COVER PAGE FOR PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official Study Title: A Phase 2 Investigator Initiated Study to Determine the Efficacy and Safety of TVB- 2640 in Combination with Bevacizumab in Patients with First Relapse of High Grade Astrocytoma

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TITLE: A Phase 2 Investigator Initiated Study to Determine the Efficacy and Safety of TVB- 2640 in Combination with Bevacizumab in Patients with First Relapse of High Grade Astrocytoma

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INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Protocol UTHSCSA CTMS# 16-0136 and will adhere to the study requirements as presented, including all statements regarding confidentially. In addition, I will conduct the study in accordance with current international conference on harmonization (ICH) guidance, Good Clinical Practice (GCP) guidance, the Declaration of Helsinki, US Food and Drug Administration (FDA) regulations and local IRB and legal requirements.

Name of Clinical Investigator: Andrew Brenner, MD, PhD

Institution: Mays Cancer Center

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Investigator Signature Date

ABBREVIATIONS

AE	Adverse Event
BISR	Biostatistics and Informatics Shared Resource
DSM	Data Safety Monitoring
DSMB	Data Safety Monitoring Board
DSMC	Data Safety Monitoring Committee
DSMP	Data Safety and Monitoring Plan
DSO	Data and Safety Officer
DQA	Director of Quality Assurance
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IIS	Investigator Initiated Protocol
IND	Investigational New Drug
IRB	Institutional Review Board
NCI	National Cancer Institute
QAD	Quality Assurance Division
PALS	Priority of Audit Level Score
PI	Principal Investigator
PRC	Protocol Review Committee
PRMS	Protocol Review and Monitoring System
PSD	Pharmacokinetic Sampling Department
SAE	Serious Adverse Event
UPIRSO	Unanticipated Problem Involving Risks to Subjects or Others
UTHSCSA	University of Texas Health Science Center at San Antonio

Contents

SYNOPSIS

Title of Study:

A Phase 2 Investigator Initiated Study to Determine the Efficacy and Safety of TVB-2640 in Combination with Bevacizumab in Patients with First Relapse of High Grade Astrocytoma.

Investigators:

PI: Andrew Brenner M.D., Ph.D.; Co-PI: Adolfo E. Diaz M.D.; Statistician: Joel Michalek Ph.D.

Study Center(s):

The trial will be conducted at the Mays Cancer Center in San Antonio, TX

Concept and Rationale:

The mainstay of treatment for GBM remains surgical removal followed by combined Chemotherapy with temozolomide and radiation therapy. Median and 2-year survival rates for patients receiving temozolomide were increased by 2.5 months (12.1 to 14.6 months) and 16.1% (10.4% to 26.5%), respectively. (4). However, once a patient progresses standard front-line therapy, prognosis is very poor and new therapies are needed. In the era of targeted therapies, clinical studies have demonstrated anti-tumor activity in patients treated with anti-angiogenic agents such as with bevacizumab, a recombinant human monoclonal antibody against VEGF receptor. Bevacizumab was FDA approved in 2009 as treatment for recurrent Glioblastoma following failure of radiation therapy and temozolomide, although the responses are not very long-lasting. (28). Median progression-free survival (PFS) on the first bevacizumab-containing regimen was 124 days (95% confidence interval (CI), 87–154 days); 6-month (6M)-PFS was 33%. (2)

In an effort to find alternate ways of treatment that might give the patients more durable responses, investigators have looked at the biologic behavior of GBM and have detected the presence of mobile lipids by proton magnetic resonance spectroscopy (1H MRS) in animal and human tumors, in cultured cells, in biopsies and *in vivo* (22). Moreover, it has been proposed that these lipid droplets could represent a temporary storage compartment (final storage compartment if the tissue does not recover) of fatty acids in the form of triglycerides. Under hypoxic or ischemic conditions, beta oxidation of fatty acids would cease.(1)

The relevance of the above findings was such that the research community started to look at the relation between fatty acids and catalytic enzymes at cellular level. Fatty acid synthase (FASN) is a homodimeric and multi-functional enzyme that catalyzes the biosynthesis of palmitate in a NADPH- dependent reaction. Published studies have confirmed that many solid and hematopoietic tumors overexpress fatty acid synthase (FASN), including non-small cell lung, breast, ovarian, prostate, colon, pancreatic cancers, non-Hodgkin lymphoma as well as gliomas (34).

TVB-2640 emerges as a novel agent that selectively inhibits FASN, enhancing tumor growth inhibition and viability of tumor cells by inducing tumor cell apoptosis via multiple mechanisms of action, both *in vitro* and *in vivo*, while having minimal effects on non-tumor cells. TVB-2640 has been tested in murine models and lately in a phase 1, international, multi-center, open-label, dose-escalation study where the MTD was established and recommended for further investigation in Phase 2. (36)

Since the progression free survival is not very long lasting on bevacizumab for patients with relapsed high-grade glioma; this phase 2 study will evaluate the potential effectiveness and safety of TVB-2640 in combination with bevacizumab.

Primary Objective(s):

To determine if the progression-free survival of patients with High Grade Astrocytoma who are treated with TVB-2640 in combination with bevacizumab is superior to treatment with bevacizumab alone.

Secondary Objective(s):

To evaluate the safety of TVB-2640 in combination with bevacizumab in patients with High Grade Astrocytoma.

Exploratory Objective:

To determine the extent by which TVB-2640 is able to penetrate the blood brain barrier where it might have the opportunity to affect tumor tissue metabolism.

Primary Endpoint(s):

Time from study enrollment to the first occurrence of relapse, progression, or death from any cause, or until last contact (if no event occurs).

Secondary Endpoint(s):

Adverse events and serious adverse events, graded according to NCI - Common Terminology Criteria for Adverse Events (CTCAE version 4.03).

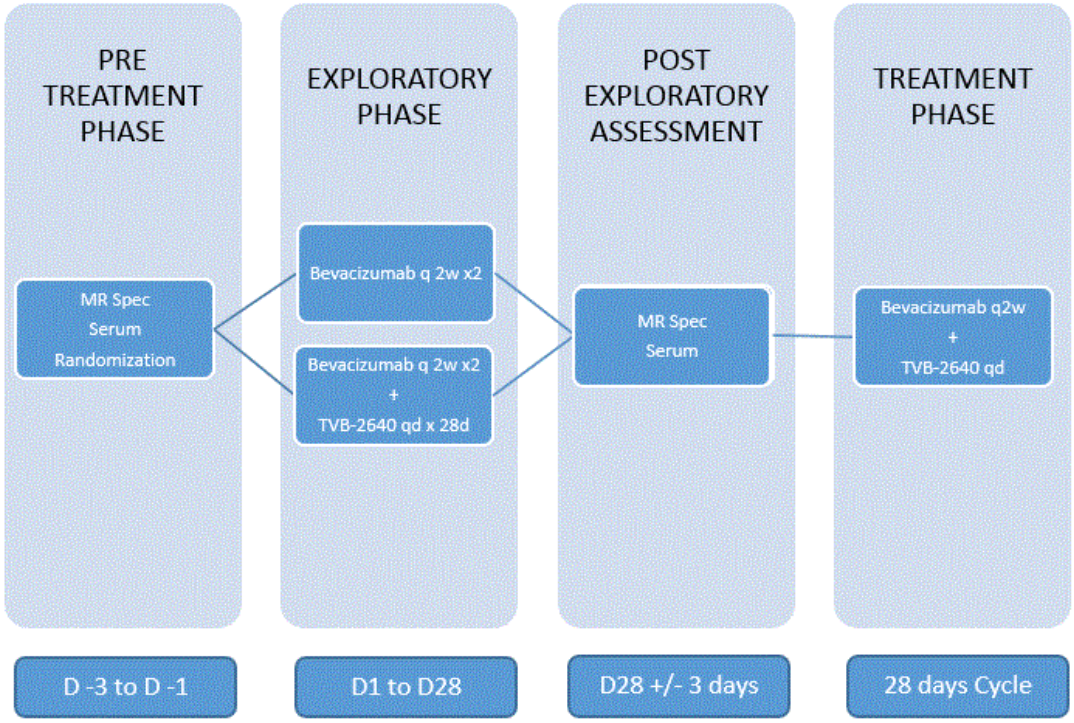
Exploratory Endpoint:

Metabolic change analysis of tumor tissue by MR-Spectroscopy.

Study Design:

- Randomized phase 2 study TVB-2640 in combination with Bevacizumab versus Bevacizumab alone.

Schema:



Number of Patients:

- On average, will expect to accrue 1 to 2 patients a month for a total of 24.
- It will take approximately 12 to 18 months to complete accrual.

Main Criteria for Inclusion/Exclusion:

INCLUSION CRITERIA

- At least 18 years of age
- Ability to understand the purposes and risks of the study and has signed a written informed consent form approved by the investigator's IRB/Ethics Committee.
- Histologically confirmed high-grade astrocytoma.
- Progression following standard combined modality treatment with radiation and temozolomide chemotherapy.

- Recovered from reversible toxicities of prior therapy to Grade 0 or Grade 1.
- ECOG Performance Status of 0 to 2.
- Life expectancy of at least 3 months.
- Adequate renal and liver function:
  - AST/ALT ≤ 3 x ULN
  - Bilirubin ≤ 1.5 times ULN
  - Creatinine ≤ ULN
- Adequate hematologic status (without hematologic support):
  - Hemoglobin ≥ 9 g/dL
  - ANC ≥ 1500 cells/ml
  - Platelets ≥ 100,000 cells/ml
- All women of childbearing potential must have a negative serum pregnancy test and male and female subjects must agree to use effective means of contraception (for example, surgical sterilization or the use of barrier contraception with either a condom or diaphragm in conjunction with spermicidal gel or an IUD) with their partner from entry into the study through three months after the last dose.

EXCLUSION CRITERIA

- Receiving warfarin (or other coumarin derivatives) and is unable to switch to low molecular weight heparin (LMWH) before the first dose of study drug.
- Evidence of acute intracranial or intratumoral hemorrhage either by MRI or CT scan. Subjects with resolving hemorrhage changes punctuate hemorrhage, or hemosiderine are eligible.
- Unable to undergo MRI scan (e.g., pacemaker).
- Received enzyme-inducing anti-epileptic agents within 14 days of study drug (e.g., carbamazepine, phenytoin, phenobarbital, primidone).
- Not recovered to a NCI CTCAE v.4.03 Grade ≤ 1 from AEs (except alopecia and lymphopenia) due to surgery, antineoplastic agents, investigational drugs, or other medications that were administered prior to study drug.
- Evidence of wound dehiscence.
- Pregnant or breast-feeding.
- Clinically significant Dry Eye or necessary contact lens use
- Serious intercurrent illness such as:
  - Hypertension (two or more blood pressure readings performed at screening of > 150 mmHg systolic or > 100 mmHg diastolic) despite optimal treatment.
  - Non-healing wound or ulcer
  - Uncontrolled life threatening cardiac arrhythmias.
  - Untreated hypothyroidism.
  - Uncontrolled active infection.
  - Symptomatic congestive heart failure or unstable angina pectoris within 3 months prior to study drug.
  - Myocardial infarction, stroke, transient ischemic attack within 6 months.

- Gastrointestinal perforation, abdominal fistula, intra-abdominal abscess within 1 year.

- Inherited bleeding diathesis or coagulopathy with the risk of bleeding.
- HIV, Hepatitis B or C documented infections.
- Received any of the following prior anticancer therapy:
  - Non-standard radiation therapy such as brachytherapy, systemic radioisotope therapy (RIT), or intra-operative radiotherapy (IORT). Note: stereotactic radiosurgery (SRS) is allowed.
  - Non-antiangiogenic therapy (including investigational agents and small molecular kinase inhibitors) within 7 days or 5 half-lives, whichever is shorter, prior to the first dose of study drug.
  - Biologic agents (antibodies, immune modulators, vaccines, cytokines) within 21 days prior to first dose of study drug
  - Nitrosoureas or mitomycin C within 42 days or metronomic/protracted low-dose chemotherapy within 14 days, or other cytotoxic chemotherapy within 28 days, prior to first dose of study drug.
  - Prior treatment with TVB-2640
  - Prior treatment with Carmustine Wafers

Intervention and Mode of Delivery:

Patients with documented High Grade Astrocytoma in first relapse, naïve to bevacizumab, will be randomized into 2 separate arms:

- Patients randomized to Arm number one will receive Bevacizumab every 2 weeks in combination with TVB-2640 dosed at 100mg/m^2 daily (rounded to 50mg cap dose), from day 1 until day 28 of the first cycle.
- Patients randomized to Arm number two will receive Bevacizumab alone every 2 weeks, on days 1 and 15 of the first day 28 cycle.
- MR-Spectroscopy will be obtained on patients (both arms) -7 to day -1 before and again from day 21 to day 28 of cycle 1. (Optional- at the Investigator's discretion)
- Starting on cycle 2 day 1, all patients will converge to a single arm and will continue to receive bevacizumab every 2 weeks in combination with TVB-2640 dosed at 100mg/m^2 daily (rounded to 50mg cap dose) for up to 6 cycles. Every cycle will last 28 days.
- The initial Bevacizumab dose will be infused over 90 minutes. Infusion may be shortened to 60 minutes if the initial infusion is well tolerated. The third and subsequent infusions may be shortened to 30 minutes if the 60 minute infusion is tolerated well. Bevacizumab will be administered on days 1 and 15 of each cycle.

Duration of Intervention and Evaluation:

Subjects will be allowed to continue treatment on study for up to six cycles (28 days each) or until they have evidence of significant treatment-related toxicity or progressive disease.

Subjects will receive study drug TVB-2640 and will be assessed for adverse events at all visits. Adverse events will be reported for all events occurring after the start of treatment until 30 days after study drug is discontinued or subsequent cancer therapy is initiated. Tumor assessments will be performed after every even cycle during treatment.

Statistical Methods:

This is a prospective, randomized, phase 2 study of TVB-2640 in combination with bevacizumab or bevacizumab alone in patients in first relapsed high grade astrocytoma. Analysis will be intent-to-treat of all randomized patients.

Evaluability : All randomized patients will be included in the intent-to-treat analysis of the PFS

POWER CALCULATIONS, ACCRUAL RATE, AND STUDY DURATION

The median time to progression of patients treated with Bevacizumab is 124 days (95% confidence interval: 87–154 days) (19). A total sample size of 24 evaluable patients enrolled within 1 – 1.5 years) will provide 91.6% power to detect a 4 month difference in the median time to progression (3 months for bevacizumab alone (historic controls) versus 7 months in TVB-2640 in combination with bevacizumab, i.e., a hazard ratio of 0.43) using a one-sided log-rank test with alpha=0.1.

We expect to accrue 1 to 2 patients a month, i.e. about 12 to 24 patients per year. The 24 patients can be enrolled in 1 – 1.5 years. With an additional 3 months of follow-up on the last patient, the total study duration is about 18 months.

The primary efficacy analyses for estimation of PFS rates will be performed using a one sided log-rank test for an overall type-I error at 0.1 for each treatment group and a power of 91.6%. Thus far we will be able to reject the null hypothesis that the experimental and control survival curves are equal.

a) Definition of primary outcome/endpoint:

Progression-free survival time of patients is defined as time from study enrollment to the first occurrence of relapse, death from any cause or until last contact (if no event occurs).

b) Definition of secondary outcomes/endpoints:

Adverse events and serious adverse events, graded according to NCI - Common Terminology Criteria for Adverse Events version (4.03).

c) Exploratory Endpoint**:** Metabolic tumor changes on patients treated with TVB-2640.

d) Analytic plan for primary objective:

We will test that the combination of bevacizumab and TVB-2640 versus bevacizumab alone will increase the rate of PFS, by using a non-parametric test (Log-Rank), with alpha of 0.1 and power of 91.6%.

e) Analytic plan for secondary objectives:

Toxicities will be tabulated by type and grade according to NCI CTCAE v. 4.03

f) Sample size justification:

A sample size of total 24 evaluable patients will provide 91.6% power to detect a 4 month difference in the median time to progression (3 months for bevacizumab alone versus 7 months in TVB-2640 in combination with bevacizumab, i.e., a hazard ratio of 0.43) using a one-sided log-rank test with alpha=0.1.

Funding, Regulatory, and Feasibility Issues:

TVB-2640 is supplied by the manufacturer as 50 mg and 200 mg strength capsules. Additional formulations of TVB-2640 may be introduced, when available. The bevacizumab will be obtained by the Mays Cancer Center through commercial supply.

1. OBJECTIVES AND ENDPOINTS:

1.1 Primary Objective

To determine if the progression-free survival of patients with High Grade Astrocytoma who are treated with TVB-2640 in combination with bevacizumab is superior to treatment with bevacizumab alone.

1.2 Secondary Objective

To evaluate the safety of TVB-2640 in combination with bevacizumab in patients with High Grade Astrocytoma.

1.3 Exploratory Objective

To determine the extent by which TVB-2640 can metabolically affect tumor tissue.

1.4 Primary Endpoint:

Time from study enrollment to the first occurrence of relapse, progression, or death from any cause, or until last contact (if no event occurs).

1.5 Secondary Endpoint:

Adverse events and serious adverse events, graded according to NCI - Common Terminology Criteria for Adverse Events version (4.03).

1.6 Exploratory Endpoints:

Metabolic change analysis of tumor tissue by MR-Spectroscopy.

Serum metabolomic changes.

2. BACKGROUND:

2.1. High Grade Glioma

Standard front-line treatment for newly diagnosed GBM consists of maximal surgical resection of primary tumor, followed by radiation therapy (RT; 2 Gy for 5 days a week, total 60 Gy) with concurrent temozolomide (TMZ, alkylating agent) at 75 mg/m^2 PO daily for 6 weeks, followed by maintenance phase of single-agent temozolomide (150-200 mg/m2 PO daily on D1-5 for 6 cycles; 28-day cycle).(3, 4) Temozolomide (a prodrug) is rapidly and non-enzymatically converted to the active alkylating metabolite MTIC ((methyl-triazene-1-yl) – imidazole-4-carboxamide). The cytotoxic effects of MTIC are manifested through alkylation of DNA at the O6, N7 guanine positions. This multimodal treatment approach has remained the standard of care and is based on

the EORTC phase III trial published by *Stupp et al*. more than a decade ago.(4) This landmark study demonstrated a median overall survival of 14.6 months in the TMZ group versus 12.1 months in the radiation alone treatment cohort. However, this still leaves much to be desired with an improvement in median survival of only 2.6 months over radiotherapy alone. At that time, radiation (RT) alone was considered standard of care in most countries. In the US, common practice was to add adjuvant nitrosurea-based chemotherapy regimen with a small survival benefit at the cost of significant adverse effects (AEs). In summary, GBMs are highly aggressive, vascular tumors associated with frequent relapses due to resistance to multimodality treatment. For recurrent and relapsing GBM, there is no clear standard of care to date.

It is also well accepted that brain tumors rely on vascularization for survival and continued growth. While normal brain vasculature is a highly organized structure of endothelial cells, pericytes, and astrocytes forming a tight barrier which restricts access to the intracerebral system, GBM displays markedly disorganized vascular structures with conspicuous endothelial cell proliferation, pericyte and basement membrane abnormalities resulting in permeability with heterogenous leakiness and abnormal blood flow.(5) This aberrant process of endothelial proliferation and loss of the blood brain barrier is related to the expression of vascular endothelial growth factor (VEGF) by the tumor cells as well as the cells in the surrounding microenvironment in response to hypoxia and acidosis. This leakiness results in an increased interstitial pressure and an impediment to drug delivery. By blocking VEGF signaling either through monoclonal antibodies to VEGF-A or inhibition of the VEGF receptors, it has been shown that prompt reduction in interstitial pressures can be achieved with presumed better drug delivery to tumor cells. While the role of VEGF signaling in angiogenesis has been extensively described, another role for VEGF has been proposed with carcinoma progression selecting for cells that depend on VEGF as a survival and migration factor.(6) This would explain the high frequency of VEGF receptor expression in GBMs and other solid tumors.(7) Targeting VEGF has proven to be clinically relevant in GBM. The addition of bevacizumab to standard RT-TMZ as first-line treatment for GBM was investigated in the AVAglio study.(8) In this study, the addition of bevacizumab to RT-TMZ improved progression free survival (PFS; 10.6 vs. 6.2 months, HR 0.64) compared with RT-TMZ alone, but resulted in increased toxicity without an improvement in overall survival (OS).(8) Similarly, the RTOG-0825 Phase III study also showed a trend towards improved PFS with the addition of bevacizumab to RT-TMZ, but no OS benefit.(9)

Despite advances in multimodal therapies, the median survival of patients with GBM is approximately 15 months with a 5 year survival rate of 5.0% after diagnosis.(10) Other current cytotoxic chemotherapeutic agents for GBM include: carmustine, lomustine or carboplatin.(11) Therapeutic agents targeting EGFR, VEGFR, PDGFR, Ras pathway, mTOR, histone acetylation and integrins (12) are under current investigation; but these therapies have resulted in poor to modest clinical response at best.(13) Identification of more potent and effective therapeutic agents, either as a single agent or in combination with existing drugs, is clearly needed for the clinical advancement of GBM.

Hypoxia promotes antiangiogenic resistance in glioblastoma**.** While normal brain vasculature is a highly organized structure of endothelial cells, pericytes, and astrocytes forming a tight barrier which restricts access to the intracerebral system, GBMs display markedly disorganized vascular

structures with conspicuous endothelial cell proliferation, pericyte and basement membrane abnormalities resulting in permeability with heterogenous leakiness and abnormal blood flow(5). This aberrant process of endothelial proliferation and loss of the blood brain barrier is related to the expression of VEGF by the infiltrating margin of the tumor (14) as well as the cells in the surrounding microenvironment in response to hypoxia and acidosis. While targeting of VEGF has proven to be clinically relevant as discussed above, given the key importance of VEGF and its receptor VEGFR2 in angiogenesis, hopes were once raised that blocking this pathway would eradicate the tumor vasculature and heal cancer. This clearly has not been the case as clinical practice reveals that therapy with angiogenesis inhibitors, including bevacizumab which is the only FDA approved drug for recurrent glioblastoma, generally does not prolong survival of cancer patients for more than months. Increasing evidence points to the root cause of angiogenesis, hypoxia, as a driving force for resistance to anti-angiogenics. In a prospective clinical trial (15) of bevacizumab and irinotecan in which biomarkers were assessed, the most significant predictor (negative) of both response to therapy and overall survival was the presence of hypoxia induced carbonic anhydrase (CA9) ($P(c^2) = 0.020$, HR 2.72, CI 1.17 to 6.36). Second to this was hypoxia-inducible factor 1-alpha (16). In a prospective clinical study in which the pan-VEGF receptor inhibitor AZD2171 was given to GBM patients (17), the most predictive blood biomarker of tumor progression was stromal derived factor 1a (18), suggesting that the correlation seen between progression on AZD2171 and presence of SDF1 is associated with increased hypoxia in human brain tumor spectra, with an associated increase in HIF1α, matrix metalloproteinases, chemokines and a more invasive phenotype(19-21).

In order to better characterize the metabolic changes associated with resistance to bevacizumab and other antiangiogenics, we performed metabolomic profiling of tumors and sera from patients having failed glioblastoma. Interestingly, the most significant change that correlated with degree of hypoxia was an increase in the presence of long chain fatty acids (Figure A). This is not an entirely surprising finding as glioblastoma has been known to be a tumor type in which large inclusions of fatty acids (referred often to as lipid droplets) develop.(22) It has been proposed that these lipid droplets could represent a temporary storage compartment of fatty acids in the form of triglycerides that could serve as reservoir that could be relied upon under metabolic stress (1).

FATTY ACID METABOLISM IN HYPOXIA

The changes observed in fatty acids with hypoxia and bevacizumab resistance suggest a potentially targetable mechanism. The precursor for fatty acid synthesis is Acetyl-CoA. While Acetyl-CoA under normoxia is derived from glucose, hypoxia induces a shift toward the production from alternate precursors. When using 13C-glutamine in labelling of cells under hypoxia, citrate and fatty acids are found to be labelled (Fan et al, 2013). Citrate itself is the precursor for AcCoA, and can be used for fatty acid synthesis, suggesting glutamine as an alternate source during hypoxia. Interestingly, what is typically considered a waste product under hypoxia, acetate, has recently been identified as a carbon source which is scavenged in cancer. Specifically, it was found that the enzyme generating AcCoA from acetate, Acetyl-CoA synthetase 2 (ACSS2), is frequently amplified in a subset of cancers and is upregulated in cells exposed to hypoxic and low serum conditions (Schug et al, 2015). Consequently, labelling of lipogenic AcCoA and hence fatty acids from 13C-acetate was found to be increased in these conditions (Kamphorst et al, 2014; Schug et al, 2015). These findings have prompted the investigation into fatty acids and their synthetic

enzymes. Fatty acid synthase (FASN) is a homodimeric and multi-functional enzyme that catalyzes the biosynthesis of palmitate in a NADPH- dependent reaction. (29) Normal cells in adult tissue ubiquitously express low to moderate levels of FASN; however, these cells, which primarily import lipids from the extracellular milieu, do not have a strict requirement for FASN activity. (30) In contrast, tumor cells have an increased requirement for lipids for functions such as membrane biosynthesis, protein modification, and signaling molecules. Consequently, tumor cells are more dependent on *de novo* palmitate synthesis catalyzed by FASN than normal cells. (31)

Two classes of FASN exist: FASN I in eukaryotes and fungi, and FASN II in plants and prokaryotes. Animal FASN I is a homodimeric protein found in the cytosol of lipogenic tissues such as the liver and brain.(32) Oncologically speaking, published studies have confirmed that many solid and hematopoietic tumors overexpress fatty acid synthase (FASN), including non-small cell lung, breast, ovarian, prostate, colon, pancreatic cancers, non-Hodgkin lymphoma as well as Gliomas.(33) (34) Moreover, FASN tumor expression has been found to be increased in a stage-dependent manner that is associated with diminished patient survival. (31)

FASN selectively inhibits growth and viability of tumor cells by inducing tumor cell apoptosis via multiple mechanisms of action, both in vitro and in vivo, while having minimal effects on non-tumor cells such as fibroblasts, astrocytes, and endothelial cells, demonstrating that tumor cells have a unique dependence on FASN function for survival that is not present in normal cells. (33) (35)

2.2 TVB-2640

TVB-2640 is a potent and reversible inhibitor of the FASN enzyme that has been validated in multiple tumor cell lines, as well as in clinical studies. TVB-2640 inhibits the ketoacylreductase (KR) enzymatic activity of the FASN enzyme. TVB-2640 is uncompetitive towards both NADPH and Acetoacetyl-CoA in inhibiting KR activity. The pharmacokinetics (PK) and metabolism of TVB-2640 have been examined with a series of *in vitro* and *in vivo* studies, including toxicokinetic studies.

Due to its rapid metabolism in the mouse, TVB-2640 cannot be tested in murine xenograft models. Thus, TVB-3166, a structural analog of TVB-2640 with similar pharmacological properties, was used as a surrogate molecule (parallel reagent) in murine xenograft models. In the PANC-1 murine xenograft tumor model, TVB-3166 administered orally once daily exhibited dose-dependent tumor growth inhibition, with significant tumor growth inhibition compared to vehicle-treated mice of 57% seen at a dose of 100 mg/kg. At a dose of 30 mg/kg, tumor growth inhibition was lower (19%) and non-significant relative to vehicle control. (35)

The pharmacokinetics (PK) and metabolism of TVB-2640 have been examined with a series of *in vitro* and *in vivo* studies, including toxicokinetic studies. Overall, the PK properties determined to-date for TVB-2640 demonstrate that it is orally absorbed in humans and has a mean half-life of approximately 15 hours. No potential for significant drug interaction has been identified. (26)

In safety pharmacology studies, TVB-2640 had no effects on respiratory or central nervous system (CNS) function. TVB-2640 exhibited concentration-related inhibition of human ether-àgo-go-

related gene (hERG) potassium channel currents and was characterized as a moderately potent hERG inhibitor. In conscious dogs, an oral dose of 1000 mg/kg caused slight, reversible prolongation of the QT/corrected QT (QTc) interval from 3 to 22 hours post dose; there were no effects noted at lower doses of 50 or 100 mg/kg. Single oral doses of TVB-2640 up to 1000 mg/kg were well tolerated in rats and dogs. Daily oral administration of TVB-2640 for 28 days was well tolerated in male rats at doses up to 250/300 mg/kg/day and in female rats at 30 mg/kg/day. TVB-2640 administration resulted in the deaths of two 250 mg/kg/day females on Study Days 15 and 28. Test article-related clinical signs were noted primarily in ≥100 mg/kg/day females (skin and coat). Test article-related body weight loss and/or decreases in mean body weight gain and decreases in food consumption were noted in ≥100 mg/kg/day females. Treatment-related microscopic findings were identified in the lungs and stomach of females given ≥30 mg/kg/day and in the skin at ≥100 mg/kg/day. Lung and skin changes were still evident in high dose females after a 14-day recovery. The noobserved-adverse-effect level (NOAEL) was 250/300 mg/kg/day for males and 30 mg/kg/day for females. The severely toxic dose (STD) was 100 mg/kg/day for females, but the STD in males is >300 mg/kg/day. Plasma area under the curve (AUC) exposures were consistently higher in females compared to males with female/male ratios ranging from 2.25- to 3.47-fold.

TVB-2640 has completed phase 1 testing both as a monotherapy and in combination with paclitaxel. A full description of clinical toxicity is available in the investigator brochure. As detailed in the table below, the most common (i.e., Incidence ≥10%) adverse events of any grade considered possibly, probably or definitely related to TVB-2640 among patients treated with TVB-2640 monotherapy include skin and subcutaneous tissue disorders, (78%); gastrointestinal disorders (65%), general disorders and administration site conditions (57%); eye disorders (50%); respiratory, thoracic, and mediastinal disorders (42%); metabolism and nutrition system disorders and nervous system disorders (each 36%); infections and infestations (31%); investigations (28%); and musculoskeletal and connective tissue disorders (22%). Few were grade 3, and included palmar-plantar erythrodysaesthesia syndrome, fatigue, anemia, and dyspnea.

MedDRA Preferred Term	TVB-2640 Monotherapy Overall N=72	
	Overall Incidence n (%)	Grade 3 Incidence n (%)
Alopecia	40 (56)	0
Palmar-plantar erythrodysaesthesia syndrome	29 (40)	8 (11)
Fatigue	24 (33)	6 (8)
Decreased appetite	18 (25)	0
Dry skin	16 (22)	0
Constipation	13 (18)	0
Nausea	13 (18)	0
Diarrhoea	12 (17)	0
Vomiting	12 (17)	0
Cough	11 (15)	0
Dry eye	11 (15)	0
Abdominal pain	10 (14)	0
Conjunctivitis	10 (14)	0
Anaemia	9 (13)	3 (4)
Asthenia	9 (13)	0
Skin exfoliation	9 (13)	0
Urinary tract infection	9 (13)	0
Dehydration	8 (11)	0
Dyspnoea	8 (11)	1 (1)
Lacrimation increased	8 (11)	0
Dysgeusia	7 (10)	0
Oedema peripheral	7 (10)	0
Pyrexia	7 (10)	0
Rash	7 (10)	0

Based upon the non-overlapping toxicity profile with bevacizumab, it is expected that the toxicity profile of the combination should be similar to those of the individual agents.

2.3 Rationale

The mainstay of treatment for GBM remains surgical removal followed by combined chemotherapy with temozolomide and radiation therapy. Median and 2-year survival rates for patients receiving temozolomide were increased by 2.5 months (12.1 to 14.6 months) and 16.1% (10.4% to 26.5%), respectively.(4) However, once a patient fails standard front-line therapy, prognosis is very poor and new therapies are needed. In the era of targeted therapies, clinical studies have demonstrated anti-tumor activity in patients treated with anti-angiogenic agents such

as with bevacizumab, a recombinant human monoclonal antibody against VEGF receptor. Bevacizumab was FDA approved in 2009 as treatment for recurrent Glioblastoma following failure of radiation therapy and temozolomide, although the responses are not very long-lasting. and no proven survival benefit has been seen in as many as 4 randomized clinical trials.(28)

TVB-2640 emerges in the horizon as a novel agent that selectively inhibits FASN enhancing tumor growth inhibition and viability of tumor cells by inducing tumor cell apoptosis via multiple mechanisms of action, both in vitro and in vivo, while having minimal effects on non-tumor cells. TVB-2640 has been tested in murine models and lately in a phase 1, international, multi-center, open-label, dose-escalation study where MTD was established and recommended for further investigation in Phase 2.(36)

Given the findings of: a) increased hypoxia with bevacizumab, b) increase in long chain fatty acids in the tumors of patients who have failed bevacizumab, and c) evidence suggesting that fatty acid metabolism could play a role in survival under hypoxia, it is rational that the addition of TVB-2640 could overcome acquired resistance to bevacizumab. Since the progression free survival is not very long lasting on bevacizumab for patients with relapsed high-grade glioma; this phase 2 study will evaluate the potential effectiveness and safety of TVB-2640 in combination with bevacizumab compared to bevacizumab alone.

2.4.1 Rationale for Dose Selection TVB-2640

Based on results from previous studies, the MTD of TVB-2640 administered PO daily (q.d.) has been stablished as monotherapy and in combination on a 21 or 28 days cycle length respectively as 100 mg/m^2 (based on BSA dosing). Particularly, protocol 3V2640-CLIN-002 was a phase 1, international, multi-center, open-label, dose-escalation study designed to evaluate the DLT and MTD of TVB-2640 administered PO and establish the TVB-2640 dose recommended for further investigation in phase 2 (i.e., RP2D) when given as monotherapy and in combination with selected commercially-available anticancer agents. In that protocol, patients with any histologically or cytologically confirmed solid tumor type were eligible and secondary objectives included characterization of the safety and PK profile of TVB-2640 and identification of preliminary anti-tumor activity in this patient population. Further data regarding dose selection of TVB-2640 can be found in the current Investigator Brochure (IB). Given the lack of significant overlap in toxicity profile with that of bevacizumab, the MTD has been selected as the phase 2 combination dose.

2.4.2 Rationale for Dose selection Bevacizumab (Avastin)

Phase II clinical studies as well as the FDA have established the standard bevacizumab dose of 10 mg/kg IV every 2 weeks when treating patients with recurrent glioblastoma.

3. PATIENT SELECTION

Inclusion Criteria

- At least 18 years of age
- Ability to understand the purposes and risks of the study and has signed a written informed consent form approved by the investigator's IRB/Ethics Committee.

- Histologically confirmed high grade astrocytoma.
- Progression following standard combined modality treatment with radiation and temozolomide chemotherapy
- Recovered from reversible toxicities of prior therapy to Grade 0 or Grade 1.
- ECOG performance Status of 0 to 2.
- Life expectancy of at least 3 months.
- Adequate renal and liver function:
    - AST/ALT ≤ 3 x ULN
    - Bilirubin ≤ 1.5 x ULN
    - Creatinine ≤ ULN
- Adequate hematologic status (without hematologic support):
    - Hemoglobin ≥ 9 g/dL
    - ANC ≥ 1500 cells/ml
    - Platelets ≥ 100,000 cells/ml
- All women of childbearing potential must have a negative serum pregnancy test and male and female subjects must agree to use effective means of contraception (for example, surgical sterilization or the use of barrier contraception with either a condom or diaphragm in conjunction with spermicidal gel or an IUD) with their partner from entry into the study through three months after the last dose.

Exclusion Criteria

- Receiving warfarin (or other coumarin derivatives) and is unable to switch to low molecular weight heparin (LMWH) before the first dose of study drug.
- Evidence of acute intracranial or intratumoral hemorrhage either by MRI or CT scan. Subjects with resolving hemorrhage changes, punctuate hemorrhage, or hemosiderine are eligible.
- Unable to undergo MRI scan (e.g., pacemaker).
- Received enzyme-inducing anti-epileptic agents within 14 days of study drug (e.g., carbamazepine, phenytoin, phenobarbital, primidone).
- Not recovered to a NCI CTCAE v.4.03 Grade ≤ 1 from AEs (except alopecia and lymphopenia) due to surgery, antineoplastic agents, investigational drugs, or other medications that were administered prior to study drug.
- Evidence of wound dehiscence.
- Pregnant or breast-feeding.
- Clinically significant dry eye or contact lens use.
- Serious intercurrent illness such as:
    - Hypertension (two or more blood pressure readings performed at screening of > 150 mmHg systolic or > 100 mmHg diastolic) despite optimal treatment.
    - Non-healing wound or ulcer
    - Uncontrolled life threatening cardiac arrhythmias.
    - Untreated hypothyroidism.
    - Uncontrolled active infection.
    - Symptomatic congestive heart failure or unstable angina pectoris within 3

months prior to study drug.
    - Myocardial infarction, stroke, transient ischemic attack within 6 months.
    - Gastrointestinal perforation, abdominal fistula, intra-abdominal abscess within 1 year.
- Inherited bleeding diathesis or coagulopathy with the risk of bleeding.
- HIV, Hepatis B or C documented infections.
- Received any of the following prior anticancer therapy:
    - Non-standard radiation therapy such as brachytherapy, systemic radioisotope therapy (RIT), or intra-operative radiotherapy (IORT). Note: stereotactic radiosurgery (SRS) is allowed.
    - Non-antiangiogenic therapy (including investigational agents and small molecular kinase inhibitors) within 7 days or 5 half-lives, whichever is shorter, prior to the first dose of study drug.
    - Biologic agents (antibodies, immune modulators, vaccines, cytokines) within 21 days prior to first dose of study drug
    - Nitrosoureas or mitomycin C within 42 days or metronomic/protracted low-dose chemotherapy within 14 days, or other cytotoxic chemotherapy within 28 days, prior to first dose of study drug.
    - Prior treatment with TVB-2640
    - Prior treatment with Carmustine Wafers

4. RANDOMIZATION

This study will be performed at a single institution (UT Heath Cancer Center), where a permuted block randomization method will be used in order to allow flexibility in achieving balanced allocation of subjects among treatment groups. We will use small blocks of 4 patients and simple randomization will be done within each block.

5. STUDY DESIGN AND METHODS.

5.1 Design

Patients with documented High Grade Astrocytoma in first relapse, naïve to bevacizumab, will be randomized into 2 separate arms:

- Patients randomized to Arm number one will receive Bevacizumab every 2 weeks in combination with TVB-2640 dosed at 100mg/m2 daily (rounded to 50mg cap dose), from day 1 until day 28 of the first cycle.
- Patients randomized to Arm number two will receive Bevacizumab alone every 2 weeks, on days 1 and 15 of the first 28 day cycle.
- MR-Spectroscopy will be obtained on patients (both arms) at day 28 +/- 3 days of first cycle. (Optional- at the investigators discretion)
- Starting on cycle 2 day 1, all patients will converge to a single arm and will continue to receive bevacizumab every 2 weeks in combination with TVB-2640 dosed at 100mg/m2

daily (rounded to 50mg cap dose) for up to 6 cycles. Every cycle will last 28 days.

- The initial Bevacizumab dose will be infused over 90 minutes. Infusion may be shortened to 60 minutes if the initial infusion is well tolerated. The third and subsequent infusions may be shortened to 30 minutes if the 60 minute infusion is tolerated well. Bevacizumab will be administered on Day 1 and Day 15 of each cycle.

TVB-2640 will be administered on a once daily (QD) schedule. Each QD TVB-2640 dose is to be taken at the same time each day under fasted conditions (i.e., at least 2 hours after last food consumption and at least 1 hour before next food consumption), with each dose separated by 24 hours (+/- 4 hrs).For TVB-2640 doses missed by more than 8 hours will not be made up, and patients will skip sand resume their schedule the following day. Dose delays for bevacizumab will be as per standard of care and at the direction of the treating physician.

On scheduled study visit days, TVB-2640 is to be taken at the study center under the observation of study center personnel. On all other study days, patients are to self-administer TVB-2640.
On study visit days when both TVB-2640 and bevacizumab are to be administered, TVB-2640 should be taken approximately 2 hours prior to the initiation of the bevacizumab infusion.

It is anticipated that patients will receive at least 1 cycle of TVB-2640. After cycle 1 patients may continue to receive TVB-2640 for up to 6 cycles or until development of progressive disease (PD), unacceptable toxicity or another withdrawal criterion is met. Patients who discontinue study drug are to attend a Final Study Visit 28 days (±5 days) after the last study drug dose.

During the study, safety is to be evaluated by documentation of adverse events (AEs) and serious adverse events (SAEs), clinical laboratory tests (hematology, clinical chemistry, and urinalysis), physical examinations, vital signs measurements, Eastern Cooperative Oncology Group (ECOG) performance status, and 12-lead electrocardiograms (ECGs).

5.2 Treatment Regimens

5.2.1 TVB-2640

TVB-2640 at a dose of 100 mg/m2 (rounded to 50mg cap dose) will be taken by mouth on day 1 – 28 of each 28 day cycle.

TVB-2640 is supplied by the manufacturer as 50 mg and 200 mg strength capsules. Additional formulations and of TVB-2640 may be introduced, when available.

TVB-2640 initially will be administered on a QD schedule; thus, patients receiving TVB-2640 QD will receive 28 doses of TVB-2640 in each cycle. Each QD TVB-2640 dose is to be taken at the same time of the day under fasted conditions (i.e., at least 2 hours after last food consumption and at least 1 hour before next food consumption), with each dose separated by 24 hours (±4 hours).
On study visit days when both TVB-2640 and the combination anticancer agent are to be administered, TVB-2640 should be taken approximately 2 hours prior to the initiation of the anticancer agent administration

5.2.2 Bevacizumab (Avastin)

Bevacizumab will be administered intravenously at 10 mg/kg on day 1 and day 15 of every cycle, with the dose regimen documented in the CRF. Any required pre- or concurrent medication is also to be administered in accordance with the prescribing information and routine clinical practice.

Prophylaxis against nausea and vomiting should be applied using a regimen intended for moderately emetogenic chemotherapy.

5.2.3 Dose Modifications

BEVACIZUMAB

Please follow the package insert for all bevacizumab dose modifications and discontinuations. See Appendix C.

TVB-2640

- If a patient develops any toxicity grade 3 (including hematologic), then TVB-2640 will be placed on hold for up to 14 days.
- If after 14 days, the patient has not improved from the above mentioned toxicity, then TVB-2640 will be kept permanently on hold until recovery of toxicity.
- If the toxicity returns to < Grade 2 or baseline, and the decision is made that the patient can resume study drug, then TVB-2640 dosing should be restarted at a lower dose level. Dose reductions will be made in 25% increments.
- If a subject requires more than 2 dose level reductions for non-hematological toxicity, he/she should discontinue from the study. Ongoing dose reductions beyond 2 dose levels are allowed for hematologic toxicity.
- Any subject who misses more than one complete cycle (four weeks) for treatment-related toxicity should discontinue from the study.

At each study center visit, the patient will be evaluated for possible toxicities that may have occurred since the previous visit. Toxicities are to be graded according to the NCI CTCAE, Version 4.03. If a toxicity is not classified in the CTCAE, then it should be classified according to the criteria presented in Section 8.2.2.1 Furthermore, the Investigator is to assess the relationship of a toxicity to study drug as described in the same section.

The table below summarizes dose modifications for non-hematologic toxicities.

Toxicity	Details	Hold Dose	% of Dose after Recovery to Grade 0-1
Grade 2 or 3 Bilirubin	Regardless of causality	Hold dose until resolution to Grade 0 or 1	100
Grade 2	except for elevated ALT/AST, nausea, vomiting, diarrhea, alopecia and fatigue	Hold dose until resolution to Grade 0 or 1	100
	Intolerable skin toxicity	Hold dose until resolution to Grade 0 or 1	75
Grade 3	Except for elevated ALT/AST, nausea and vomiting	Hold dose until resolution to Grade 0 or 1	75
Grade 4	Life-threatening conditions (study drug-related)	Treatment should be discontinued	NA
Grade 4	Other grade 4 events such as fatigue and non-life-threatening pulmonary embolism that are adequately treated	Hold dose until resolution to Grade 0 or 1	50

5.2.4 Concomitant Medications

All prescription and non-prescription medications and therapies, including pharmacologic doses of vitamins, herbal medicines, or other non-traditional medicines, taken from 28 days prior to the first dose of TVB-2640 through the Final Study Visit must be recorded in the CRF.

5.2.5 Excluded Medications

The following medications and treatments are prohibited during study participation.

- Any investigational agent or device other than TVB-2640, including agents that are commercially available for indications other than the.
- In Monotherapy Cohort, any anti-neoplastic treatment with activity against solid tumors other than study drug. This includes high doses of corticosteroids for any reason other than brain metastases.
- Strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4). (Refer to the following

for examples:
Drug Interactions & Labeling > Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.)

- Medications known or suspected to prolong the QT/QTc interval, with the exception of drugs with low risk of QT/QTc prolongation that are used as standard premedication (e.g., diphenhydramine, famotidine, ondansetron). (Refer to the following for examples: http://crediblemeds.org/everyone/composite-list-all-qtdrugs/?rf=US.)

5.2.6 Permitted Medications

Medications and treatments other than those specified in Section 5.2.5, including palliative and supportive care for disease-related symptoms, are permitted during the study. Patients should be closely monitored, and treatment is to be instituted for disease-related symptoms, as appropriate.

6. PROCEDURES

A summary of visits and clinical procedures is found in Section 14.

Subjects who withdraw from the study before all follow-up procedures have been performed will be managed and documented as described in Section 9, Removing Subjects from the Study.

When a subject has completed the study termination or early termination visit, he/she and/or a family member will be contacted for survival information every 3 months until one year from first dose.

All subjects will be screened within 21 days prior to Cycle 1 Day 1. Vital signs, clinical laboratory test results, weight and AEs will be used to assess safety. Efficacy will be assessed based on tumor assessments (objective response rate, progression-free survival and duration of response) conducted at intervals during the study. Subjects who have not progressed after 6 cycles may be permitted to continue therapy on a case-by-case basis.

During screening, candidates for the study will be fully informed about the nature of the study and possible risks, and will receive a copy of the informed consent for review. Candidates must read the consent form and sign the document after the investigator has answered all questions to the candidate's satisfaction. Further procedures can begin only after the consent form has been signed. The original signed consent form will be retained by the investigator and a copy will be given to the candidate. Candidates will be evaluated for entry into the study according to the stated inclusion and exclusion criteria (Section 3, Patient Selection). The investigator will evaluate the results of all examinations, including clinical laboratory tests, and will determine each candidate's suitability for the study. The investigator must know the baseline results before enrollment. The pregnancy test for females of reproductive potential must be negative for those subjects to proceed to enrollment. All screening procedures must be done within 21 days of cycle 1 day 1, unless otherwise specified.

The following procedures will be performed to establish each candidate's general health and qualifications for possible enrollment into the study:

* Obtain signed, written informed consent and permission to use protected health information, (in accordance with the Health Insurance Portability and Accountability Act or HIPAA). Refusal to sign informed consent and permission excludes an individual from the study.

* Record medical history including cancer history: histology of tumor, date of GBM diagnosis, types and dates of prior anti-tumor therapy (including surgery, radiation therapy, systemic therapy), and date of most recent disease progression.

* Record recent (taken within 28 days prior to C1D1) medication history, including vitamins, herbal preparations, blood products, and other over the counter (OTC) drugs.

* Record blood pressure (BP), heart rate (HR), respiratory rate (RR) and temperature measurements. In subjects with known significant pulmonary disease, measure oxygen saturation using pulse oximeter after a 2 minute walk.

* Perform a complete physical examination, including height and weight.

* Assess Eastern Cooperative Oncology Group (ECOG) Performance Status score (see Appendix A, Eastern Cooperative Oncology Group Performance Status Scale)

* Obtain a baseline CXR or Chest CT scan.

* Obtain a baseline ECG to assess for cardiac arrhythmias or evidence of recent cardiac events.

* Obtain a baseline Ophtalmologic Evaluation.

* Draw blood samples for hematology, chemistry and coagulation.

* Obtain a blood sample for serum HCG pregnancy test in female subjects of child- bearing potential (all female subjects unless surgically sterilized or at least 1 year post-menopausal).

* Obtain a urine sample for urinalysis with microscopic analysis.

* Perform tumor assessment with MRI of the brain per RANO criteria. (refer to Appendix B)

* Review inclusion and exclusion criteria (see Section 3, Patient Selection).

6.1 Treatment Period Cycles 1 – 6

Study drug should be administered within ±2 days of the nominal time point. Lab tests used for determining dosing must be done within 5 days before the first dose of study drug (Cycle l/Day 1), and within 3 days before Days 1 and 15 of all subsequent cycles. All other required study assessments should be obtained within 5 days of the nominal time point unless otherwise specified. Subjects must receive the first dose of study drug within 21 days of signing the informed consent form.

6.1.1 Procedures

Day 1 of each cycle

Before administering TVB-2640, the following procedures will be done in all subjects, within 3 days of Cycle 1 Day 1:

- Record interim medical history since screening;
- Confirm that subject continues to meet inclusion/exclusion criteria;
- Record concomitant medications for previous 14 days;
- Draw serum and whole blood samples for analysis
- A separate serum sampling will be drawn to analyze presence of Microvesicles (proteomic and lipidomic analysis) by standard centrifugation techniques. *Only required within 3 days of C1D1 and within 3 days of C1D28.*

The following procedures will be done prior to TVB-2640/Bevacizumab administration within 3 days prior to Cycle 1 Day 1 and within 3 days prior to Day 1 for **All Future Cycles** (unless otherwise specified):

- Assess Eastern Cooperative Oncology Group (ECOG) Performance Status score
- Assess whether subject is adequately hydrated for administration of study drugs
- Cycle 2 and all subsequent cycles: Record AEs since last visit
- Any skin or mucosal lesions considered due to TVB-2640 should be photographed and, if possible, also biopsied.
- Record concomitant medications since last cycle;
- Record weight and vital signs;
- Detailed physical exam including neurologic assessment.
- Draw blood samples for hematology and chemistry;
- Obtain (serum or urine) pregnancy test in females of childbearing potential
- Urine dipstick for protein and glucose. If positive and a change from baseline or previous cycle, complete urinalysis including microscopic analysis should be performed
- Administer TVB-2640 (Plus or minus 2days.)
- Administer bevacizumab (Plus or minus 2 days.)
- Draw serum and whole blood samples for analysis

Day 15 of each cycle

- A physical exam will be done on Day 15 of Cycles 1 and 2. This may occur up to 3 days prior to Day 15.
- Physical exam on Day 15 for Cycle 3 and beyond will only be done if clinically indicated. If done, this may occur up to 3 days prior to Day 15.
- Record concomitant medications drugs since the last visit. This may occur up to 3 days prior to Day 15.
- Record AEs since the last visit. This may occur up to 3 days prior to Day 15.
- Measure and record vital signs (BP, HR, RR, temperature). This may occur up to 3 days prior to Day 15.
- Obtain blood samples for hematology, chemistry. This may occur up to 3 days prior to Day 15.
- Urine dipstick for protein and glucose. If positive and a change from baseline or previous cycle, complete urinalysis including microscopic analysis should be performed
- Administer TVB-2640 (Plus or minus 2 days.)
- Administer bevacizumab (Plus or minus 2 days.)

6.2 Study Termination / Early Study Termination and Survival Follow up.

6.2.1 Study Termination / Early Study Termination

This visit will occur 3-4 weeks after the start of Cycle 6 or at least 2 weeks after the last dose of TVB-2640 treatment for subjects who terminate early. Subjects who have not progressed after 6 cycles may be permitted to continue therapy on a case-by-case basis after discussion with the PI. The following will be done at the Termination/Early Termination visit:

- Record concomitant medications, including vitamins, herbal preparations, blood products, and other OTC drugs since the last visit
- Record AEs since the last visit
- Perform a complete physical examination, including weight
- Assess Eastern Cooperative Oncology Group (ECOG) Performance Status score
- Measure and record vital signs (BP, HR, RR, temperature)
- Obtain blood samples for hematology, chemistry and INR
- Obtain serum and whole blood samples for biomarker analysis
- Obtain urine sample for HCG HCG pregnancy test in female subjects of child-bearing potential (all female subjects unless surgically sterilized or at least 1 year post-menopausal)
- Obtain a urine sample for urinalysis
- Perform tumor assessments, using the same imaging assessments done at baseline, if not done within past 4 weeks
- Any ongoing study drug-related AE present at study termination, including a clinically significant laboratory test abnormality, will be followed until resolved or until the event stabilizes and the overall clinical outcome has been ascertained.
- Adverse events starting up to 30 days after the last dose of study medication may be collected by telephone contacts.

6.2.2 Survival Follow-up

When a subject has completed the study termination or early termination visit, he/she and/or a family member will be contacted for survival information every 3 months until one year from first dose. Anti-tumor therapy (description and dates) since the last contact will be collected at each survival follow up.

6.3 Assessment of Safety

6.3.1 Physical Examination

A complete physical examination will be performed at screening and at study termination or early study termination, results will be recorded by the investigator (or designee). Limited physical examination will be done on day 1 and 15 of each cycle until last visit throughout the study. Body weight will be measured on Day 1 of every cycle. The results of the physical examinations will be used for safety monitoring purposes only. At each study visit, according to good medical practice, the subject's general health (e.g., appearance, adequacy of hydration, presence of illness or injury, temperature, and vital signs indicative of a concurrent illness) will be assessed to determine whether continued dosing is appropriate.

6.3.2 Vital Signs

BP, HR, RR and temperature will be measured at the following time points:

- Screening
- Day 1 and Day 15 of every cycle (predose and postdose for each study drug administered)
- Study Termination or Early Study Termination

Blood pressure and HR measurements should be obtained with the subject's arm unconstrained by clothing or other material and supported at the level of the heart. The measurements will be obtained with the appropriate cuff size from the arm opposite that used for blood sampling. All BP measurements will be obtained from the same arm throughout the dosing period. The cuff should be placed on the designated arm at least 10 minutes prior to taking BP measurements.

6.3.3 Chest X-Ray or Computed Tomography

A chest X-ray or CT is to be performed during Screening within 28 days of Baseline.

6.3.4 Electrocardiogram

At Screening, 12-lead ECG will be performed for all patients at Baseline and at the Final Study visit.

6.3.5 Hematology, Clinical Chemistry and Urinalysis

Blood samples for hematology and clinical chemistry and urine samples for urinalysis are to be

collected for all patients during Screening, up to 72 hours before scheduled clinic visits on Day 1, and 15 of every cycle; and at the Final Study Visit.

Hematology and clinical chemistry results must be reviewed by the Investigator prior to study drug administration. If any clinically relevant hematology or clinical chemistry abnormalities are identified after the patient leaves the clinic, the patient is to be contacted and appropriate follow-up performed.

Hematology
CBC w/differential

Coagulation Studies
Prothrombin time (PT)/INR
Activated partial thromboplastin time (aPTT)

Chemistry
Blood urea nitrogen (BUN)
Creatinine
Albumin
Total protein
ALT/AST
Alkaline phosphatase (ALP)
Total bilirubin
Creatine phosphokinase (CPK)
Carbon dioxide (C02)
Chloride (Cl)
Sodium (Na)
Potassium (K)
Calcium
Magnesium
Glucose

Standard lipid panel (Screening only)
(i.e., low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, and total cholesterol)

Urinalysis
Specific gravity
pH
Blood
Glucose
Protein
Ketones
Microscopic examination of sediment

Clinical laboratory evaluations are to be repeated as necessary during treatment at a schedule determined by the Investigator, based on the patient's clinical status.

Laboratory abnormalities considered by the Investigator to be clinically significant during Screening and before study drug administration at Baseline are to be reported as part of the patient's medical history. Clinically significant laboratory abnormalities occurring after the start of study drug will be reported as an AE when the finding represents a change from Baseline.

6.3.6 Pregnancy Testing

For women of child-bearing potential, a serum β-human chorionic gonadotropin (hCG) pregnancy test will be performed during Screening and a serum or urine β-hCG pregnancy test will be performed within 48 hours before Baseline, D 1 of each subsequent treatment cycle, and the Final Study Visit.

The patient must agree to adequate birth control from the time the Screening pregnancy test is performed through 3 months after the final study drug dose. Study drug is to be discontinued for any patient with positive pregnancy test findings.

6.3.7 Ophthalmologic Examinations

Ophthalmologic examinations are to be performed during Screening, on D1 (+3 days) of C2, and and at the Final Study Visit. After C2D1, ophthalmologic examinations are to be repeated as clinically indicated.

Near and far visual acuity is to be assessed by an ophthalmologist using standard measures (e.g., Early Treatment Diabetic Retinopathy Study (ETDRS) or similar) in each eye. If the patient wears corrective lenses (e.g., glasses), then visual acuity is to be checked first with corrective lenses and then without correction. (A best-corrected examination is not required.) Note that contact lens wearers are to abstain from contact lens use during study drug treatment (i.e., from Baseline through the final TVB-2640 dose).

6.3.8 Disease Assessment

Patients will be assessed at screening, within 3 days prior to Cycle 1 Day 1, and at the end of every even cycle, with MRI per the modified RANO criteria as detailed in Appendix B.

7 PHARMACEUTICAL INFORMATION

7.1 Study Drug Supplies

TVB-2640 is supplied by 3-V Biosciences, Inc. as 50 mg and 200 mg strength capsules. Additional formulations of TVB-2640 may be introduced, when available. The bevacizumab will be obtained by the study center through commercial supplies.

7.2 Study Drug Packaging and Labeling

TVB-2640 will be packaged in bulk, screw-top plastic bottles. TVB-2640 will be labeled in accordance with applicable regulatory requirements. Study drug labels will not bear any statement

that is false or misleading in any manner or represents that the study drug is safe or effective for the purposes for which it is being investigated.

Bevacizumab will be commercially packaged and labeled.

7.3 Study Drug Storage

TVB-2640 is to be stored at room temperature. Refer to the Investigator Brochurel for more detailed information regarding study drug storage.

7.4 Study Drug Accountability

The US Food and Drug Administration (FDA) and other applicable regulatory authorities require accounting of all investigational drug received by each study center. Records of drug disposition required include the date received by the center, date administered, quantity administered, and the patient to whom study drug was administered. The Investigator is responsible for the accountability of all used and unused study drug containers and unused study drug. The study center also will maintain records for bevacizumab distribution, including the date administered, quantity administered, and the patient to whom the agent was administered.

The patient identification number and patient initials are to be recorded on each study drug accountability log. Each time study personnel dispense study drug for a patient, he or she is to record the date dispensed, amount of study drug dispensed, and his or her initials. Study personnel are to monitor the inventory of clinical supplies and maintain a count of all used and unused study drug. Pharmacy records will be reviewed during each audit performed by the QAU.

7.5 Study Drug Dose and Administration

Unless an alternate schedule is specified by the Sponsor, all patients are to receive TVB-2640 PO Continuously. For the purposes of this study, a treatment cycle is considered to be 28 days. The amount (in mg) of TVB-2640 to be administered initially is based on BSA, as calculated at Baseline and on Dl of every other cycle thereafter, starting with C3. As TVB-2640 is supplied as 50 mg and 200 mg strength capsules, the actual dose administered was to be within -20 to + 15% of the calculated dose. The flat dose of TVB-2640 to be administered, based on the patient's BSA, is as follows:

- BSA <1.5 m2 : TVB-2640 100 mg flat dose
- BSA >l .5 and <2.0 m2 : TVB-2640 150 mg flat dose
- BSA >2.0 and <2.5 m2 : TVB-2640 200 mg flat dose
- BSA >2.5m2: TVB-2640 250 mg flat dose

TVB-2640 initially will be administered on a QD schedule; thus, patients receiving TVB-2640 QD will receive 28 doses of TVB-2640 in each cycle. Each QD TVB-2640 dose is to be taken at the same time of the day under fasted conditions (i.e., at least 2 hours after last food consumption and at least 1 hour before next food consumption), with each dose separated by 24 hours (±4 hours).

Bevacizumab will be administered as per the prescribing information or per institutional standard of care, with the dose regimen documented in the eCRF. Any required pre- or concurrent medication is also to be administered in accordance with the prescribing information and routine clinical practice. On study visit days when both TVB-2640 and bevacizumab are to be administered, TVB-2640 should be taken approximately 2 hours prior to the initiation of the anticancer agent administration.

8 MANAGEMENT OF INTERCURRENT EVENTS

Comprehensive assessments of any apparent toxicity experienced by the subject will be performed throughout the course of the study. Study site personnel will report any clinical AE, whether observed by the investigator or reported by the subject.

8.1 Grading of Toxicity and Monitoring/Treatment of Toxicity

Clinical AEs or abnormal laboratory test results will be assessed by the principal investigator or other designated other physician, in accordance with the CTCAE v 4.03 criteria.

A physician or other qualified medical professional (e.g. Physician Assistant, Nurse Practitioner) designated by the Principal Investigator will manage and treat any toxicity. Subjects should be referred to an ophthalmologist for evaluation if clinically significant ophthalmologic abnormalities are noted. The ophthalmologist should be directed to perform examinations as clinically indicated.

8.2 Adverse Events

The most common (i.e., Incidence ≥10%) adverse events of any grade considered possibly, probably or definitely related to TVB-2640 among patients treated with TVB-2640 monotherapy were as detailed below and should be considered in the evaluation of patients. Given the non-overlapping toxicity profile with bevacizumab, it is expected that the toxicity profile of the combination should be similar to those of the individual agents. A physician or other qualified medical professional (e.g. Physician Assistant, Nurse Practitioner) designated by the Principal Investigator will assess the seriousness, severity, and causality of an AE based on the following definitions.

MedDRA Preferred Term	TVB-2640 Monotherapy Overall N=72 Overall Incidence n (%)	Grade 3 Incidence n (%)
Alopecia	40 (56)	0
Palmar-plantar erythrodysaesthesia syndrome	29 (40)	8 (11)
Fatigue	24 (33)	6 (8)
Decreased appetite	18 (25)	0
Dry skin	16 (22)	0
Constipation	13 (18)	0
Nausea	13 (18)	0
Diarrhoea	12 (17)	0
Vomiting	12 (17)	0
Cough	11 (15)	0
Dry eye	11 (15)	0
Abdominal pain	10 (14)	0
Conjunctivitis	10 (14)	0
Anaemia	9 (13)	3 (4)
Asthenia	9 (13)	0
Skin exfoliation	9 (13)	0
Urinary tract infection	9 (13)	0
Dehydration	8 (11)	0
Dyspnoea	8 (11)	1 (1)
Lacrimation increased	8 (11)	0
Dysgeusia	7 (10)	0
Oedema peripheral	7 (10)	0
Pyrexia	7 (10)	0
Rash	7 (10)	0

8.2.1 Defining Adverse Events

An adverse event (AE) is any undesirable event occurring to or in a subject enrolled in a clinical trial, whether or not the event is considered related to the study drugs (TVB-2640, &/or bevacizumab). This includes the time periods beginning after the first administration of study drug until 30 days after the last dose of study drug.

Adverse events include the following types of occurrences:

1) Suspected adverse reactions;

2) Other medical experiences, regardless of their relationship to the study drug, such as injury, causes for surgery, accidents, increased severity of pre-existing symptoms, apparently unrelated illnesses, and significant abnormalities in clinical laboratory values, physiological testing, or physical examination findings; and

3) Reactions from drug overdose, abuse, withdrawal, sensitivity, or toxicity.

8.2.1.1 Serious Adverse Events

A serious adverse event (SAE) is any adverse' experience that occurs at any dose and results in any of the following outcomes.

1) Death. This includes any death that occurs during the conduct of the clinical study, including deaths that appear to be completely unrelated to the study drug (e.g., car accident). However, deaths that occur due to disease progression are not considered SAEs, but should be reported as a death on study. If a subject dies during the study, and an autopsy is performed, the autopsy results should be sent to 3-V Biosciences. Possible evidence of organ toxicity and the potential relationship of the toxicity to the study drug are of particular interest. The autopsy report should distinguish between the relationship between the underlying diseases, their side effects, and the cause of death.

2) Life-threatening adverse experience. This includes any AE during which the subject is, in the view of the investigator, at immediate risk of death from the event as it occurs. This definition does not include any event that may have caused death if it had occurred in a more severe form.

3) Persistent or significant disability or incapacity.

4) Inpatient hospitalization or prolongation of existing hospitalization.

5) Congenital anomaly or birth defect.

6) Other medically important event which, according to appropriate medical judgment, may require medical or surgical intervention to prevent one of the outcomes listed above.

7) Pregnancy occurring in subjects treated with TVB-2640 should be reported using the serious adverse event reporting form (MedWatch form can be used for reporting).

8.2.1.2 Nonserious adverse events

A nonserious AE includes any AE that is not defined as an SAE.

8.2.1.3 Unexpected adverse events

An unexpected AE is any AE that is not identified in nature, severity or frequency.

8.2.2 Documenting All Adverse Events

Record all AEs as descriptive findings (symptoms, or laboratory, physical exam, or vitals abnormalities) or diagnoses if etiology is known. Included are all AEs that occur after the start of treatment or within 30 days of administration of the last dose of study drug. Record AEs of any severity and AEs that are assessed as serious or not serious.

Note: Unchanged, chronic conditions and cancer symptoms present at baseline are NOT AEs and should not be recorded unless there is an exacerbation or worsening in severity of a chronic condition or cancer symptom after the first administration of study drug until 30 days after the last dose of study drug. Chronic conditions and/or cancer symptoms that exacerbate or worsen in severity should be documented as a "worsening" condition. Death due to disease progression and measures of disease progression collected as efficacy endpoints (eg: increasing tumor size or new lesions) are not considered adverse events, but should be collected as termination reasons (if applicable) and/or noted in tumor assessment appropriate. Other reasons for death occurring during the AE reporting period are SAEs and should be reported as such.

8.2.2.1 Grading of Adverse Events

Severity of AEs or clinically significant laboratory test results will be assessed in accordance with the grading scale presented in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. A copy of this document can be found at the following internet site: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Clinically significant abnormal laboratory results and lab results requiring an intervention will be recorded as AEs and should describe whether the lab result was increased or decreased. The following definitions for rating severity of AEs will be used for events not covered in the CTCAE.

Grade 1: Mild; awareness of signs or symptoms that are easily tolerated, are of minor irritant type, cause no loss of time from usual activities, do not require medication or further medical evaluation, and/or are transient.

Grade 2: Moderate; signs or symptoms sufficient to interfere with function but not activities of daily living.

Grade 3: Severe; signs or symptoms sufficient to interfere with activities of daily living; signs and symptoms may be of a systemic nature, or require further medical evaluation and/or treatment.

Grade 4: Disabling or with life-threatening consequences. (This definition does not include any event that might have caused death if it had occurred in a more severe form.)

Grade 5: Death

8.2.2.2 Relationship to Study Drug

The causal relationship of each AE to study drug will be determined by the Investigator according to best medical judgment, as follows:

Definitely related: This category applies when, after careful medical consideration, there is almost no consideration of other causation.

Probably related: There is a clinically plausible time sequence between onset of the AE and study drug administration. The AE is unlikely to be caused by a concurrent and/or under lying illness, other drugs, or procedures. If applicable, the AE follows a clinically consistent resolution pattern upon withdrawal of study drug.

Possibly related: There is a clinically plausible time sequence between onset of the AE and study drug administration, but the AE could also have been caused by the concurrent/underlying illness, other drugs, or procedures. Information regarding study drug withdrawal may be lacking or unclear. "Possible" should be used when study drug administration is one of several biologically plausible causes of the AE.

Unlikely related: The AE is most likely due to a non-study drug-related cause. However, association with the study drug cannot be completely ruled out.

Unrelated: Another cause of the AE is most plausible and a clinically plausible temporal sequence is inconsistent with the onset of the AE and study drug administration and/or a causal relationship is considered biologically implausible.

If the relationship between the AE/SAE and study drug is determined to be "possible", "probable", or "definite", the event will be considered to be treatment-related for the purposes of expedited regulatory reporting and safety analyses.

8.2.2.3 Abnormal Laboratory Test Results as Adverse Events

The investigator will monitor the laboratory test results and determine the clinical significance of any result that falls outside of the reference range. In accordance with good medical practice, any clinically significant abnormal laboratory test results must be followed until resolved or stabilized. Abnormal laboratory test results should not be reported as AEs unless, in the opinion of the investigator, the results constitute or are associated with a clinically relevant condition or require intervention.

In the event of unexplained, clinically significant abnormal laboratory test results, the tests should be repeated immediately and followed up until the values have returned to within the reference range or to baseline for that subject.

8.2.3 Reporting and Documenting Serious Adverse Events

Serious adverse events (SAE) that occur at any time point after the first dose of study drug until 30 days after the last dose of study drug must be reported. SAEs must be reported as per institutional policy and as required under the Data Safety Monitoring Plan (see Section 11.6 for DSMP).

1) Submit all known subject information (listed below) within 24 hours of knowledge of the SAE occurrence. The following information should also be entered in the database (or as much as

possible to obtain and still report the event within 24 hours):

a) Subject's Demographic Data

b) Subject's weight

c) Description of SAE, including date of onset and duration, severity, and outcome

d) All dosing data of study drugs administered up to the date the SAE occurred

e) Action taken regarding study drug administration

f) Relationship of SAE to study drugs

g) Concomitant medications, including regimen and indication

h) Intervention, including concomitant medications used to treat SAE

i) Pertinent laboratory data and diagnostic tests conducted and date

j) Pertinent medical history of subject

k) Date of hospital admission discharge (if applicable)

i) Date of death (if applicable)

2) Perform appropriate diagnostic tests and therapeutic measures, and submit all follow-up substantiating data, such as diagnostic test reports and autopsy report to 3-V Biosciences.

3) Conduct appropriate consultation and follow-up evaluations until the events are resolved, stabilized, or otherwise explained by the principal investigator.

4) Review each SAE report and evaluate the relationship of the SAE to study treatment and to the underlying disease. The Investigator Brochure developed by 3-V Biosciences will be used to determine whether the SAE is unexpected in nature.

5) Based on a cooperative assessment of the SAE with 3-V Biosciences, a decision for any further action will be made. The primary consideration is subject safety. If the discovery of a new SAE related to the study drug raises concern over the safety of its continued administration to subjects, 3-V Biosciences will be notified first, subsequent notification to the FDA will be generated by the PI and 3-V Biosciences.

6) The investigator must report all SAEs and unexpected problems promptly to the IRB/IEC, as appropriate (see ICH Guidelines, Good Clinical Practice (E6)).

Other actions regarding SAEs might include the following:

a) Protocol amendment

b) Discontinuation or suspension of the protocol

c) Modification of informed consent to include recent findings

d) Informing current study participants of new findings

e) Identification of specific AEs as drug-related

8.2.4 Follow Up of Adverse Events

All AEs are followed until they are resolved or determined to be irreversible or otherwise explained by the principal investigator.

8.3 Concomitant and Excluded Therapy

All medications and blood products (prescription and over-the-counter including herbal preparations) taken within 14 days of Cycle l/Day 1 will be recorded by the investigator (or designee). The reason(s) for treatment, dosage, and dates of treatment should be recorded in the source documents. In addition, concomitant medications used to treat adverse events occurring up to 30 days after the last dose of study drug will be recorded.

Female subjects who have been on hormone replacement therapy (HRT) for menopausal symptoms for a period of at least 2 months will not be excluded from the study provided the HRT regimen remains unchanged during the conduct of the study.

9 REMOVING SUBJECTS FROM THE STUDY

9.1 Criteria for Termination

Subjects are free to discontinue (withdraw) at any time during this clinical trial. If a subject withdraws from participation in the study during the treatment period, he or she should be encouraged to return for an early termination visit for evaluation of safety (see Section 6.2.1, Study Termination/Early Study Termination).

The investigator has the right to discontinue any subject from study drug administration or study participation. Reasons for subject discontinuation may include, but are not limited to, the following:

- Clinically significant deterioration of the subject's condition;
- Disease progression;
- Requirement for other anti-tumor therapy during the study; Noncompliance;
- Pregnancy; Significant AE;

- Subject's right to withdraw from the study at any time, with or without stated reason;
- Significant protocol violation;
- Lost to follow-up;
- Death;

Any other reason that, in the opinion of the principal investigator, would justify the removal of a subject from the study. The primary consideration in any determination to discontinue a subject's participation must be the health and welfare of the subject.

All subjects will be instructed on the importance of complying with the requirements of the study. It is expected that subjects will complete all of the necessary visits. If a subject does not return for follow-up visits as directed or does not adhere to the study requirements, the investigator will determine if early withdrawal should occur.

9.2 Documentation

The primary reason for early removal of a subject from the study must be documented clearly, and must be completed for any subject who has received any amount of drug during the treatment period. If the reason for early withdrawal is an AE or an abnormal laboratory value, the specific event or test result must also be recorded.

9.3 For Participants who withdraw early

Following early termination, the subject should be informed about which evaluations are necessary to monitor his or her safety. In addition, subjects should be encouraged to complete any procedures or evaluations outlined in Section 6.2.1 Study Termination/Early Study Termination.

9.4 Replacement of Subjects

Subjects who have not received TVB-2640 will be replaced. Subject enrollment numbers are unique and will not be re-assigned.

10 CONDITIONS FOR INITIATING, MODIFYING, OR TERMINATING THE STUDY

10.1 Institution Review

The investigator will submit this protocol, any protocol modifications, and the subject consent form to be used in this study to the local Institutional Review Board (IRB) for review and approval.

10.2 Informed Consent

The investigator or his or her designee must explain to the subject, in the presence of a witness, the purpose and nature of the study, the study procedures, and the possible adverse effects, and all other elements of consent as defined in 21 CFR Part 50 and Clinical Trial Directive or ICH E6 guidelines before enrolling that subject in the study. It is the investigator's (or

designee's) responsibility to obtain informed written consent from each subject, or if appropriate, the subject's parent or legal guardian.

10.3 Modifications

If any modifications in the experimental design, dosages, parameters, subject selection, or any other sections of the protocol are indicated or required, the investigator will consult with 3-V Biosciences before such changes are instituted. Modifications will be accomplished through formal amendments and approval from the appropriate IRB.

10.4 Deviations

The PI will consider any deviations from the protocol on a case by case basis. The investigator or other designated alternate in his absence will contact the local DSMB (DSMB2) as soon as possible to discuss the associated circumstances. The principal investigator and the DSMB will then decide whether the subject should continue to participate in the study. All protocol deviations and the reasons for such deviations must be noted in the source documents and will be reported to the Mays Cancer Center DSMC and to the IRB as per standard institutional policy.

10.5 Termination

The investigator reserves the right to terminate the study at any time. If the investigator discovers conditions arising during the study that suggest the study should be halted, he will alert the DSMB and the local IRB. Conditions that may warrant study or study center termination include, but are not limited to:

- The discovery of any unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence to the protocol requirements.

Should the study be closed prematurely, all study materials (study drug, etc.) must be returned to 3V biosciences or designee (or disposed of as directed by the 3VB or designee).

11 INVESTIGATOR'S RESPONSIBILITIES

11.1 Responsibilities / Performance

The investigator will ensure that this study is conducted in accordance with all regulations governing the protection of human subjects. The investigator will adhere to the basic principles of "Good Clinical Practice," as outlined in Title 21 of the Code of Federal Regulations (CFR), Part 312, Subpart D, "Responsibilities of Sponsors and Investigators"; 21 CFR, Part 50, "Protection of Human Subjects"; 21 CFR, Part 56, "Institutional Review Boards"; and the US Food and Drug Administration (FDA) guideline entitled "Good Clinical Practice: Consolidated Guideline". For studies conducted outside of the USA, the investigator will ensure adherence to the principles outlined in the International Conference on Harmonization (ICH) E6 "Guideline for Good Clinical Practice". Additionally, this study will be conducted in compliance with the Declaration of Helsinki and with any local laws and regulations of the country in which the research is conducted.

The investigator will ensure that all work and services described in or associated with this protocol will be conducted in accordance with the investigational plan, applicable regulations, and the highest standards of medical and clinical research practice. The investigator is responsible for the control of drugs under investigation. The investigator will provide copies of the study protocol and Investigator's Brochure to all sub-investigators, pharmacists, and other staff responsible for study conduct.

11.2 Confidentiality

The investigator must ensure that each subject's anonymity will be maintained and each subject's identity will be protected from unauthorized parties. A number will be assigned to each subject upon study entry and the number and the subject's initials will be used to identify the subject for the duration of the study. Documents submitted to 3-V Biosciences should not identify a subject by name. Documents that are not submitted to 3-V Biosciences (eg, signed consent form) will be maintained by the investigator in strict confidence.

11.3 Institutional Review

The investigator will submit this protocol, any protocol modifications, and any accompanying material provided to the subject (eg, informed consent form, subject information sheets, or descriptions of the study used to obtain informed consent) to the appropriate IRB for review and approval. A letter confirming IRB approval of the protocol and subject consent forms, and an IRB approved informed consent form must be forwarded to 3-V Biosciences prior to the enrollment of subjects into the study. A copy of the approved subject consent form will also be forwarded to 3-V Biosciences.

11.3.1 Modifications

If any modifications in the experimental design, dosages, parameters, or subject selection are indicated or required, the investigator will consult with 3-V Biosciences (or vice versa) before such changes are instituted. Modifications will be accomplished through formal amendments to this protocol and approval by the appropriate IRB. Copies of all subsequent IRB approvals (e.g., protocol amendments) must be sent to 3-V Biosciences.

11.3.2 Protocol Deviations

The PI will consider any deviations from the protocol on a case-by-case basis. The investigator or other designated alternate in his absence will contact the local DSMB (DSMB2) as soon as possible to discuss the associated circumstances. The principal investigator and the DSMB will then decide whether the subject should continue to participate in the study. All protocol deviations and the reasons for such deviations must be noted in the source documents and will be reported to the Mays Cancer Center DSMC and the IRB as per standard institutional policy.

11.3.3 Termination

If 3-V Biosciences and/or the investigator(s) discover conditions during the course of the study that indicate it should be discontinued, an appropriate procedure for terminating the study will

be instituted, including notification of the appropriate regulatory agencies and the IRB.

11.4 Informed Consent and permission to use protected Health Information

It is the responsibility of the investigator to obtain written informed consent from each subject participating in this study after adequate explanation, in lay language, of the methods, objectives, anticipated benefits, and potential hazards of the study. The investigator must also explain that the subject is completely free to refuse to enter the study or to discontinue participation at any time (for any reason) and receive alternative conventional therapy as indicated. Prior to study participation, each subject will sign an IRB approved informed consent form, and receive a copy of same. For participant subjects not qualified or able to give legal consent, consent must be obtained from a parent, legal guardian, or custodian.

The investigator or designee must explain to the subject before enrollment into the study that for valuation of study results, the subject's protected health information obtained during the study may be shared with 3-V Biosciences, regulatory agencies, and IECs/IRBs. It is the investigator's (or designee's) responsibility to obtain permission to use protected health information per HIPAA from each subject, or if appropriate, the subjects' parent or legal guardian.

11.5 Source Documentation and Investigator Files

The investigator must maintain adequate and accurate records to fully document the conduct of the study and to ensure that study data can be subsequently verified. These documents should be classified into 2 separate categories: (1) investigator study file and (2) subject clinical source documents that corroborate data collected.

Subject clinical source documents would include hospital clinic patient records; physician's and nurse's notes; appointment book; original laboratory, ECG, EEG, radiology, pathology, and special assessment reports; pharmacy dispensing records; subject diaries; signed informed consent forms; consultant letters; and subject screening and enrollment logs.

The following will be documented in source documents at the site:

1) Medical history/physical condition and diagnosis of the subject before involvement in the study sufficient to verify protocol entry criteria (if not already present);

2) Study number, assigned subject number, and verification that written informed consent was obtained (each recorded in dated and signed notes on the day of entry into the study);

3) Progress notes for each subject visit (each dated and signed);

4) Study drug dispensing and return;

5) Review of laboratory test results;

6) Adverse events (action taken and resolution);

7) Concomitant medications (including start and stop dates); and

8) Condition of subject upon completion of or early termination from the study.

11.5.1 Exclusion Log

The investigator must keep a record listing all patients considered for entry into the study but subsequently excluded. The reason for each exclusion will be recorded in the Subject Exclusion Log.

11.6 Data Safety Monitoring Plan

A Data and Safety Monitoring Plan is required for all an individual protocols conducted at Mays Cancer Center. All protocols conducted at UT Health Cancer Center are covered under the auspices of the Mays Cancer Center Institutional Data Safety Monitoring Plan (DSMP).

The MaysCancer Center Institutional DSMP global policies provide individual trials with:

- Institutional policies and procedures for institutional data safety and monitoring
- An institutional guide to follow
- Monitoring of protocol accrual by the Mays Cancer Center Protocol Review Committee
- Review of study forms and orders by the Forms Committee
- Independent monitoring and source data verification by the Mays Cancer Center QA Monitor/Auditor tools for monitoring safety events
- Monitoring of UPIRSO's by the Director of Quality Assurance and DSMC
- Determining level of risk (Priority of Audit Level Score – PALS)
- Oversight by the Data Safety Monitoring Committee (DSMC), and verification of protocol adherence via annual audit for all Investigator Initiated Studies by the Mays Cancer Center Quality Assurance Division.

11.6.1 Monitoring Safety

Due to the risks associated with participation in this protocol, the Mays Cancer Center DSMB2 in conjunction with the Principal Investigator will perform assessment of adverse events, adverse event trends and treatment effects on this study. The Mays Cancer Center DSMB2 acts as an independent Data Safety Monitoring Board (DSMB) for IIS conducted at Mays Cancer Center. The Mays Cancer Center will monitor data throughout the duration of a study to determine if continuation of the study is appropriate scientifically and ethically. An additional layer of review is provided by the Mays Cancer Center Data Safety Monitoring Committee (DSMC) who will review the DSMB's quarterly reports.

Baseline events and adverse events will be captured using the Mays Cancer Center Master Adverse Events Document for each patient using CTCAE V4.0 for the grading and attribution of adverse events. Usage of the Mays Cancer Center Master Adverse Events Document centrally documents:

- the event and grades the seriousness of the event,
- if the event was a change from baseline,
- the determination of the relationship between the event and study intervention,
- if the event was part of the normal disease process, and
- actions that were taken as a result of the event.

11.6.2 Reporting Requirements

For this study, the Master Adverse Events Documents collected on patients for this protocol will be reviewed by the Principal Investigator on a monthly basis to determine if a serious safety problem has emerged that result in a change or early termination of a protocol such as:

- Dose modification,
- Suspending enrollment due to safety or efficacy, or
- Termination of the study due to a significant change in risks or benefits.

The PI will provide the DSMB2 with the quarterly findings for discussion and review during their meetings.

Specific areas of concern that will be reported to the DSMB2 regarding this study that would qualify as an endpoint are:

- Evidence from metabolic change analysis of tumor tissue by MR-Spectroscopy and serum metabolomic changes that TVB-2640 does in fact NOT penetrate the blood brain barrier and as such would have no therapeutic benefit to patients on study
- Unacceptable toxicity that would prevent patients from receiving treatment and therefore benefit

As per the Mays Cancer Center DSMP, any protocol modifications, problematic safety reports, unanticipated problems, and suspension or early termination of a trial must be reported to all members of the research team. Suspension and early termination of a trial must also be reported immediately to the Director of Quality Assurance who will promptly notify the sponsor and the UTHSCSA IRB.

The PI will review the Master Adverse Events documents to determine the significance of the reported events and will provide findings using the Investigator Initiated Study Quarterly DSMC Report Form.. The DSMB2 will reviewthe information provided by the PI and report to the Mays Cancer Center DSMC on a quarterly basis unless an emergent issue has been identified. The Investigator Initiated Study Quarterly DSMC Report Form includes information on adverse events, current dose levels, number of patients enrolled, significant toxicities per the protocol, patient status (morbidity and mortality) dose adjustments with observed response, and any interim findings. Any trend consisting of three or more of the same event will be reported to the Mays Cancer Center DSMC for independent review outside of the quarterly reporting cycle, which begins three months following protocol start up. The DSMB2 will also provide its findings to the

Mays Cancer Center's Regulatory Affairs Division so that it may be provided to the UTHSCSA IRB with the protocol's annual progress report. Conflict of interest is avoided by the independent reviews of the Mays Cancer Center DSMB2, UT Health Cancer Center DSMC and by ongoing independent review of UPIRSO's by the Director of Quality Assurance.

All SAE and UPRISO's will be reported following Mays Cancer Center and UTHSCSA institutional guidelines. 3-V Biosciences will be notified as well.

UTHSCSA SAE/UPIRSO REPORTING REQUIREMENTS		
Type Event	Report to	Timeframe
All AE, SAE and UPIRSO	Regulatory affairs and DQA	Per institutional requirements as noted below.
SAE	PI	Within 24 hours
AE/SAE	UTHSCSA IRB	Annually
UPIRSO - All	PI	Within 24 hours of the PI determining a UPIRSO exists
UPIRSO - life threatening	UTHSCSA IRB	Within 48 hours of the PI determining a UPIRSO exists
UPIRSO - non-life threatening	UTHSCSA IRB	Within 7 days of the PI determining a UPIRSO exists

Serious adverse events on NCI sponsored trials utilizing a commercially available agent (with no IND's involved) will additionally be reported via the FDA's Medwatch program.

11.6.3 Assuring Compliance with Protocol and Data Accuracy

As with all studies conducted at Mays Cancer Center, the PI has ultimate responsibility for ensuring protocol compliance and data accuracy/integrity. Protocol compliance, data accuracy and reporting of events is further ensured by an annual audit conducted by the Data Safety Officer, whose audit report is shared with the PI, the research team and will be reviewed by the Mays Cancer Center DSMC.

Mays *Cancer Center DSMB Membership*

The Mays Cancer Center has two DSMB's with a primary set of members specific to the histology of the study consisting of UTHSCSA faculty and staff. This Protocol will utilize DSMB#2 for Solid Tumor Studies.

As per NCI guidelines and to eliminate conflict of interest (financial, intellectual, professional, or

regulatory in nature), the Mays Cancer Center DSMB specific to this study will not treat patients on this protocol. Usage of the DSMB specific to the histology has been created to ensure that experts in that histology are represented on the DSMB assembled for this protocol, but may be expanded, at the PI's discretion, to include other members which may include:

- Experts in the fields of medicine and science that are applicable to the study (if not currently represented on the DSMB),
- Statistical experts,
- Lay representatives,
- Multidisciplinary representation, from relevant specialties including experts such as bioethicists, biostatisticians and basic scientists, and
- Others who can offer an unbiased assessment of the study progress.

Additional or alternate membership of in the DSMB is selected by the DSMC chair, in conjunction with the PI of this protocol.

Mays Cancer Center DSMB Charter and Responsibilities

The Mays Cancer Center DSMB will provide information on the membership composition, including qualifications and experience to both the UTHSCSA IRB and Mays Cancer Center PRC for review. The Mays Cancer Center DSMB for this study will act as an independent advisory board to the PI and will report its findings and recommendations to the PI, the UTHSCSA IRB and the Mays Cancer Center DSMC. Mays Cancer Center DSMB reports will utilize the Investigator Initiated Study Quarterly DSMC Report Form and meetings will occur quarterly to review any updates from the prior meeting.

Once the protocol is activated, if not already established elsewhere in the protocol the Mays Cancer Center DSMB will establish and provide:

- procedures for maintaining confidentiality;
- statistical procedures including monitoring guidelines, which will be used to monitor the identified primary, secondary, and safety outcome variables;
- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study;
- plans for changing frequency of interim analysis as well as procedures for recommending protocol changes;
- recommendation of dose escalation, MTD recommendation of early termination based on efficacy results;
- recommendation of termination due to unfavorable benefit-to-risk or inability to answer study questions;
- recommendation of continuation of ongoing studies;
- recommend modification of sample sizes based on ongoing assessment of event rates; and
- review of final results and publications.

12 STATISTICAL CONSIDERATIONS

This is a prospective, randomized, phase 2 study of TVB-2640 in combination with bevacizumab or bevacizumab alone in patients in first relapsed high grade astrocytoma. Analysis will be intent-to-treat of all randomized patients.

Evaluability – Patients will be evaluable for inclusion in the analysis of the EFS comparison between treatment arms if they are randomized.

The median time to progression of patients treated with Bevacizumab is 124 days (95% confidence interval: 87–154 days)(2). A sample size of total 24 evaluable patients will be enrolled.

- Study Design / End Points *Primary outcome/endpoint:*

We will measure progression-free survival of patients with High Grade Astrocytoma who are treated with TVB-2640 in combination with bevacizumab versus bevacizumab alone, defined as time from study enrollment to the first occurrence of relapse, death from any cause or until last contact (if no event occurs)

- *Secondary outcomes/endpoints:*

We will evaluate and grade Incidence of adverse events as assessed by NCI CTCAE v. 4.03

- *Analytic plan for primary objective:*

We will test that the combination of bevacizumab and TVB-2640 versus bevacizumab alone will increase the rate of PFS, by using a non parametric test (Log-Rank), for a given alpha of 0.1 and power of 91.6%.

- *Analytic plan for secondary objectives:*

Toxicities will be tabulated by type and grade according to NCI CTCAE v. 4.03

12.2 Sample Size / Accrual rate

A sample size of total 24 evaluable patients (enrolled within 1 – 1.5 years) will provide 91.6% power to detect a 4 month difference in the median time to progression (3 months for bevacizumab alone versus 7 months in TVB-2640 in combination with bevacizumab, i.e., a hazard ratio of 0.43) using a one-sided log-rank test with alpha=0.1.

We expect to accrue 1 to 2 patients a month, i.e. about 12-24 patients per year. The 24 patients can be enrolled in 1 – 1.5 years. With an additional 3 months of follow-up on the last patient, the total study duration is about 18 months.

The primary efficacy analyses for estimation of PFS rates will be performed using a one sided log-rank test for an overall type-I error at 0.1 for each treatment group and a power of 91.6%. Thus far we will be able to reject the null hypothesis that the experimental and control survival curves are equal.

13. REFERENCES

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14. STUDY CALENDAR

Study Procedures	Screening (w/in 21 days of C1D1)	Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		EOT [G]
		Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	
Day		1	15	28	1	15	1	15	1	15	1	15	1	15	
Informed Consent	X														
Demographics	X														
Med/Surg History	X														
Physical Exam (to include Adverse events and conc meds)[F]	X	X[B]	X[B]		X[B]	X[B]	X[B]		X[B]		X[B]		X[B]		X
Vital signs	X	X[B,I]	X[B,I]		X[B,I]	X[B,I]	X[B,I]	X[B,I]	X[B,I]	X[B,I]	X[B,I]	X[B,I]	X[B,I]	X[B,I]	X
Height	X	X[B]			X		X								
Weight	X	X[B]	X[B]		X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X
ECOG	X	X[B]	X[B]		X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X
CXR or CT	X														
ECG	X														X
MR-SPEC		X[B]		X[B]											
Serum Sampling[H]		X[B]		X[B]	X[B]		X[B]		X[B]		X[B]		X[B]		X[B]
Ophtalmology Eval.	X				X[B]										X
Hematology labs	X	X[B]	X[B]		X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X
Chemistry labs	X[J]	X[B]	X[B]		X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X
Coagulation labs[C]	X														X
Urinalysis [D]	XX[B]	X[B]	X[B]		X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X Pregnancy	
test	X	X[B]			X[B]		X[B]		X[B]		X[B]		X[B]		X
TVB-2640		X	X		X	X	X	X	X	X	X	X	X	X	
Bevacizumab[F]		X	X		X	X	X	X	X	X	X	X	X	X	
~~Tumor Assessment~~ with Brain MRI[E]	X	X[BE]					X[BE]				X[BE]				X

B. May be done up to 3 days prior to visit.
C. INR only if pt is on warfarin
D. Screen & EOT: UA with micro. Other visits, urine dipstick for protein & glucose. If positive or change from baseline, complete urinalysis w/ micro.
E. Tumor Assessments: At screening & after every even cycle (within 3 days)
F. See dose level instructions in the protocol. Plus or minus 2 days.
G. Occurs 3-4 weeks after the start of C6 or at least 2 weeks after the last dose of TVB-2640 for subjects who terminate early.
H. Serum samples to analyze presence of Microvesicles (proteomic and lipidomic analysis) by standard centrifugation techniques.
I. To be obtained predose and post-dose.
J. Include standard Lipid Panel at Screening only.

APPENDIX A: EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE SCORE SCALE

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

APPENDIX B: RANO TUMOR RESPONSE

Table: Summary of the RANO Response Criteria

	CR	PR	SD	PD#
T1-Gd +	None	≥50% decrease	<50% decrease-<25% increase	≥25% increase*
T2/FLAIR	Stable or decrease	Stable or decrease	Stable or decrease	Increase*
New Lesion	None	None	None	Present*
Corticosteroids	None	Stable or decrease	Stable or decrease	**NA**
Clinical Status	Stable or increase	Stable or increase	Stable or increase	Decrease*
Requirement for Response	All	All	All	Any*

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease

Progression occurs when any of the criteria with * is present

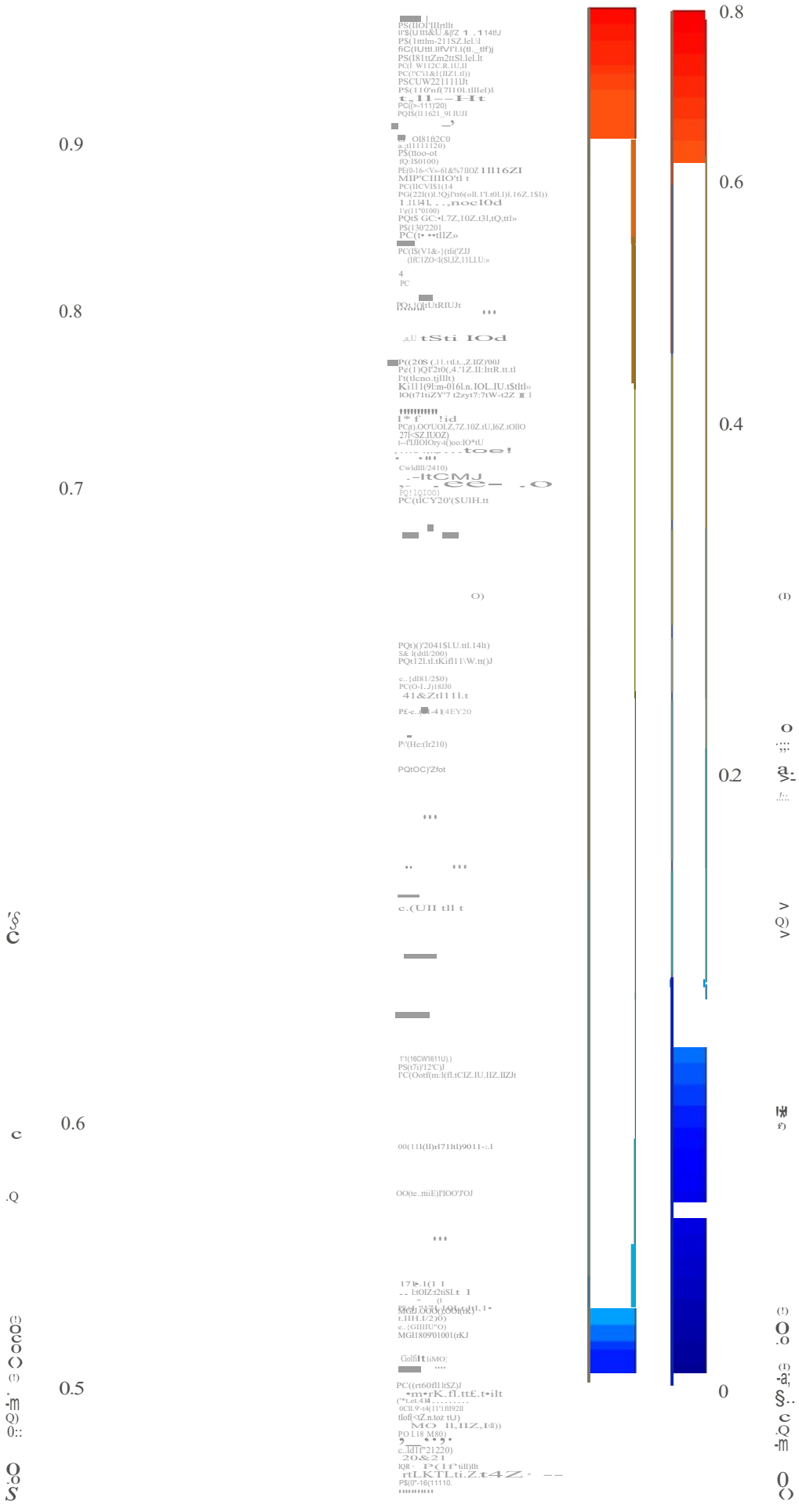
NA: Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration

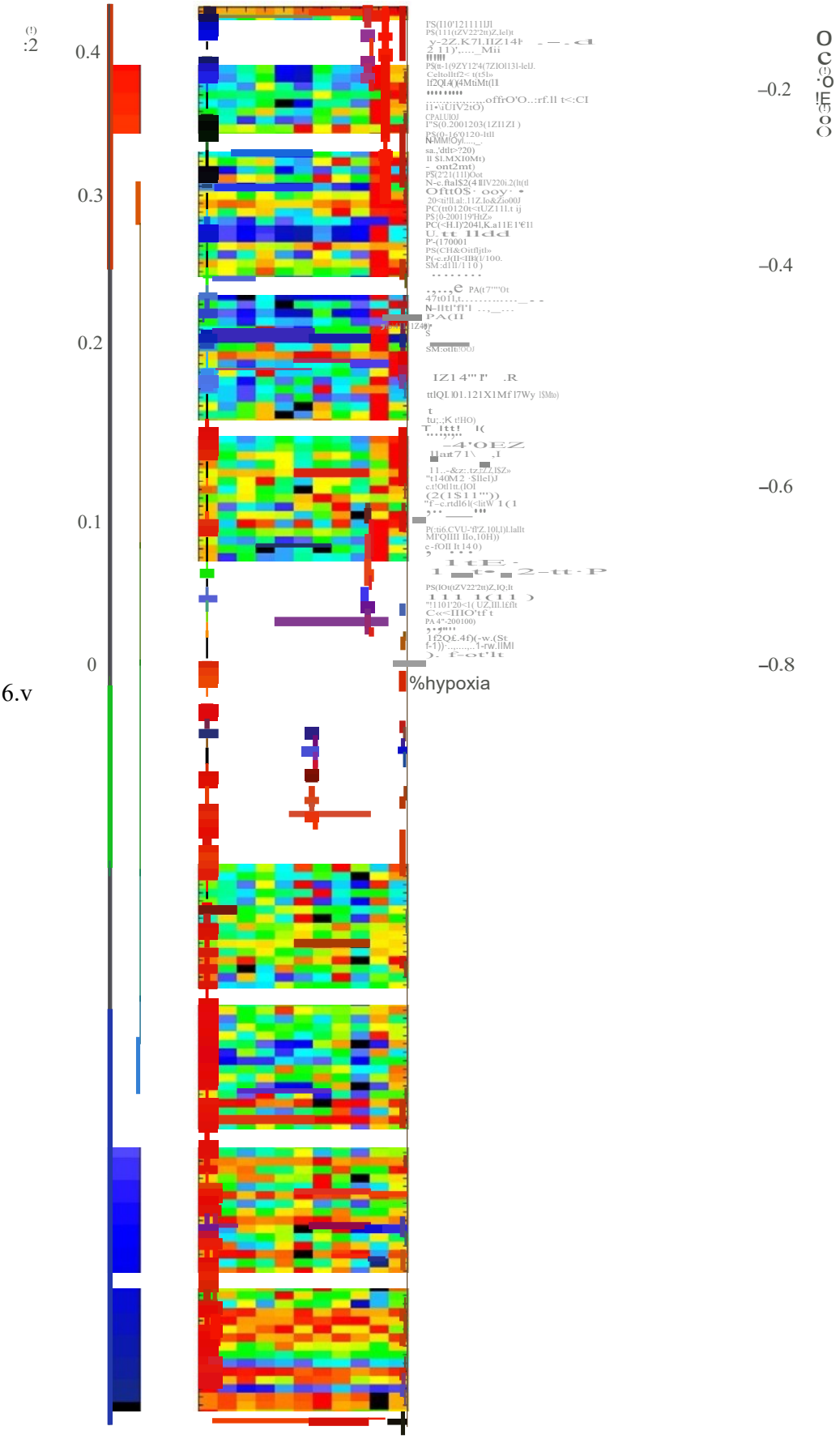
APPENDIX C: Bevacizumab Dose Modifications

Important treatment considerations—Dose modifications

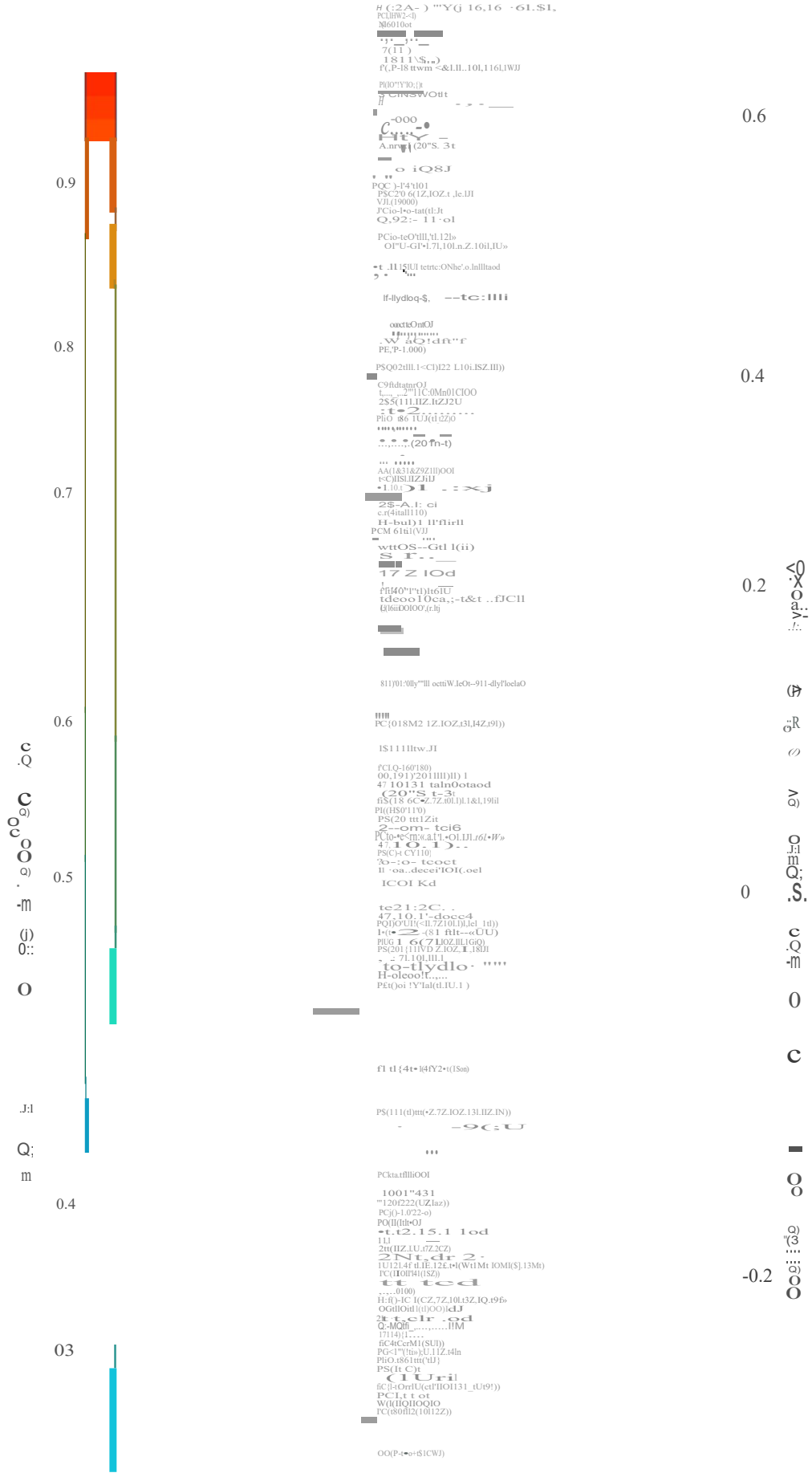
- There are no recommended dose reductions
- Discontinue Avastin in patients with
  - Gastrointestinal (GI) perforations (GI perforations, fistula formation in the GI tract, intra-abdominal abscess)
  - Fistula formation involving an internal organ
  - Wound dehiscence and wound healing complications requiring medical intervention
  - Serious hemorrhage [Ie, requiring medical intervention)
  - Severe arterial thromboembolic event (ATE)
  - Life-threatening (grade 4) venous thromboembolic events, including pulmonary embolism
  - Hypertensive crisis or hypertensive encephalopathy
  - Posterior reversible encephalopathy syndrome (PRES)
  - Nephrotic syndrome
- Temporarily suspend Avastin for: at least 4 weeks prior to elective surgery, severe hypertension not controlled with medical management, moderate to severe proteinuria, and severe infusion reactions
- The safety of resumption of Avastin therapy in patients that experienced PRES or ATE is unknown

FIGURE A
BLOOD

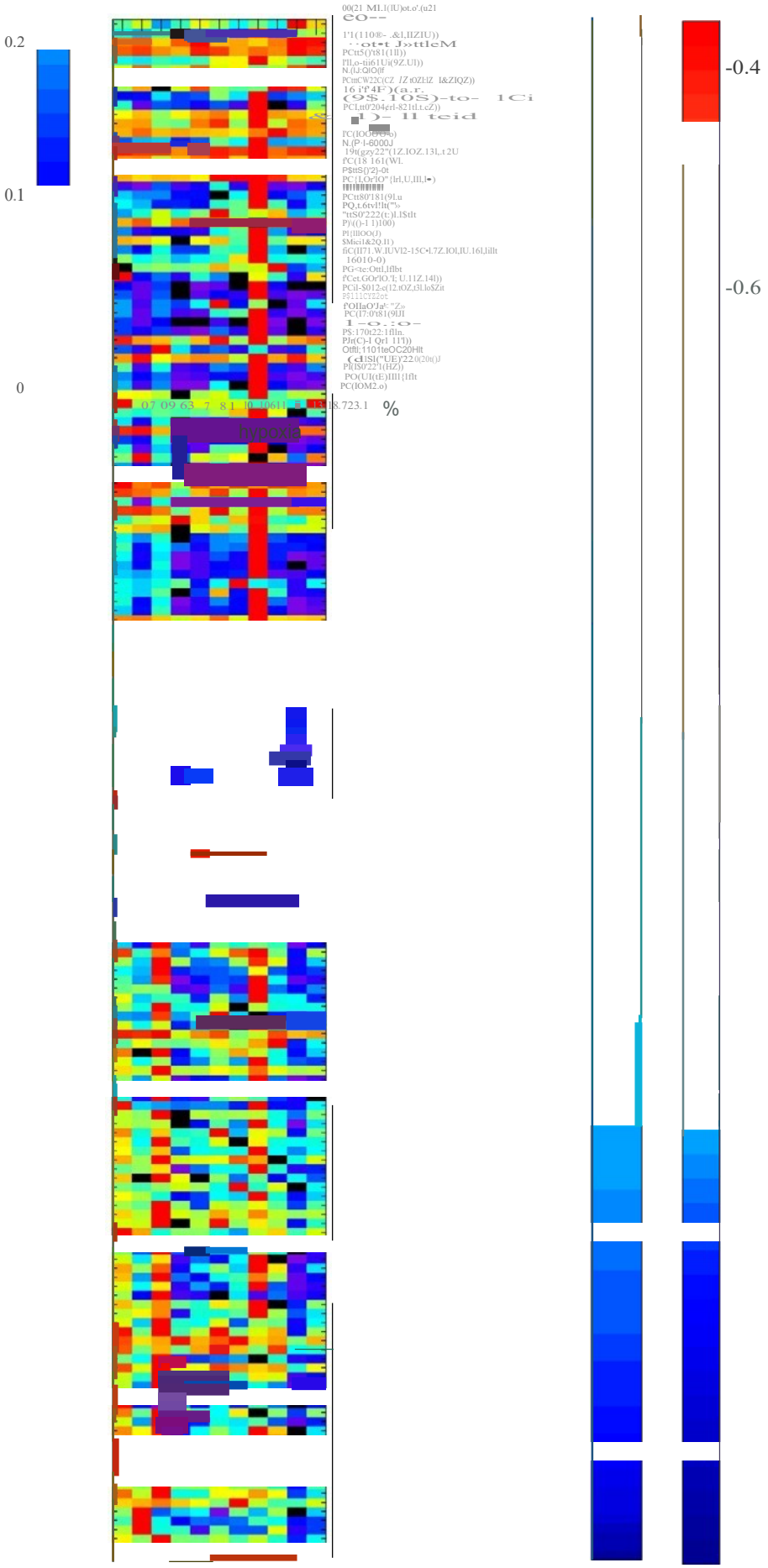



0.4
0.3
0.2
0.1
0
–0.2
–0.4
–0.6
–0.8
%hypoxia

TISSUE



Protocol Version



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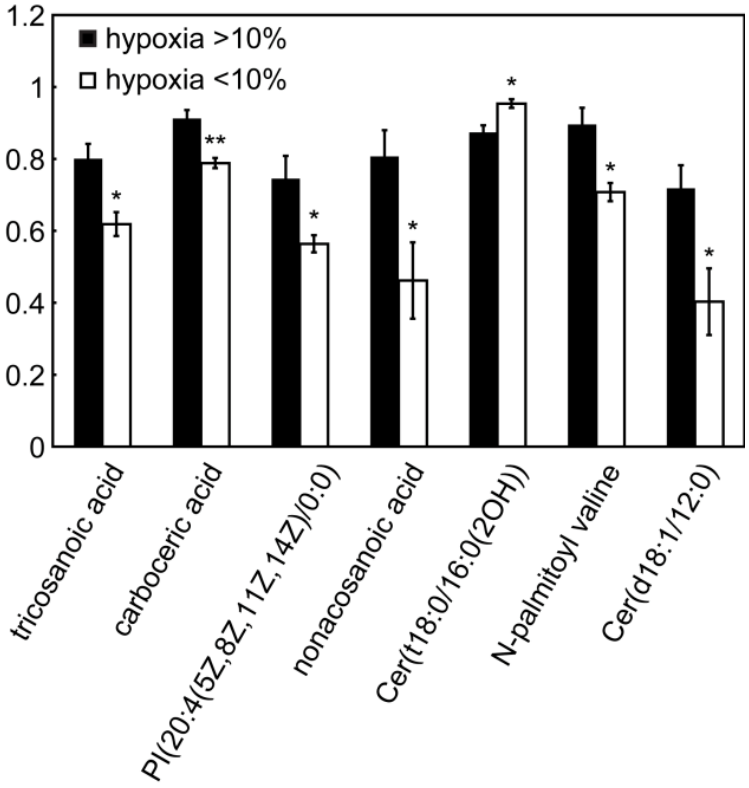
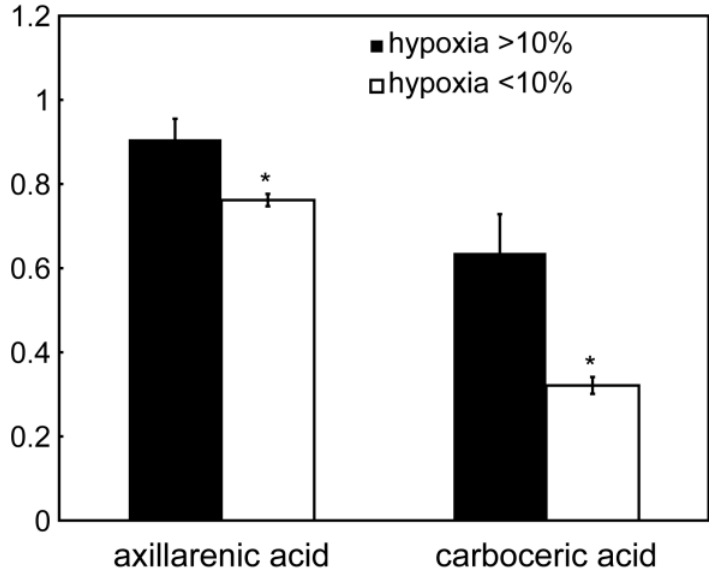


TISSUE



PLASMA VS TISSUE HYPOXIA