# Updated Results from a Prospective, Randomized Phase 2 Study in Patients with First Relapse of High-grade Astrocytoma Using TVB-2640 in Combination with Avastin versus Avastin Alone

Brandon Konkel, Laura Caflisch, Enriqe Diaz Duque, and Andrew Brenner

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

Cancer Prevention & Research Institute of Texas

## Introduction

Standard of care for glioblastoma multiforme (GBM) is surgical resection followed by temozolomide, with Avastin given at relapse.[1] Responses to Avastin remain brief (historically with median PFS 17 weeks, median OS 35.5 weeks).[2,3] Resistance may involve overexpression of Fatty Acid Synthase (FASN), inhibitors of which may cause changes in membrane-bound receptors due to FASN's critical role in palmitoylation.[4] Our institution is conducting a phase 2 study of Avastin with or without the FASN inhibitor TVB-2640 in patients with GBM in first relapse.

## Study Design

- Prospective, randomized, phase 2 study of Avastin with or without TVB-2640 in patients with GBM in first relapse.
- Key eligibility criteria: age ≥ 18, ECOG 0 to 2, GBM progression following standard combined modality treatment, Avastin naïve, intact renal/hepatic/hematopoietic function.
- Primary end point: progression free survival (PFS).
- Secondary End Points: Survival, Adverse events per NCI - Common Terminology Criteria for Adverse Events version 4.03.
- Exploratory End Point: Metabolic change analysis of tumor tissue by MR-Spectroscopy and exosomal profiling.

## Patients and Methods

- Patients in arm 1 receive Avastin every 2 weeks in combination with TVB-2640 100mg/m2 daily, from day 1 until day 28 of the first cycle.
- Patients in arm 2 receive Avastin alone every 2 weeks.
- MR-Spectroscopy (MRS) and serum sampling for exosome analysis are obtained on all patients at day 1 and 28 of first cycle.
- Starting on cycle 2 day 1, all patients converge to a single arm and continue to receive Avastin in combination with TVB-2640 dosed at 100mg/m2 daily for up to 6 cycles.
- A total sample size of 24 patients will provide 90% power to detect a 4 month difference in PFS (3 months for Avastin alone (historic controls) versus 7 months for TVB-2640 in combination with Avastin, (i.e., a hazard ratio of 0.43) using a one-sided log-rank test with alpha=0.1.

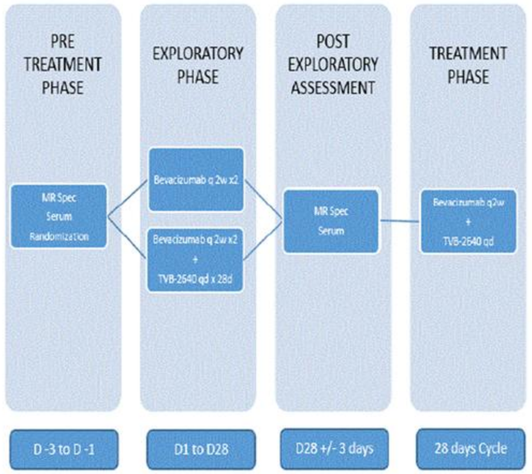


**Figure 1: Schema**

| Adverse Event | Number of patients reporting (%) |
|---|---|
| Palmar-Plantar Erythrodysesthesia | 12 (63%) |
| Mucositis/Stomatitis | 12 (63%) |
| Alopecia | 2 (10%) |
| Pruritis, hypomagnesemia, dry eye, papular rash on trunk, LE edema, flatulence, conjunctivitis, tearing of the eye, myalgias, diarrhea | 1 each (5% each) |

**Table 1: Adverse events**
ADR for 19 patients, current to 10/3/18. All events have been grade 1.

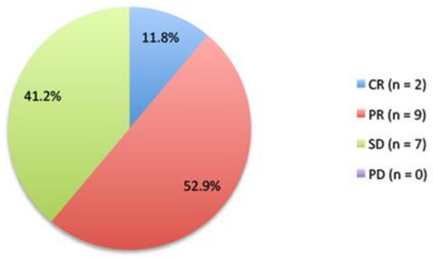


**Figure 2: Best response by RANO criteria**
Response data for 18 patients was available as of 11/07/18. 2 patients achieved a complete response, 9 achieved a partial response, and 6 achieved stable disease. No patients had best response of progressive disease.

## Results

22 patients have enrolled to date. 2 failed screening. 11 came off study (6 progressed, 3 for clinical decline or death, 2 withdrew consent). 9 remain active. Median time to best response was 54 days. Median PFS was 175 days (25 weeks); median OS was 293 days (41.9 weeks). One of the patients who died had experienced an intracerebral hemorrhage thought unrelated to treatment; no treatment-associated grade 4 or higher events have occurred. One patient experienced grade 3 stomatitis attributed to treatment. PFS and OS data thus far are similar to or better than historical controls. Further data regarding biomarker analysis (exosome, MRS) is still being collected.

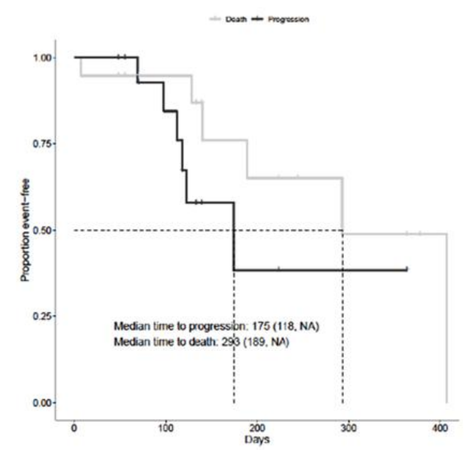


**Figure 3: Kaplan-Meier curves for progression and death**
Paired KM curves for progression and death in 19 patients censored to 11/07/18. Median time to progression was 175 days; median time to death was 293 days.

## Conclusion

The combination of TVB-2640 with Avastin appears to be well tolerated with only 1 report of a grade 3 reaction (mucositis) and no grade 4 or higher reactions attributable to treatment. Enrollment will continue with planned completion in early 2019.

## References

(1) "National Comprehensive Cancer Network Guidelines." Central Nervous System Cancers, 20 Mar. 2018.
(2) Friedman HS, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol. 2009 Oct 1;27(28):4733-40. Epub 2009 Aug 31.
(3) BELOB: Taal W, et al. Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial. Lancet Oncol. 2014 Aug;15(9): 943-53. Epub 2014 Jul 15.
(4) Lee JE, Lim JH, Hong YK, Yang SH. High-Dose Metformin Plus Temozolomide Shows Increased Anti-tumor Effects in Glioblastoma In Vitro and In Vivo Compared with Monotherapy. Cancer Res Treat. 2018 Jan 10.