

TVB-2640 with Bevacizumab in Relapsed High-grade Astrocytoma

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DISCLOSURE INFORMATION

I have no personal, professional or financial relationships which would constitute a conflict of interest.

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Introduction

- Glioblastoma (GBM, Grade IV astrocytoma) is the most common and devastating glioma with limited frontline options and no standard of care in the recurrent setting.
- Hypoxia has been implicated in the resistance of GBM to second-line anti-angiogenics such as bevacizumab.
- Our previous research has suggested that the degree of hypoxia in progressive GBM correlates with the presence of long chain fatty acids as assessed by metabolic profiling of tumors and sera.
- Fatty Acid Synthase (FASN) is a homodimeric enzyme which catalyzes the biosynthesis of palmitate in a NADPH-dependent fashion¹.
- Tumor cells have increased lipid requirements and therefore are more dependent on FASN catalysis of palmitate than normal cells².
- TVB-2640 is a potent and reversible inhibitor of the FASN as demonstrated by in vitro tumor models.
- TVB-2640 was recently tested in a phase 1 dose-escalation trial where 100mg/m² was the recommended phase II study dose³.

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- Therefore, we hypothesized that TVB-2640 plus bevacizumab would overcome acquired resistance and prolong progression-free survival (PFS) beyond historical controls^{4,5}.
- To this end we conducted a prospective single-center phase II study of patients with bevacizumab-naïve, glioblastoma in first relapse.
- Patients were randomized for the first month (cycle 1) to either TVB-2640 plus bevacizumab or bevacizumab alone for biomarker evaluation.
- Following this all patients received TVB-2640 (100mg/m² PO QD) plus bevacizumab (10mg/kg IV D1,15) until significant treatment-related adverse event (TRAE) or progressive disease.
- The study was designed to detect a doubling of PFS over historical control data for bevacizumab alone (3m), with 91.6% power and using a one-sided log-rank test with alpha = 0.1.

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Results

- 25 patients were enrolled over a 1.5-year period.
- The patients enrolled were balanced for sex and had a mean age of 61.
- Most were white (96%).
- IDH mutant %, MGMT meth %
- The most frequently reported AEs were palmar-plantar erythrodysesthesia (PPE) consistent with previous reporting and likely due to decreased sebum production.
- Hypertension (HTN), mucositis, dry eye, fatigue and skin infection were also frequently reported.
- Most AEs were grade 1 or 2.
- Grade 3 TRAEs occurred in PPE (4 events) as well as ALT elevation (1), deep vein thrombosis (1), HTN (1), mucositis, optic neuritis (1), perirectal abscess (1) and vomiting (1).
- There were no TRAE grade 4-5.

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Results

- The ORR was 65% (CR 20%, PR 45%).
- PFS6 was 47%.
- Statistically significant improvement in PFS6 ($p=0.01$) over historical single agent Bev⁴ (PFS6).
- OS6 was 66%, NS for OS.
- Favorable PFS compared to Bev/Lom⁵ (PFS6 47% v 28.5%) but did not reach significance ($p=0.15$).
- Exosome analysis of serum collected before and after C1 showed adequate purification and there were differences observed that we continue to explore.

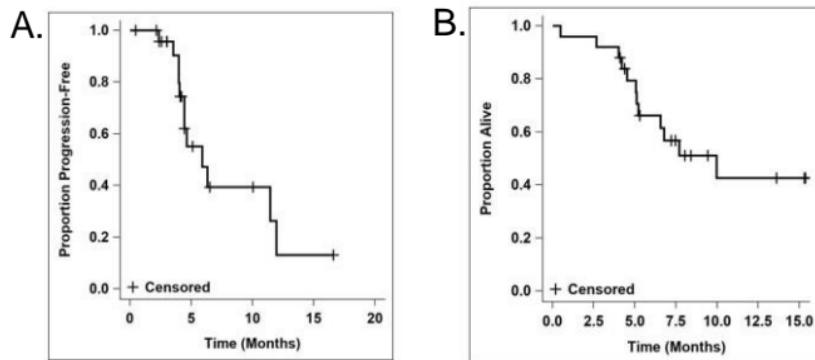


Figure 1. Kaplan-Meier plot of progression (A) and survival (B)

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Conclusions

- TVB-2640 is a well tolerated oral drug and can safely be combined with bevacizumab for the treatment of recurrent glioblastoma.
- The addition of TVB-2640 statistically improved progression free survival over bev monotherapy, and numerically trended toward prolonged progression compared to Bev/Lom.
- This study was powered as a pilot trial involving a small number of patients (n=25), and therefore these findings are preliminary and require further validation.
- The favorable safety profile and trend towards significance would indicate the utility of a larger multicenter trial.

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