TRC105 (Anti-endoglin Antibody) in Combination with Bevacizumab (BEV) and as a Single Agent for Platinum Resistant Ovarian Cancer


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INTRODUCTION

• TRC105 is a chimeric IgG1 anti-endoglin monoclonal antibody with very high avidity (Kd < 5 pM)

• Endoglin is a membrane receptor required for angiogenesis (Li 1999) that is highly expressed by proliferating endothelial cells in solid tumors (Seon 2011). Endoglin is required for angiogenesis and its expression is up-regulated by hypoxia in response to VEGF inhibition (Bockhorn 2003, Davis 2004).

• High tumor microvessel density as measured by endothelial immunohistochemistry correlates with poor prognosis across more than 10 solid tumor types including ovarian cancer

• Reduced endoglin expression is associated with the Oster-Wirbel-Werner syndrome that results in telangiectasia and is associated with improved cancer survival (Duarte 2013)

• TRC105 inhibits VEGF-driven and sVEGF-driven angiogenesis (Novel-Stevaux 2012) and mediates ADCC

• TRC105 potentiates the activity of VEGF inhibitors in preclinical models

• The MTD of TRC105 given as a single agent was 10 mg/kg by weekly intravenous infusion. Dose escalation was limited by anemia, an on-target effect of TRC105 treatment, without significant hypertension or proteinuria. Telangiectasia, a characteristic finding of endoglin receptor modulation, were observed routinely at the MTD and immunogenicity was not observed (Rossen 2012)

METHODS

• Patients with advanced metastatic ovarian cancer, who were treated with escalating doses of IV TRC105 (3, 6, 8 or 10 mg/kg/wk) plus BEV at 15 mg/m² q3w or 10 mg/m² q4w (n=11) in a phase 1b trial were compared with patients with advanced metastatic ovarian cancer, who were treated with 10 mg/m² wk TRC105 as a single agent (n=23) in a phase 2 trial

• Patients were assessed for safety, PK, immunogenicity and response

• Key exclusion criteria included: Previous use of VEGF or VEGFR inhibitors, or treatment with non-VEGF inhibitors in the past 4 weeks

• Key inclusion criteria included: Prior Bevacizumab therapy within 4 weeks, major surgery within 4 weeks, and major bleeding within 6 months

RESULTS

• Target TRC105 serum concentrations were achieved in all patients who received TRC105 at 10 mg/kg/wk as a single agent or combined with BEV

• Immunogenicity was not observed in any patient who received TRC105 as a single agent or combined with BEV

• TRC105 was well tolerated as a single agent at the recommended phase 2 dose of 10 mg/kg/wk

• In the combination study, dose escalation to the recommended phase 2 dose of both drugs was well tolerated when the initial TRC105 dose was split over two days to limit the frequency of headaches

• The concurrent administration of BEV and TRC105 did not otherwise potentiate known toxicities of TRC105 or BEV

• Mucocutaneous telangiectasia, a marker of TRC105 target modulation, was observed at higher frequency with the combination of the two drugs (46% vs 35%, P=0.15)

• In the combination study, antitumor activity (radiographic responses and tumor marker reductions) was observed in patients who progressed on prior BEV or VEGF TKI therapy

• Reductions in tumor volume 25% were seen in 7 of 9 evaluable patients (78%) treated with the combination, one of whom had a partial response by RECIST 1.1

• Reductions in tumor volume 25% were seen in 8 of 9 patients who received prior BEV or VEGF TKI, including three patients who remained on TRC105 + BEV treatment for longer than the most recent prior treatment with BEV or VEGF TKI therapy

OBJECTIVES

• To describe the safety and efficacy of intravenous TRC105 given as a single agent when combined with BEV in patients with advanced metastatic ovarian cancer

• To evaluate pharmacokinetics and immunogenicity

• To determine maximum tolerated dose of TRC105 when combined with BEV

• To determine maximum tolerated dose of BEV when combined with TRC105

• To determine maximum tolerated dose of the combination of TRC105 + BEV

• To determine the best overall response rate of TRC105 + BEV

• To determine the best overall response rate of BEV and TRC105 as single agents

• To determine the best overall response rate of the combination of TRC105 + BEV

• To determine the overall response rate of the combination of TRC105 + BEV

• To determine the overall response rate of single agents

• To determine the duration of objective response in patients treated with TRC105 + BEV

• To determine the duration of objective response in patients treated with single agents

SUMMARY & CONCLUSIONS

• TRC105 at 10 mg/kg weekly was well tolerated with and without BEV at 10 mg/kg q3w in patients with advanced platinum resistant ovarian cancer

• In the combination study, antitumor activity (radiographic responses and tumor marker reductions) was observed in patients who progressed on prior BEV or VEGF TKI, and these patients had longer time on treatment with BEV + TRC105 than on the prior BEV or VEGF TKI containing regimen

• Further study of TRC105 with BEV in advanced ovarian cancer is justified

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