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

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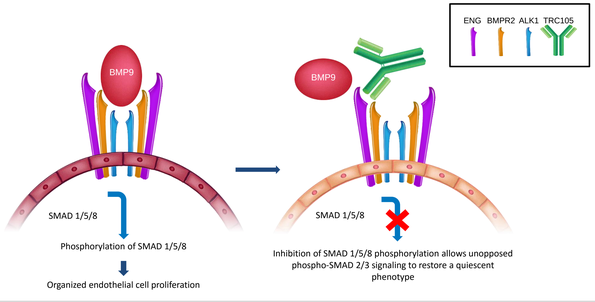
INTRODUCTION

- 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 (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)
- TRC105 combined safely and demonstrated anti-tumor activity with bevacizumab, sorafenib, axitinib and pazopanib in separate Phase 1/2 studies (Gordon 2014, Duffy 2015, Choueiri 2015, Attia 2015)
- The 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



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
- Histologically confirmed glioblastoma
- Progression on chemoradiation
- Progression on bevacizumab or other anti-VEGF therapy
- Up to 3 prior recurrences
- 1° Endpoint: mTTP

Part 2 (n=16; TRC105 + bevacizumab)
- Open-label, single arm
- Histologically confirmed glioblastoma
- Progression on chemoradiation
- Progression on bevacizumab therapy
- Up to 3 prior recurrences
- 1° Endpoint: OS

- 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
- 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

RESULTS

Baseline Patient Characteristics (N=22)	
Age	• Median: 54.5 • Range: 31 - 70
Gender	• Male: 16 • Female: 6
# Prior Therapies	• Median: 3 • Range: 1 - 5
Histology	• Glioblastoma: 20 • Astrocytoma: 1 • Giant Cell Glioblastoma: 1

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

	Maximum Grade					Total N = 16	
Preferred Term	Gr 1	Gr 2	Gr 3	Gr 4	Gr 5	n	Percent
Epistaxis	9	0	1	0	0	10	63%
Fatigue	4	4	1	0	0	9	56%
Headache	6	0	1	0	0	7	44%
Decreased appetite	2	1	0	0	0	3	19%
Flushing	3	0	0	0	0	3	19%
Gingival bleeding	3	0	0	0	0	3	19%
Rash	3	0	0	0	0	3	19%
Anemia	1	1	0	0	0	2	13%
Dermatitis acneform	2	0	0	0	0	2	13%
Infusion related reaction	0	2	0	0	0	2	13%
Weight decreased	2	0	0	0	0	2	13%
Embolism	0	0	1	0	0	1	6%
Periorbital cellulitis	0	0	1	0	0	1	6%
Sinusitis	0	0	1	0	0	1	6%

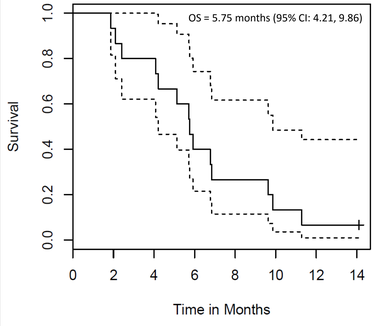
Most Common (n > 1) and all Grade 3 and Above TRC105 Related Adverse Events by Preferred Term and Grade (TRC105 Single Agent)

	Maximum Grade					Total N = 6	
Preferred Term	Gr 1	Gr 2	Gr 3	Gr 4	Gr 5	n	Percent
Fatigue	1	2	0	0	0	3	50%
Headache	1	2	0	0	0	3	50%

Table shows frequencies and percentages of TRC105 Drug-related Adverse Events occurring in > 1 patient or at Grade 3 or above in the safety population.
Percentages are computed by using the number of patients in the safety population as the denominator.
Adverse Events are coded by using MedDRA dictionary version 14.1.
If more than one event of a type is recorded for a patient, the patient is only counted once at the highest grade.

RESULTS

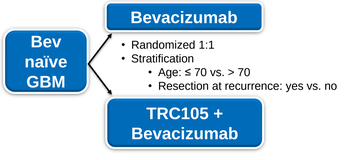
Kaplan-Meier Survival Curve (including 95% CI) of Bevacizumab Refractory Glioblastoma Patients Treated with TRC105 + Bevacizumab



- 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 (95% CI: 4.21, 9.86), 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)

CONCLUSION

- The combination of TRC105 and bevacizumab was well tolerated in bevacizumab refractory GBM patients
- OS of 5.75 months was observed in bevacizumab refractory patients treated with TRC105 and bevacizumab, which exceeded the historic OS of 4.0 months in a similar patient population treated with bevacizumab as a single agent
- Single agent TRC105 was not active in bevacizumab refractory GBM, possibly as a result of increased VEGF expression which has been noted in other tumor types treated with TRC105 as a single agent (Karzai 2015)
- Treatment with the combination of TRC105 and bevacizumab compared to single agent bevacizumab is currently being evaluated in bevacizumab naïve GBM patients in a randomized Phase 2 trial (NCT01648348)



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