A Phase 1b Dose-Escalation Study of TRC105 (anti-Endoglin Antibody) in Combination with Axitinib in Patients with Metastatic Renal Cell Carcinoma (mRCC)

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INTRODUCTION

• TRC105 is a chimeric IgG1 anti-endothelial monomeric antibody with high avidity (Kd = 5 µM) that inhibits angiogenesis by competitively inhibiting bone morphogenetic protein (BMP) binding to endoglin (Choueiri 2012).
• Endoglin is a membrane receptor required for angiogenesis (Li 1999) that is highly expressed by proliferating endothelial cells in solid tumors (Gordon 2014, Duffy 2015).

• Reduced endoglin expression is associated with the Osher-Weber-Randall syndrome that results in telangiectasia and is associated with improved cancer survival (Duarte 2008).
• Telangiectasia, a characteristic finding of the Osher-Weber-Randall syndrome, is observed routinely at the recommended phase 2 dose 25 mg/kg and immunochemistry is very (Rosen 2012, Gordon 2014).

STUDY RATIONALE

• Axitinib is an oral VEGFR-2 tyrosine kinase inhibitor (VEGFR TKI) that inhibits multiple receptor tyrosine kinases including VEGFR-1, VEGFR-3, and PDGFR-α.
• 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 7 months following treatment with prior VEGFR TKI.
• Axitinib is combined safely with bevacizumab and with sorafenib in separate Phase 1/2 studies and demonstrated anti tumor activity (Davis DW, Cancer Research 64:4601, 2004).

• By targeting a non-VEGF pathway that is upregulated following VEGF inhibition, TRC105 has the potential to complement axitinib in patients with RCC.

RESULTS

• SUMMARY OF EFFICACY

- PRIOR THERAPY - Axitinib is randomized to Early or Late Cohort (3:1) with a median starting dose of 5 mg p.o. BID in 5.9% of patients who progressed on axitinib immediately prior to study entry.
- RECIST 1.1: 61/98 (62%) patients achieved partial or complete response when the two drugs were administrated together (Choueiri 2015).
- RECIST 1.1 PFS of axitinib in the AXIS trial following one prior VEGFR TKI (Beavis et al. Cancer 25, 2013) was 11.3 months (ccRCC).

• Phase 1b Dose-Escalation Study of TRC105 (anti-Endoglin Antibody) in Combination with Axitinib in Patients with Metastatic Renal Cell Carcinoma (mRCC) (NCT01806064)

• TRC105 dose escalation proceeded from 8 mg (n=8) to 10 mg (n=10) to 15 mg (n=11) without dose limiting toxicity.
• TRC105 at RP2D of 10 mg was well tolerated with axitinib in renal cell carcinoma patients.
• Axitinib dose escalation to 10 mg was possible with the RP2D of TRC105.

• The most common adverse events were generally low grade and included diarrhea, nausea, fatigue, headache, asthenia, and pruritus.
• Adverse events characteristic of each individual drug were not increased in frequency or severity when the two drugs were administrated together.

• Overall, the most common adverse events were generally maintained at the continuous concentrations were maintained continuously at the third dose level.
• TRC105 and axitinib demonstrated encouraging preliminary signs of activity including RECIST partial responses (29%) in patients who were prior non-responders and longer TRPs than expected with axitinib as a single agent.
• A multicenter randomized Phase 2 trial of axitinib +/- TRC105 is ongoing at the time that 150 patients in the US at approximately 25 sites.

Most Common (n = 2) and all Grade 3 and Above TRC105 Possibly Drug Related Adverse Events by Preferred Term and Possibly By Drug

REFERENCES

• Busolotti B, FASER 23:2639-2705, 2008
• Davis CH, Cancer Research 64:4601-2004
• Duffy AG, JNCI 2011, Abstract #293
• Li D, Science 284:1534-1537, 1999
• Ngage-Stevaux G,EUROS Onc 45001, 2012
• Rosen L, Clinical Cancer Research 18:4820-2013
• Seon BK, Current Drug Delivery 8:135, 2011

All patients have been assessed for response by either investigator or central reader. Of 105 patients who received TRC105, 29% (20) showed RECIST partial response (PR) with a median duration of 19 weeks. Patients who had prior VEGFR TKI therapy that resulted in PR showed a significantly increased response to TRC105 combination. The median duration of PFS was 11.3 months. Approximately 70% of patients who achieved RECIST partial response proceeded to full dose axitinib (10 mg). The median duration of PFS for patients who achieved RECIST partial response was 11.3 months.

• Table shows descriptive statistics and proportions of TRC105 Drug Related Adverse Events (n = 105) with axitinib +/- TRC105. A complete list of demographic characteristics is provided in Table S1. A complete description of adverse events is provided in Table S2. A complete list of adverse events with frequency greater than or equal to 10% is provided in Table S3. A complete list of adverse events with frequency greater than or equal to 15% is provided in Table S4. A complete list of adverse events with frequency greater than or equal to 20% is provided in Table S5. A complete list of adverse events with frequency greater than or equal to 25% is provided in Table S6. A complete list of adverse events with frequency greater than or equal to 30% is provided in Table S7. A complete list of adverse events with frequency greater than or equal to 35% is provided in Table S8.

• FILED Dose by Level (mg)

• FIGURE 1: When the two drugs were administrated together.

• FIGURE 2: Overall, the most common adverse events were generally maintained at the continuous concentrations were maintained continuously at the third dose level.

• FIGURE 3: TRC105 and axitinib demonstrated encouraging preliminary signs of activity including RECIST partial responses (29%) in patients who were prior non-responders and longer TRPs than expected with axitinib as a single agent.

• FIGURE 4: A multicenter randomized Phase 2 trial of axitinib +/- TRC105 is ongoing at the time that 150 patients in the US at approximately 25 sites.

• FIGURE 5: Study design is shown in Figure 5. Will enroll 150 patients in the US at approximately 25 sites.

• FIGURE 6: In addition to expected toxicities, patients who had prior VEGFR TKI therapy that resulted in PR showed a significantly increased response to TRC105 combination.

• FIGURE 7: The median duration of PFS was 11.3 months. Approximately 70% of patients who achieved RECIST partial response proceeded to full dose axitinib (10 mg). The median duration of PFS for patients who achieved RECIST partial response was 11.3 months.

• FIGURE 8: Safety data is shown in Figure 8. Table shows descriptive statistics and proportions of TRC105 Drug Related Adverse Events (n = 105) with axitinib +/- TRC105. A complete list of demographic characteristics is provided in Table S1. A complete description of adverse events is provided in Table S2. A complete list of adverse events with frequency greater than or equal to 10% is provided in Table S3. A complete list of adverse events with frequency greater than or equal to 15% is provided in Table S4. A complete list of adverse events with frequency greater than or equal to 20% is provided in Table S5. A complete list of adverse events with frequency greater than or equal to 25% is provided in Table S6. A complete list of adverse events with frequency greater than or equal to 30% is provided in Table S7. A complete list of adverse events with frequency greater than or equal to 35% is provided in Table S8.

• FIGURE 9: The most common adverse events were generally low grade and included diarrhea, nausea, fatigue, headache, asthenia, and pruritus.

• FIGURE 10: Adverse events characteristic of each individual drug were not increased in frequency or severity when the two drugs were administrated together.

• FIGURE 11: Overall, the most common adverse events were generally maintained at the continuous concentrations were maintained continuously at the third dose level.

• FIGURE 12: TRC105 and axitinib demonstrated encouraging preliminary signs of activity including RECIST partial responses (29%) in patients who were prior non-responders and longer TRPs than expected with axitinib as a single agent.

• FIGURE 13: A multicenter randomized Phase 2 trial of axitinib +/- TRC105 is ongoing at the time that 150 patients in the US at approximately 25 sites.

• FIGURE 14: Study design is shown in Figure 14. Will enroll 150 patients in the US at approximately 25 sites.