A Phase 2 Trial of TRC105 with Bevacizumab for Bevacizumab Refractory Glioblastoma


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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 upregulated following VEGF inhibition
• 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 (Quante 2014)

• TRC105 is a chimeric IgG1 endoglin monoclonal antibody with high avidity (KD = 5 nm) that inhibits angiogenesis (Nolan-Steele 2012) and potentiates the activity of VEGF inhibitors in preclinical models, and causes telangiectasia and increased serum VEGF concentrations at the recommended Phase 2 dose (RPP2; Rose, 2014; Gordon 2014)
• TRC105 combined safely and demonstrated anti-tumor activity with bevacizumab, sorafenib, and pazopanib in selected Phase 1/2 studies (Gordon 2014, Dufly 2015, Czucei 2015, Attia 2015)
• The RPDR of TRC105 was 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

STUDY RATIONALE

• Antiangiogenic strategies are of interest in treating glioblastoma multiforme (GBM) due to the vascular nature of these tumors
• Bevacizumab is approved for the treatment of GBM following chemoradiation
• GBM patients who progress on bevacizumab have poor survival
• TRC105 dosed in combination with bevacizumab reduced tumor volume in colorectal cancer and ovarian cancer patients who progressed following prior bevacizumab treatment (Gordon 2014)
• By targeting a non-VEGF pathway that is essential for angiogenesis, TRC105 has the potential to complement VEGF inhibitors and advance GBM treatment

STUDY DESIGN

Part 1 (n=6; TRC105 single agent)
• Open-label, single arm trial
• Histologically confirmed glioblastoma
• Progression on chemotherapy
• Up to 3 prior recurrences
• 1’ End point: mTTP
• The trial initially assessed the activity of TRC105 as a single agent
• Due to the lack of activity of TRC105 as a single agent, the trial was amended to assess the activity of TRC105 with bevacizumab in patients who progressed on prior bevacizumab treatment
• The primary endpoint for treatment with TRC105 and bevacizumab was overall survival (OS), with the null hypothesis being OS of 4.0 months and alternative hypothesis being OS of 7.0 months

Part 2 (n=16; TRC105 + bevacizumab)
• Open-label, single arm trial
• Histologically confirmed glioblastoma
• Progression on chemotherapy
• Up to 3 prior recurrences
• 1’ End point: OS

RESULTS

Most Common (n > 1) and at Grade 3 and Above TRC105 Related Adverse Events by Preferred Term and Grade (TRC 105 + Bevacizumab)

<table>
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<tr>
<th>Most Common (n &gt; 1) and at Grade 3 and Above TRC105 Related Adverse Events by Preferred Term and Grade (TRC 105 Single Agent)</th>
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| Table above lists frequencies and percentages of TRC105 Related Adverse Events occurring in > 1 patient or at Grade 3 or greater. Percentages are computed using the number of patients as the sample size on the denominator.
| TRC105 was well tolerated in patients with GBM when given as a single agent or with bevacizumab
| Adverse events characteristic of each drug were not increased in frequency or severity during concurrent dosing
| Intracranial hemorrhage was not observed following treatment with TRC105 and bevacizumab
| Fifteen patients were evaluable for efficacy of the combination. Median overall survival (OS) was 5.75 months, which exceeded the historic OS of 4.0 months in a similar patient population treated with bevacizumab as a single agent (Magnuson 2014)
| No responses were seen by RANO criteria and median PFS was 1.81 months (95% CI: 1.25, 2.07)

REFERENCE

Bevacizumab is approved for the treatment of GBM following VEGF therapy
Bevacizumab was well tolerated in patients with GBM when given as a single agent or with bevacizumab
Adverse events characteristic of each drug were not increased in frequency or severity during concurrent dosing
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