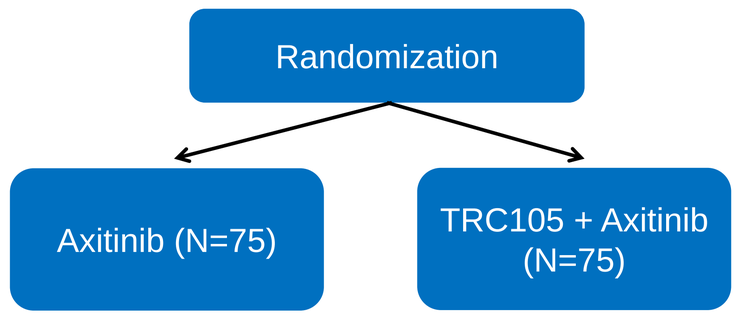
PHASE 2 ELIGIBILTY

- Advanced or metastatic renal cell carcinoma with a clear cell component
- Progression on treatment with one and only one VEGF inhibitor (prior axitinib not allowed)
- Prior mTORi allowed
- Prior immunotherapy allowed
- ECOG ≤ 1

PHASE 2 STUDY DESIGN

PHASE 2: ENROLLING

- Randomized (N=150)
- 1° Endpoint: PFS
- Advanced or metastatic clear cell RCC
- Progression on 1 prior VEGF inhibitor
- 1 prior mTOR inhibitor allowed
- 1 prior immunotherapy allowed



SUMMARY

- TRC105 inhibits angiogenesis by competitively inhibiting BMP binding to endoglin
- Based on the results from Phase 1b, the combination of TRC105 and axitinib was well tolerated in patients with advanced renal cell carcinoma
- The combination of TRC105 and axitinib demonstrated encouraging preliminary signs of activity including RECIST 1.1 partial responses (29%) in patients that were prior non-responders and mPFS was more than double that expected for axitinib monotherapy
- Enrollment into Phase 1b is complete and the Phase 2 TRAXAR Study is actively enrolling at approximately 50 sites in the US and Europe
- TRAXAR study design details are at https://clinicaltrials.gov/show/NCT01806064

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