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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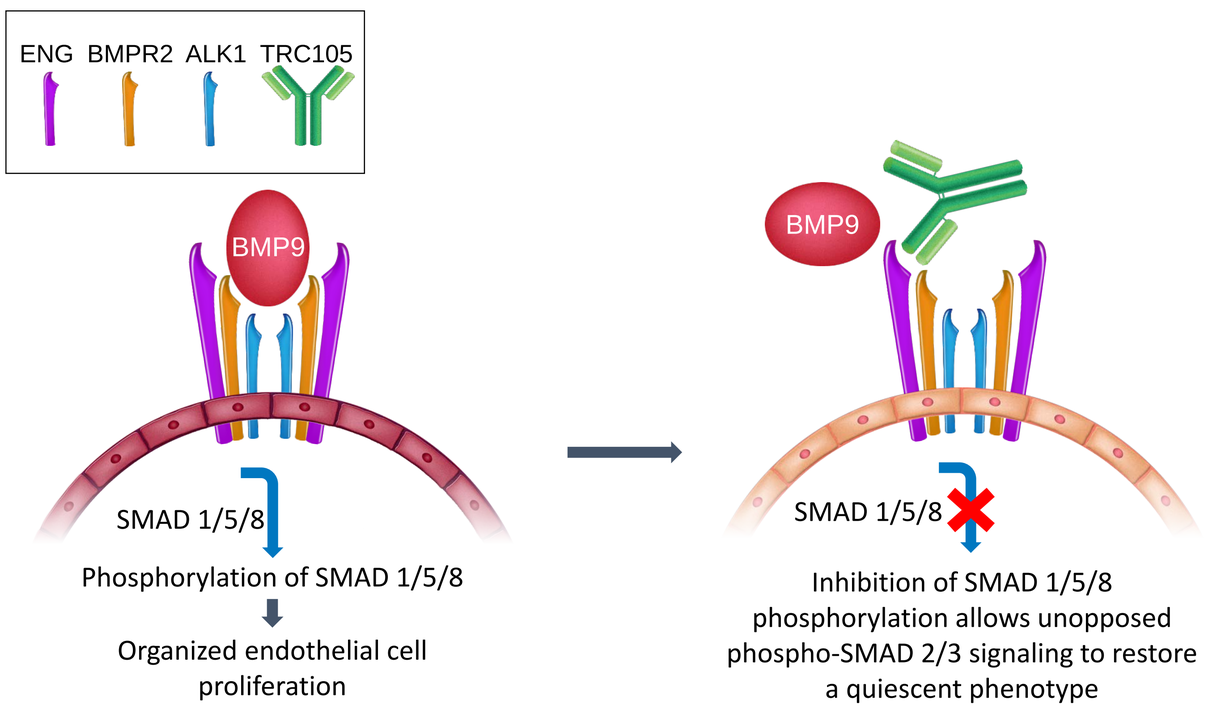
INTRODUCTION

- TRC105 is a chimeric IgG1 anti-endoglin monoclonal antibody with high avidity (K_D = 5 pM) that inhibits angiogenesis by competitively inhibiting bone morphogenic protein (BMP) binding to endoglin (Nolan-Stevaux 2012) that also mediates ADCC
- 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)
- Endoglin heterozygosity is a cause of the Osler-Weber-Rendu syndrome that results in telangiectasia and is associated with improved cancer survival (Duarte 2013)
- Endoglin expression is up-regulated by hypoxia in response to VEGF inhibition (Bockhorn 2003, Davis 2004) and TRC105 potentiates the activity of VEGF inhibitors in preclinical models
- The recommended phase 2 dose (RP2D) of TRC105 given as a single agent or when given with bevacizumab is 10 mg/kg by weekly intravenous infusion. TRC105 treatment is not associated with hypertension or proteinuria
- 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 overall was 8.4 months in all patients and 9.6 months in patients with clear cell RCC by Kaplan-Meier
- Axitinib dose-escalation occurred to 7 mg BID in 23.5% of patients and to 10 mg BID in 5.9% 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 30 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

Randomization

- Axitinib (N=75)
- TRC105 + Axitinib (N=75)

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 in patients that were prior non-responders and doubling of the PFS expected with axitinib as a single agent
- Enrollment into Phase 1b is complete and the Phase 2 TRAXAR Study is actively enrolling at approximately 30 sites in the US.
- TRAXAR study design details are at https://clinicaltrials.gov/show/NCT01806064

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