Updated Results from a Prospective Phase 2 Study in Patients with First Relapse of High-grade Astrocytoma Using TVB-2640 in Combination with bevacizumab

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Abstract

BACKGROUND: Standard of care for glioblastoma (GBM) is surgical resection followed by temozolamide, with bevacizumab (bev) given at relapse. Responses to bev remain brief; resistance may involve overexpression of Fatty Acid Synthase (FASN). Our institution is conducting a phase 2 study of bev with or without the FASN inhibitor TVB-2640 in patients with GBM in first relapse. METHODS: This is a prospective phase 2 study of bev with or without TVB-2640 in patients with GBM in first relapse. Primary end point is progression free survival (PFS). Inclusion criteria are: age ≥ 18, ECOG 0 to 2, GBM progression following standard combined modality treatment. Exploratory phase randomization is into 2 separate arms. Patients in arm 1 receive bev every 2 weeks in combination with TVB-2640. Patients in arm 2 receive bev alone every 2 weeks. MR-Spectroscopy (MRS) and serum sampling for exosome analysis will be obtained on all patients at day 1 and 28 of first cycle. Starting on cycle 2 day 1, all patients will converge to a single arm and continue to receive bev in combination with TVB-2640. A total sample size of 24 patients will provide 90% power to detect a 4 month difference in PFS (3-4 months for Bev alone (historic controls) versus 7 months for TVB-2640 in combination with Bev, (i.e., a hazard ratio of 0.43) using a one-sided log-rank test with alpha=0.1. RESULTS: We have enrolled 27 patients to date. 3 failed screening. 21 came off study (12 progressed, 5 for clinical decline or death, 4 withdrew consent); 3 are active, and 1 slot remains open. No grade 4 or higher treatment-related AEs have occurred. 95.2% of patients have achieved at least stable disease by Rano Criteria, with a 66.7% overall response rate (ORR). Median time to progression and median overall survival were 5.9 and 7.7 months, respectively. Further patient data, as well as biomarker analysis (exosome, MRS), is pending. CONCLUSIONS: The combination of TVB2640 with bev appears well tolerated. PFS6 is significantly improved over historical controls. The trial needs only one further patient to complete enrollment. (Clinical trial registry number: NCT03032484; NIH grant P30CA054174; TVB-2640 provided by 3-V Biosciences.)

Introduction

Standard of care for glioblastoma (GBM) is surgical resection followed by temozolomide, with bev given at relapse.[1] Responses to bev remain brief (historically with median PFS 3 months and median OS 8 months).[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 bev with or without the FASN inhibitor TVB-2640 in patients with GBM in first relapse.

Study Design

- Prospective phase 2 study of TVB-2640 in combination with bev in patients with GBM in first relapse.
- Key eligibility criteria: age ≥ 18, ECOG 0 to 2, GBM progression following standard combined modality treatment, bev 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 bev every 2 weeks in combination with TVB-2640 100mg/m2 daily, from day 1 until day 28 of the first cycle (Figure 1).
- Patients in arm 2 receive bev 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 bev 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 bev alone (historic controls) versus 7 months for TVB-2640 in combination with bev, (i.e., a hazard ratio of 0.43) using a one-sided log-rank test with alpha=0.1.

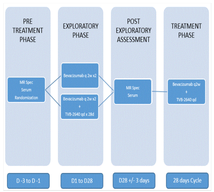

Figure 1: Schema

Results

27 patients have enrolled to date. 3 failed screening. 21 came off study (12 progressed, 5 for clinical decline or death, 4 withdrew consent). 3 remain active. One slot remains open. 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. CTCAE Grade 3 events included 3 cases of palmar-plantar erythrodysesthesia; 1 each of hypertension, stomatitis, optic neuritis, DVT, vomiting, and wound infection (Figure 2). Median time to best response was 54 days on a prior analysis. The ORR was 66.7% (Figure 3). Median PFS was 5.9 months (95% CI 4.0 to 11.9); median OS was 7.7 months (95% 5.1 to 14.1 months) (Figure 4). PFS thus far is significantly better than historical control (PFS6 in current trial = 0.463; BELOB Bev arm PFS6 = 0.16, p=0.01 by two-sided one-sample Z-test). Further data regarding biomarker analysis (exosome, MRS) is still being collected.

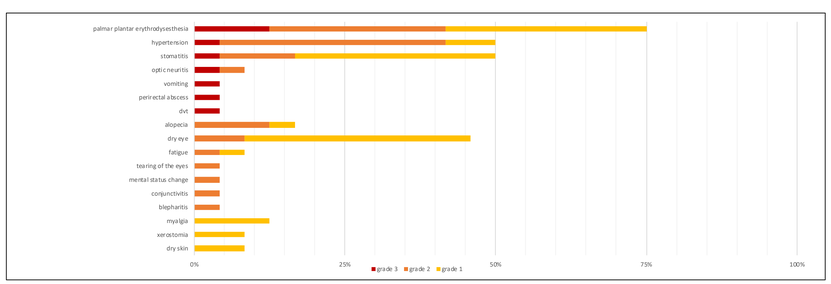

Figure 2: Adverse events
Includes patient's highest CTCAE grade definitely or possibly attributed to treatment. Grade 1 events with <5% incidence omitted for brevity. Current to 5/31/19.

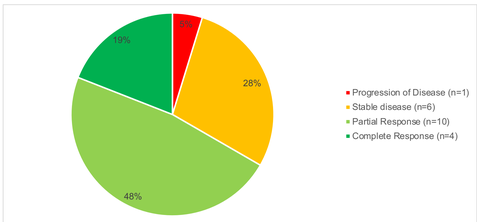

Figure 3: Best response by RANO criteria
Response data for 21 patients was available as of 5/31/19. Complete response = 4, partial response =10, 6 stable disease = 6, progression of disease only = 1. Not included: 2 patients came off study prior to RANO assessment, 1 still pending RANO assessment.

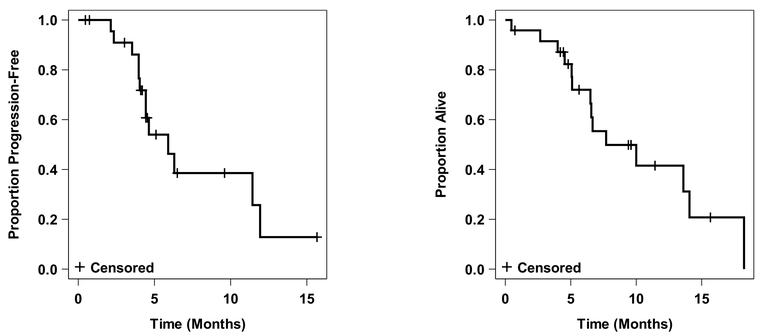

Figure 4: Kaplan-Meier curves for PFS (left) and OS (right)
KM curves for progression and death in 24 patients censored to 5/30/19. Median time to progression and median overall survival were 5.9 and 7.7 months, respectively.

Conclusion

The combination of TVB-2640 with bev appears to be well tolerated with no grade 4 or higher reactions attributable to treatment. The most common grade 3 reaction was palmar-plantar erythrodysesthesia in 12.5% of patients. PFS is thus far significantly better than historical control. Enrollment is nearly complete.

References

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(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.