

Initial Review

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Protocol Title: Phase I/II Adaptive Randomized Trial of Bevacizumab versus Bevacizumab plus Vorinostat in Adults with Recurrent Glioblastoma

Abbreviated Title: PH I/II Bev Vorinostat GBM

Study Status when Initial Review Submission Form Approved by IRB will be:

No Recruitment Planned Not Yet Recruiting Recruiting Enrolling by Invitation

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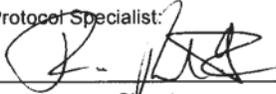
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Protocol# 16-C-N116

NCI APPENDIX

Abbreviated Title: *PhI/II Bev Vorinostat GBM*

NCI Protocol #: pending

BTTC Protocol #: BTTC11-02

Title: Phase I/II Adaptive Randomized Trial of Bevacizumab versus Bevacizumab plus Vorinostat in Adults with Recurrent Glioblastoma

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AGENTS

Name/s: Vorinostat &
Bevacizumab

A DISCLAIMER STATEMENT FOR BTTC PROTOCOLS

This is a research protocol of the Brain Tumor Trials Collaborative describing an experimental treatment procedure. It is a privileged document and is not intended to be circulated or used for other purposes. The Brain Tumor Trials Collaborative assumes no responsibility for its use outside of the constraints of this research protocol or by investigators other than those approved by the Consortium.

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PRÉCIS

Background

- Glioblastoma (GBM) is the most common primary brain tumor. With optimal treatment, consisting of focal radiotherapy with concurrent chemotherapy, followed by adjuvant chemotherapy, median survival is 14.6 months. Most patients have evidence of tumor progression within one year of diagnosis despite treatment. At progression, treatment options are limited and mostly ineffective.
- Given the importance of angiogenesis in GBM, anti-angiogenic therapy is a promising strategy in recurrent GBM. Bevacizumab, the first angiogenesis inhibitor approved against cancer by FDA based on improved survival of advanced colon cancer patient, has recently been studied in the GBM.
- The present study aims to determine the potential of vorinostat, an HDAC inhibitor plus bevacizumab, versus bevacizumab alone, in an attempt to increase the anti-angiogenic effects of VEGF by blocking the evasive resistance by combination with vorinostat and to also not only provide the potential of the independent effects of both agents but also the potential for synergy.

Objectives

- To determine the maximum tolerated dose (MTD) of vorinostat plus bevacizumab in adult patients with malignant glioma.
- To determine the efficacy of vorinostat plus bevacizumab versus bevacizumab alone in patients with recurrent WHO grade IV glioma (glioblastoma and gliosarcoma) as determined by progression free survival (PFS) using an adaptive randomization phase II trial design.

Eligibility

- Patients must have histologically proven glioblastoma, gliosarcoma or anaplastic glioma to be eligible for the **Phase I** component of this protocol. Anaplastic gliomas include anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), anaplastic mixed oligoastrocytoma (AMO), or malignant glioma NOS (not otherwise specified). Patients will be eligible if the original histology was low-grade glioma and a subsequent histological diagnosis of a malignant glioma is made. Only patients with histologically proven or imaging proven recurrent glioblastoma or gliosarcoma will be eligible for the **Phase II** component.
- Patients must have shown unequivocal evidence for tumor progression as determined by an MRI scan done prior to study entry which will be reviewed by the treating physician to confirm and document recurrence.
- No prior treatment with bevacizumab or Vorinostat

Design

The phase I component will assess the MTD of Vorinostat in combination with Bevacizumab. A conventional phase I design will be used and the MTD will be selected using a 3+3 accrual design at each dose level until MTD is determined. A maximum of 18 patients will be recruited to this component of the study.

The phase II component of the trial compares Bevacizumab to Vorinostat+ Bevacizumab in patients with recurrent GBM. The primary outcome is progression free survival. Patients will be randomized between the two arms using a Bayesian adaptive algorithm. Patients will be randomized fairly between the two arms at the start of the trial (for the first 20 patients). Thereafter, as the trial progresses and data accrue, the randomization will become unbalanced in favor of the treatment that, on average, has better results in terms of failure time. Therefore, each successive patient is more likely to receive the treatment with better results, on average. A minimum of 20 and a maximum of 90 patients will be accrued.

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1 INTRODUCTION

The study is currently in data analysis at all BTTC participating institutions. The study will be opened at NIH, which has replaced MD Anderson as the coordinating center, for data analysis only.

The main body of the study is included for historical purposes and remains unchanged with the exception of procedures related to data collection and reporting.

The following guidelines will govern reporting of data and unanticipated problems/ deviations to the NIH.

2 DATA COLLECTION AND EVALUATION

2.1 DATA COLLECTION

Data will be collected/reported in a secure research database. The PI will be responsible for overseeing entry of data and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts.

Sites will enter data on paper Case Report Forms; then transfer study data to NCI via fax, mail or Secure E-mail and File Transfer Service (SEFT). Contracted Data Managers will enter the data into a secure research database.

Using the Secure E-mail and File Transfer Service (SEFT) ensures the protection of all data and information being sent via email. When an email is sent to an external research site via SEFT, the external site will receive an email with a link to the SEFT site and the specific email.

End of study procedures: Data will be stored according to HHS and FDA regulations as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

2.2 DATA SHARING PLANS

2.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

- De-identified data in an NIH-funded or approved public repository.
- De-identified data in BTRIS (automatic for activities in the Clinical Center)
- De-identified or identified data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

- An NIH-funded or approved public repository. Insert name or names: clinicaltrials.gov.

- BTRIS (automatic for activities in the Clinical Center)
- Approved outside collaborators under appropriate individual agreements.
- Publication and/or public presentations.

When will the data be shared?

- Before publication.
- At the time of publication or shortly thereafter.

2.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

3 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

At time of transition to NIH, accrual is complete and the study status is long term follow-up. The following requirements and plan are for events during long term follow-up and incidental to data collection upon transition to NIH.

3.1 DEFINITIONS

3.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of at least possibly related to the agent/intervention should be recorded and reported as per sections [3.3.1](#), [3.4](#) and [3.5](#).

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact

- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

3.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

3.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

3.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

3.1.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

3.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

3.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

3.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

3.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

3.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to
 - (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
 - (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

3.2 ASSESSING CAUSALITY

Investigators are required to assess whether there is a reasonable possibility that the study agent/s caused or contributed to an adverse event. The following general guidance may be used.

Yes: If the temporal relationship of the clinical event to the study agent/s administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No: If the temporal relationship of the clinical event to the study agent/s administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

3.3 NCI-IRB REPORTING

3.3.1 NCI-IRB Expedited Reporting of Unanticipated Problems and Deaths

The administrative PI will report to the NCI-IRB:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations

- All Unanticipated Problems
- All serious non-compliance

Reports must be received by the NCI-IRB within 7 working days of PI awareness via iRIS.

3.3.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The administrative PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
 - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
 - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
 - All Grade 5 events regardless of attribution;
 - All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

3.3.3 Multi-Institutional Guidelines

3.3.3.1 IRB Approvals

The Administrative PI will provide the NCI IRB and Central Registration Office with a copy of the participating institution's approved yearly continuing review. Registration will be halted at any participating institution in which a current continuing approval is not on file at the NCI IRB.

3.3.3.2 Amendments

The Administrative PI will provide the NCI IRB with copies of all amendments, and approvals from each participating institution.

3.4 GUIDELINES FOR REPORTING SERIOUS ADVERSE EVENTS TO BTTC

What to Report?	When to Report?
1. All Deaths, except that due to progressive disease, occurring from the time the consent is signed through 30 days after the last day of active treatment	Within 1 working day (24 hours) from the time the research team becomes aware of event

What to Report?	When to Report?
2. Other Serious Unexpected Suspected Adverse Reactions (that did not result in death) occurring from the time the consent is signed and for the duration of the subject’s participation on the study	Within 5 working days from the time the research team becomes aware of event
3. All protocol deviations, non-compliance and unanticipated problems	Within 5 working days from the time the research team becomes aware of event
4. Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.	Within 5 working days from the time the research team becomes aware of event

The CCR problem report form will be used to submit adverse events to BTTC. See [Appendix A](#). Participating centers must also submit the report to their IRB in accordance with their institutional policies.

The BTTC Coordinating Center will maintain documentation of all Serious Adverse Events from each institution. The BTTC Coordinating Center will notify all investigators of any serious and unexpected adverse experiences that are possibly related to the study agent/s. The investigators are to file a copy with their protocol file and send a copy to their IRB according to their local IRB’s policies and procedures.

3.4.1 Guidelines & Procedures for reporting Deviations and Unanticipated Problems

Neither the FDA nor the ICH GCP guidelines define the term “protocol deviation.” The definition is often left to the Lead Institution IRB. Accordingly, since NCI, Center for Cancer Research is the Coordinating Center and the Administrative PI must adhere to those policies set by the NCI IRB, the definitions for unanticipated problem and protocol deviation as described by the NCI IRB will be applied for reporting purposes for all institutions participating in the NCI Center for Cancer Research Multi-center Project. Definitions are listed in section **3.1**.

Protocol Deviations or Unanticipated problems occurring at a participating institution will be submitted to that institution’s own IRB in accordance with local policies and procedures. However, the participating institution must submit a report to the BTTC Coordinating Center even in instances where the local IRB does not require a report.

Deviations or Unanticipated problems must be submitted to the NCI BTTC Coordinating Center within 5 working days after the original submission to the IRB, or after becoming aware of the event (if not reportable to the local IRB). When Deviations or Unanticipated Problems are reported to BTTC, but, the local IRB does not require a report, the report that is submitted to the NCI BTTC

Coordinating Center must be accompanied by a formal memo explaining the local policy and the rationale for not reporting the event to the local IRB.

Deviation or Unanticipated problem Reports and any accompanying documentation (to include the local IRB acknowledgement of the event when applicable) are to be submitted to the NCI BTTC Coordinating Center using the problem report form in [Appendix A](#) via fax at: 301-451-5429.

NCI Center for Cancer Research Coordinating Center: Upon receipt of the deviation/unanticipated problem report from the participating institution, the NCI BTTC Coordinating Center will submit the report to the Academic PI for review. Subsequently, the participating institution's IRB deviation/unanticipated problem report will be submitted to the NCI IRB for review.

3.5 REPORTING TO THE STUDY DRUG MANUFACTURERS

The NCI BTTC Coordinating Center will forward all SAE reports to the lead IRB via the lead investigator, FDA (when applicable), and Genentech Drug Safety and Merck Sharp and Dohme Corp Worldwide safety.

Genentech Drug Safety and Merck Sharp and Dohme Corp Worldwide Safety	FDA MedWatch 15-day Alert Report
<p>Genentech Drug Safety Fax: (650) 225-4682 or (650) 225-5288 (Using the safety reporting fax cover sheet attached to this document)</p> <p>Merck Sharpe and Dohme Corp. (Attn: Worldwide Product Safety)</p> <p>Fax: 215-993-1220</p> <p>AND:</p> <p>Study Coordination Center/Principal Investigator</p> <p>Contact Information and fax # (713) 792-2883 and (713) 794-4999</p>	<p>Phone: 1-800-FDA-1088</p> <p>FAX: 1-800-FDA-0178 or by mail to MedWatch</p> <p>Center for Biologics Evaluation and Research Food and Drug Administration Suite 200N 1401 Rockville Pike Rockville, MD 20852-1448</p> <p>FAX: 1-800-FDA-0178 or by mail to MedWatch, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857-9787</p>

SAEs will be forwarded to Genentech Drug Safety and Merck Sharp and Dohme Corp Worldwide Safety via the NCI BTTC Coordinating Center in accordance with the following:

All serious adverse events should be reported to Genentech Drug Safety and Merck Sharp and Dohme Corp Worldwide Safety within 24 hours. In the event of an SAE, the investigator should refer to the Pharmacovigilance section of the contract for reporting procedures. In brief:

The Investigator/Sponsor may report serious adverse drug reactions (SADRs) using either:

A MedWatch form available at <http://www.fda.gov/medwatch/>

Occasionally BTTC may contact the reporter for additional information, clarification, or current status of the subject for whom an adverse event was reported.

3.6 DATA AND SAFETY MONITORING PLAN

3.6.1 Principal Investigator/Research Team

The clinical research team will have a teleconference every other week when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the Principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The Principal Investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The Principal Investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

3.6.2 Data Safety Monitoring Board

The MD Anderson DSMB met and reviewed the report of progress and adverse events of the above listed protocol. Based on the information reviewed, the MD Anderson DSMB has made the following determination:

- The Committee approved to end active DSMB monitoring of the trial.
- Release the data to the PI.
- Provide a final report to the DSMB when all data is collected.

4 COLLABORATIVE AGREEMENTS

4.1 AGREEMENT TYPE

There is a BTTC consortia agreement in place between all of the participating institutions listed on the title page of this study.

5 HUMAN SUBJECTS PROTECTIONS

5.1 RATIONALE FOR SUBJECT SELECTION

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. Males and females will be recruited with no preference to gender. No exclusion to this study will be based on race. Minorities will actively be recruited to participate. Glioblastomas occur in patients of all races and although there is a slight predominance in men, this is a disease that is also found in women. The molecular targets of bevacizumab and vorinostat within the tumor are not known to be different among patients based on gender or race; hence this study will be open to all adults.

5.2 PARTICIPATION OF CHILDREN

Individuals under the age of 18 will not be eligible to participate in this study because they are unlikely to have glioblastoma, and because of unknown toxicities of the study agents in the pediatric patient. Furthermore, the targets of bevacizumab and vorinostat are not as prevalent in pediatric glioblastoma and therefore, the efficacy of this regimen will be initially determined in the adult population before consideration of its use in pediatrics.

5.3 NIH Informed Consent

Given the accrual completion and follow-up status of the study, subjects will not be re-consented.

5.4 RISKS/BENEFITS ANALYSIS

5.4.1 Benefits

There is no direct benefit to patients previously enrolled on this study. Completion of data analysis is likely to yield generalizable knowledge about the treatment of subjects with recurrent glioblastoma, including a determination as to whether toxicities occurring on this study would preclude future investigations of this agents.

5.4.1 Risks

The current study at NCI is limited to data analysis only. This data has already been obtained and thus pose no risk to the individual with regard to obtaining them.

Since sites will be transmitting paper CRFs with study subject numbers only, there is no risk of a breach of patient's medical records. The study data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Once the data is transferred to NCI, the primary and final analyzed data will have identifiers so that research data cannot be attributed to an individual human subject participant. Additional information is found in Data Collection [Section 2.1](#)

5.4.2 Risks/Benefits Analysis

The potential benefits of completing data analysis are the yielding of generalizable information about the condition under study. Given the efforts to minimize risk of transferring the information, this protocol poses risk no greater than minimal risk.

6 PHARMACEUTICAL INFORMATION

As no patients remain on study treatment at any site, no study drug will be administered.

This study meets the criteria for exemption for an IND as this investigation is not intended to support a new indication for use or any other significant change to the labeling; the drugs are already approved and marketed and the investigation is not intended to support a significant change in advertising; and the investigation does not involve a route of administration or dosage level in use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

APPENDIX A: CCR PROBLEM REPORT FORM

NCI Protocol #:	Protocol Title:
	Report version: <i>(select one)</i> <input type="checkbox"/> Initial Report <input type="checkbox"/> Revised Report <input type="checkbox"/> Follow-up
Site Principal Investigator:	
Date of problem:	Location of problem: <i>(e.g., patient's home, doctor's office)</i> Date PI was notified of problem: __/__/____ If delay in reporting to IRB (> 5 days for serious events; > 14 days for not serious events), please explain:
Who identified the problem? <i>(provide role (not name of person): nurse, investigator, monitor, etc...)</i>	
Brief Description of Subject <i>(if applicable)</i> <i>(Do NOT include personal identifiers)</i>	Sex: <input type="checkbox"/> Male <input type="checkbox"/> Female Age: <input type="checkbox"/> Not applicable (more than one subject is involved)
Diagnosis under study:	
Name the problem: <i>(select all that apply)</i> <input type="checkbox"/> Adverse drug reaction <input type="checkbox"/> Abnormal lab value <input type="checkbox"/> Death <input type="checkbox"/> Cardiac Arrest/ code <input type="checkbox"/> Anaphylaxis <input type="checkbox"/> Sepsis/Infection <input type="checkbox"/> Blood product reaction <input type="checkbox"/> Unanticipated surgery/procedure <input type="checkbox"/> Change in status (e.g. increased level of care required) <input type="checkbox"/> Allergy (non-medication) <input type="checkbox"/> Fall <input type="checkbox"/> Injury/Accident (not fall) <input type="checkbox"/> Specimen collection issue <input type="checkbox"/> Informed consent issue <input type="checkbox"/> Ineligible for enrollment <input type="checkbox"/> Breach of PII <input type="checkbox"/> Tests/procedures not performed on schedule <input type="checkbox"/> Other, brief 1-2 word description: _____	

Detailed Description of the problem: <i>(Include any relevant treatment, outcomes or pertinent history):</i>	
*Is this problem unexpected? <i>(see the definition of unexpected in the protocol)</i> __ YES __ NO Please explain:	
*Is this problem related or possibly related to participation in the research? __ YES __ NO Please explain:	
*Does the problem <u>suggest</u> the research places subjects or others at a greater risk of harm than was previously known or recognized? __ YES __ NO Please explain:	
Is this problem? <i>(select all that apply)</i> [] An Unanticipated Problem* that is: [] Serious [] Not Serious [] A Protocol Deviation that is: [] Serious [] Not Serious [] Non-compliance <i>*Note if the 3 criteria starred above are answered, "YES", then this event is also a UP.</i>	
Is the problem also <i>(select one)</i> [] AE [] Non-AE	
Have similar problems occurred on this protocol at your site? __ YES __ NO If "Yes", how many? ____ Please describe:	
Describe what steps you have already taken as a result of this problem:	
In addition to the NCI IRB, this problem is also being reported to: <i>(select all that apply)</i> [] Local IRB [] Study Sponsor [] Manufacturer : _____ [] Institutional Biosafety Committee [] Data Safety Monitoring Board [] Other: _____ [] None of the above, not applicable	
INVESTIGATOR'S SIGNATURE:	DATE:

BRAIN TUMOR TRIALS COLLABORATIVE (BTTC)

BTTC11-02: Phase I/II Adaptive Randomized Trial of Bevacizumab versus Bevacizumab plus Vorinostat in Adults with Recurrent Glioblastoma

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A DISCLAIMER STATEMENT FOR BTTC PROTOCOLS

Bevacizumab + Vorinostat Protocol

This is a research protocol of the Brain Tumor Trials Collaborative describing an experimental treatment procedure. It is a privileged document and is not intended to be circulated or used for other purposes. The Brain Tumor Trials Collaborative assumes no responsibility for its use outside of the constraints of this research protocol or by investigators other than those approved by the Consortium.

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1.0 **OBJECTIVES AND STUDY DESIGN**

1.1 **OBJECTIVES**

Primary endpoint:

Phase I

- To determine the maximum tolerated dose (MTD) of vorinostat plus bevacizumab in adult patients with malignant glioma.

Phase II

- To determine the efficacy of vorinostat plus bevacizumab versus bevacizumab alone in patients with recurrent WHO grade IV glioma (glioblastoma and gliosarcoma) as determined by progression free survival (PFS) using an adaptive randomization phase II trial design.

Secondary endpoint:

Phase II

- To determine the radiological response, TTP and OS in the treatment arms.
- To determine the efficacy and safety of combination of Vorinostat and Bevacizumab including in a subset of patients whose tumors exhibit a mesenchymal-pro-angiogenic phenotype associated with poor outcome.
- To determine the effects of bevacizumab with and without vorinostat upon biomarkers of angiogenesis.
- To evaluate the occurrence of symptoms and correlate to disease progression and tolerance to treatment using the MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT) self-reporting tool.

1.2 **STUDY DESIGN**

1.2.1 **Description of the Study**

Phase I component:

A conventional Phase I design will be used and the MTD will be selected using a 3+3 accrual design at each dose level until MTD is determined.

Phase II component:

This is a randomized phase II trial of the combination of bevacizumab plus vorinostat compared with bevacizumab alone in patients with recurrent grade IV malignant glioma. The primary

endpoint is progression free survival. Patients will be randomized between the two arms using a Bayesian adaptive algorithm. Patients will be randomized fairly between the two arms at the start of the trial (for the first 20 patients). Thereafter, as the trial progresses and data accrue, the randomization will become unbalanced in favor of the treatment that, on average, has better results in terms of failure time. Therefore, each successive patient is more likely to receive the treatment with better results, on average. A minimum of 20 and a maximum of 90 patients will be accrued and there will be 6 months follow up after the last patient is accrued. Based on an anticipated accrual rate between 3 and 5 patients per month, the maximum trial accrual period will be between 12 and 24 months.

The operating characteristics of the design are detailed in section 11.0 in the detailed table provided. The historical median progression free survival used for this study will be 4 months. This is in keeping with the data provided from the BRAIN study that led to the recent FDA approval of bevacizumab; median PFS in that study for single agent bevacizumab was 4.2 months (95% CI, 2.9, 5.8). The calculations used for the current assume an accrual rate of either 3 or 5 patients per month. The trial will be stopped early and a treatment selected as being “better” if the probability that one treatment’s median PFS is larger than the other’s PFS exceeds 0.995. If the trial does not stop early and the maximum 90 patients are accrued, a treatment is selected as being “better” if the probability that one treatment’s median PFS is larger than the other’s PFS exceeds 0.975. The “number of patients treated” row is the average number of patients treated on a given arm under the given scenario. When the medians are equal, the probability of selecting either of the two arms (i.e., a false positive result) is 9% for both accrual rates. The probability of selecting the better treatment (i.e., a true positive result) for a doubling in the median PFS is 85% for 3 per month and 83% for 5 per month.

At each evaluation when a new patient comes in the study, the data for patients who have been followed until that time and not yet progressed are accounted in the analysis. The trial will be conducted using a web based program, the Clinical Trial Conduct site, developed by the Department of Biostatistics at MD Anderson Cancer Center. Through the website interface, the users will have the ability to randomize patients, update the current patients’ status. The results of randomization are displayed for the user to review.

1.2.2 Rationale for Study Design

Phase I component:

A recent phase I trial tested the combination of vorinostat with bevacizumab and CPT-11 in patients with recurrent glioblastoma. The MTD of vorinostat has been established at a dose of 400 mg daily given on days 1-7 and 15-21 on a 4 week cycle when combined with CPT-11 (125 mg/m²) and bevacizumab (10 mg/kg) given on days 1 and 15. Toxicities not reaching DLT levels have to date included fatigue, diarrhea, mucositis and hematological toxicities. Common toxicities of the combination included fatigue and diarrhea. DLTs included fatigue, hypertension/hypotension, and central nervous system ischemia (Chinnaiyan et al 2012).

Given that our study proposes to use bevacizumab and vorinostat only, we anticipate less toxicity than seen in the 3-drug combination utilized in the trial described above. These results provide a rationale for our starting dose of 400 mg/day on days 1-7 and 15-21 of vorinostat in combination with bevacizumab at 10 mg/kg on days 1 and 15. We will incorporate dose escalation of

Bevacizumab + Vorinostat Protocol

vorinostat by one level to 500 mg and also provide two dose de-escalation levels at 300 and 200 mg/day in the unlikely event that the starting dose level is above MTD.

Phase II component:

To assess the activity of a new treatment regimen, conventional phase II designs use either a single arm design compared with historical controls or a randomized design with a control arm of standard treatment, if such a standard is identified. For patients with recurrent GBMs, there are no extant standards of care. In a paradigm such as the one being studied in the proposed trial, testing each combination against historical controls would involve separate trials, a process that will not provide timely answers to the question at hand nor allow utilization of resources in an efficient manner. To overcome some of these hurdles and test these combinations against each other as well as historical controls, this study proposes to utilize a Bayesian adaptive randomization design, which will pit the two treatment regimens against each other. This will result in progressive bias of randomization towards the best of the two regimens in a single trial. The "winner" of these two regimens will be considered the best regimen for further testing in a larger trial if it compares favorably with historical controls (Berry and Eick, 1994; Thall et al., 2002; Wong et al., 1999).

2.0 BACKGROUND

2.1 DISEASE BACKGROUND

Glioblastomas are the most common adult gliomas. In United State, there are 21, 810 new cases of primary brain tumor estimated in 2008 and about 13,070 death from the brain tumor. GBM is the most common and aggressive malignant primary brain tumor, accounting more than half of the primary brain tumor with approximately 4–6 per 100,000 people per year (Gurney and Kadan-Lottick, 2001). Malignant gliomas are the second leading cause of cancer death in patients under 35 years of age and the fourth leading cause in those patients younger than 45 yrs.

Histologically, glioblastomas display high mitotic index, cellular pleomorphism, extensive vascular proliferation or necrosis. They are characterized by their intrinsic heterogeneity, high morbidity and mortality. Despite aggressive multimodality treatment approach in surgery, radiation therapy and cytotoxic chemotherapeutic agents, the prognosis of patients with GBM is only 14.6 month (Stupp et al., 2005) in newly diagnosed GBM. Recurrent GBM has an even more dismal prognosis with a median overall survival of ~25 weeks (Wong et al., 1999) and PFS6 15%. Recent studies of bevacizumab either as a single agent or in combination with irinotecan have demonstrated a significant improvement in response rate compared to historical agents. Single-agent Bevacizumab treatment was associated with an overall response rate of 28.2% with a median duration of response was 5.6 months. Six-month PFS and median overall survival (OS) were 42.6% and 9.2 months, respectively; based on the response rate, bevacizumab was recently granted FDA approval for use in patients with recurrent GBM. However, progression after Bevacizumab therapy is often dramatic and associated with poor prognosis. Hence, there remains an unmet need for development of new approaches against these tumors and their characteristic biologic heterogeneity

Therapies targeting a single biological feature or pathway in these tumors have historically been unsuccessful in making any meaningful clinical impact. This has led to strategies aimed at rationally combining agents that target various processes critical to tumor biology. On the other hand, resistance to anti-angiogenic therapy may cause the overall failure of the therapy. Therefore, combination target therapy may be able to inhibit tumor growth by distinct and synergistic mechanisms but also have non-overlapping toxicities allowing better tolerability.

2.2 BEVACIZUMAB CLINICAL EXPERIENCE

Bevacizumab has been studied in a multitude of Phase I, II, and III clinical trials in more than 5000 patients and in multiple tumor types. In addition, data are available from 3,863 patients enrolled in two postmarketing studies in metastatic colorectal cancer (CRC). Approximately 130,000 patients have been exposed to bevacizumab as a marketed product or in clinical trials. The following discussion summarizes bevacizumab's safety profile and presents some of the efficacy results pertinent to this particular trial. Please refer to Investigator's Brochure of bevacizumab for descriptions of all completed Phase I, II, and III trials reported to date.

In a large phase III study (AVF2107g) in patients with metastatic colorectal cancer, the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), to irinotecan/5-fluorouracil/leucovorin (IFL) chemotherapy resulted in a clinically and statistically significant increase in duration of survival, with a hazard ratio of death of 0.67 (median survival 15.6 vs. 20.3 months; $p < 0.001$). Similar increases were seen in progression-free survival (6.2 vs. 10.6 months; $p < 0.001$), overall response rate (35% vs. 45%; $p < 0.01$) and duration of response (7.1 vs. 10.4 months; $p < 0.01$) for the combination arm versus the chemotherapy only arm (bevacizumab, Investigator Brochure, October 2005).

Based on the survival advantage demonstrated in Study AVF2107g, bevacizumab was designated for priority review and was approved on 26 February 2004 in the United States for first-line treatment in combination with IV 5-FU-based chemotherapy for subjects with metastatic colorectal cancer.

Additional data from Phase III trials in metastatic CRC (E3200), non-small cell lung cancer (NSCLC; E4599), and metastatic breast cancer (E2100) have also demonstrated clinical benefit from bevacizumab when added to chemotherapy. In Study E3200, the addition of bevacizumab to FOLFOX chemotherapy resulted in improved overall survival compared with FOLFOX alone (13.0 vs. 10.8 months, respectively, HR = 0.75; $p < 0.01$) in a population of previously treated CRC patients.

There was also improved overall survival in first-line NSCLC patients (E4599) treated with carboplatin/paclitaxel + bevacizumab compared with chemotherapy alone (12.3 vs. 10.3 months, respectively; HR = 0.80; $p = 0.003$). The results from this trial were the basis for FDA approval of bevacizumab for use in combination with carboplatin + paclitaxel as first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic, non-squamous NSCLC in October 2006. Finally, patients with untreated metastatic breast cancer (E2100) who received bevacizumab in combination with weekly paclitaxel had a marked improvement in PFS compared with chemotherapy alone (13.3 vs. 6.7 months, respectively; HR = 0.48; $p < 0.0001$) (see the bevacizumab Investigator Brochure for additional details).

A Phase II, open-label, multicenter, randomized, non-comparative study (AVF3708g, BRAIN), evaluated the efficacy and safety of Bevacizumab alone, or in combination with irinotecan in 167 glioblastoma (GBM) patients with progressive disease following prior therapy. For single-agent Bevacizumab (n=85), ORR was 28.2% and median duration of response was 5.6 months. Six-month PFS and median overall survival (OS) were 42.6% and 9.2 months, respectively; median PFS was 4.2 months (95% CI 2.9, 5.8). Based on these data, Bevacizumab, as a single agent, was approved by the FDA for the treatment of glioblastoma with progressive disease following prior therapy.

a. Bevacizumab Safety Profile

In the initial Phase I and II clinical trials, four potential bevacizumab-associated safety signals were identified: hypertension, proteinuria, thromboembolic events, and hemorrhage. Additional completed Phase II and Phase III studies of bevacizumab as well as spontaneous reports have further defined the safety profile of this agent. Bevacizumab-associated adverse events identified in phase III trials include congestive heart failure (CHF) primarily in metastatic breast cancer, gastrointestinal perforations, wound healing complications, and arterial thromboembolic events (ATE). Visceral arterial ischemia and disseminated intravascular coagulation resulting in death was reported in a single case recently. These and other safety signals are described in further detail as follows and in the bevacizumab Investigator Brochure.

Hypertension: An increased incidence of hypertension has been observed in patients treated with bevacizumab. Grade 4 and 5 hypertensive events are rare. Clinical sequelae of hypertension are rare but have included hypertensive crisis, hypertensive encephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS) (Glusker et al., 2006; Ozcan et al., 2006).

There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Therefore, caution should be exercised before initiating bevacizumab therapy in these patients. Monitoring of blood pressure is recommended during bevacizumab therapy. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.

Temporary interruption of bevacizumab therapy is recommended in patients with hypertension requiring medical therapy until adequate control is achieved. If hypertension cannot be controlled with medical therapy, bevacizumab therapy should be permanently discontinued. Bevacizumab should be permanently discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy.

Proteinuria: An increased incidence of proteinuria has been observed in patients treated with bevacizumab compared with control arm patients. In the bevacizumab-containing treatment arms of clinical trials (across all indications), the incidence of proteinuria (reported as an adverse event) was up to 38% (metastatic CRC Study AVF2192g). The severity of proteinuria has ranged from asymptomatic and transient events detected on routine dipstick urinalysis to nephrotic syndrome; the majority of proteinuria events have been grade 1. NCI-

CTC Grade 3 proteinuria was reported in up to 3% of bevacizumab-treated patients, and Grade 4 in up to 1.4% of bevacizumab-treated patients. The proteinuria seen in bevacizumab clinical trials was not associated with renal impairment and rarely required permanent discontinuation of bevacizumab therapy. Bevacizumab should be discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome)

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence from the dose-finding, Phase II trials (AVF0780g, AVF0809s, and AVF0757g) suggesting that Grade 1 proteinuria may be related to bevacizumab dose.

Proteinuria will be monitored by urine protein:creatinine (UPC) ratio at least every 6 weeks. If the UPC ratio is not available, a dipstick urinalysis may be used to allow treatment to proceed.

Thromboembolic Events: Both venous and arterial thromboembolic (TE) events, ranging in severity from catheter-associated phlebitis to fatal, have been reported in patients treated with bevacizumab in the colorectal cancer trials and, to a lesser extent, in patients treated with bevacizumab in NSCLC and breast cancer trials.

Venous thromboembolism (including deep venous thrombosis, pulmonary embolism, and thrombophlebitis): In the phase III pivotal trial in metastatic CRC, there was a slightly higher rate of venous TE events in patients treated with bevacizumab plus chemotherapy compared with chemotherapy alone (19% vs. 16%).

In Study AVF2107g, a Phase III, pivotal trial in metastatic CRC, VTE events, including deep venous thrombosis, pulmonary embolism, and thrombophlebitis, occurred in 15.2% of patients receiving chemotherapy alone and 16.6% of patients receiving chemotherapy + bevacizumab.

The incidence of NCI-CTC Grade ≥ 3 venous VTE events in one NSCLC trial (E4599) was higher in the bevacizumab-containing arm compared to the chemotherapy control arm (5.6% vs. 3.2%). One event (0.2%) was fatal in the bevacizumab-containing arm; not fatal events were reported in the carboplatin/paclitaxel arm (see Bevacizumab Investigator Brochure). In metastatic CRC clinical trials, the incidence of VTE events was similar in patients receiving chemotherapy + bevacizumab and those receiving the control chemotherapy alone.

In clinical trials across all indications the overall incidence of VTE events was 2.8%–17.3% in the bevacizumab-containing arms compared with 3.2%–15.6% in the chemotherapy control arms. The use of bevacizumab with chemotherapy does not substantially increase the risk of VTE event compared with chemotherapy alone. However, patients with metastatic CRC who receive bevacizumab and experienced a VTE event may be at higher risk for recurrence of VTE event.

Arterial Thromboembolic Events: An increased incidence of ATE events was observed in patients treated with bevacizumab compared with those receiving control treatment. ATE events include cerebrovascular accidents, myocardial infarction, transient ischemic attacks

(TIAs), and other ATE events. In a pooled analysis of data from five randomized Phase II and III trials (mCRC [AVF2107g, AVF2192g, AVF0780g]; locally advanced or metastatic NSCLC [AVF0757g]; metastatic breast cancer [AVF2119g]), the incidence rate of ATE events was 3.8% (37 of 963) in patients who received chemotherapy + bevacizumab compared with 1.7% (13 of 782) in patients treated with chemotherapy alone. ATE events led to a fatal outcome in 0.8% (8 of 963) of patients treated with chemotherapy + bevacizumab and 0.5% (4 of 782) of patients treated with chemotherapy alone. Cerebrovascular accidents (including TIAs) occurred in 2.3% of patients treated with chemotherapy + bevacizumab and 0.5% of patients treated with chemotherapy alone. Myocardial infarction occurred in 1.4% of patients treated with chemotherapy + bevacizumab compared with 0.7% of patients treated with chemotherapy alone (see the Bevacizumab Investigator Brochure for additional details).

Aspirin is a standard therapy for primary and secondary prophylaxis of arterial thromboembolic events in patients at high risk of such events, and the use of aspirin \leq 325 mg daily was allowed in the five randomized studies discussed above. Use of aspirin was assessed routinely as a baseline or concomitant medication in these trials, though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and arterial thromboembolic events, retrospective analyses of the ability of aspirin to affect the risk of such events were inconclusive. However, similarly retrospective analyses suggested that the use of up to 325 mg of aspirin daily does not increase the risk of grade 1-2 or grade 3-4 bleeding events, and similar data with respect to metastatic colorectal cancer patients were presented at ASCO 2005 (Hambleton et al., 2005). Further analyses of the effects of concomitant use of bevacizumab and aspirin in colorectal and other tumor types are ongoing.

Gastrointestinal perforation: Patients with metastatic carcinoma may be at increased risk for the development of gastrointestinal perforation and fistula when treated with bevacizumab and chemotherapy. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation. A causal association of intra-abdominal inflammatory processes and gastrointestinal perforation to bevacizumab treatment has not been established. Nevertheless, caution should be exercised when treating patients with intra-abdominal inflammatory processes with bevacizumab. Gastrointestinal perforation has been reported in other trials in non-colorectal cancer populations (e.g., ovarian, renal cell, pancreas, breast, and NSCLC) and may be higher in incidence in some tumor types.

Fistula: Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae in the GI tract are common (1%–10% incidence) in patients with metastatic CRC, but uncommon (0.1%–1%) or rare (0.01%–0.1%) in other indications. In addition, fistulae that involve areas of the body other than the GI tract (e.g., tracheoesophageal, bronchopleural, urogenital, biliary) have been reported uncommonly (0.1%–1%) in patients receiving bevacizumab in clinical studies and postmarketing reports. Events were reported at various timepoints during treatment, ranging from 1 week to > 1 year following initiation of bevacizumab, with most events occurring within the first 6 months of therapy.

Permanently discontinue bevacizumab in patients with tracheoesophageal fistulae or any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in

patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

Wound healing complications: Wound healing complications such as wound dehiscence have been reported in patients receiving bevacizumab. In an analysis of pooled data from two trials in metastatic colorectal cancer, patients undergoing surgery 28-60 days before study treatment with 5-FU/LV plus bevacizumab did not appear to have an increased risk of wound healing complications compared to those treated with chemotherapy alone (Scappaticci et al., 2005). Surgery in patients currently receiving bevacizumab is not recommended. No definitive data are available to define a safe interval after bevacizumab exposure with respect to wound healing risk in patients receiving elective surgery; however, the estimated half life of bevacizumab is 21 days. Bevacizumab should be discontinued in patients with severe wound healing complications.

If patients receiving treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4–8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin or restart bevacizumab until 4 weeks after that procedure (in the case of high-risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 weeks and bevacizumab no earlier than 8 weeks after surgery).

Hemorrhage: Overall, grade 3 and 4 bleeding events were observed in 4.0% of 1132 patients treated with bevacizumab in a pooled database from eight Phase I, II, and III clinical trials in multiple tumor types (bevacizumab Investigator Brochure, October 2005). The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage (see below) and minor muco-cutaneous hemorrhage.

Tumor-Associated Hemorrhage: Major or massive pulmonary hemorrhage or hemoptysis has been observed primarily in patients with NSCLC. Life-threatening and fatal hemoptysis was identified as a bevacizumab-related adverse event in NSCLC trials. These events occurred suddenly and presented as major or massive hemoptysis. Among the possible risk factors evaluated (including squamous cell histology, treatment with anti-rheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, bevacizumab therapy, previous medical history of atherosclerosis, central tumor location, and cavitation of tumors during therapy), the only variables that showed statistically significant correlations with bleeding were bevacizumab therapy and squamous cell histology.

GI hemorrhages, including rectal bleeding and melena have been reported in patients with CRC, and have been assessed as tumor-associated hemorrhages.

Tumor-associated hemorrhages were also seen rarely in other tumor types and locations, including a case of CNS bleeding in a patient with hepatoma with occult CNS metastases and a patient who developed continuous oozing of blood from a thigh sarcoma with necrosis.

Mucocutaneous Hemorrhage: Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen.

There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

Reversible Posterior Leukoencephalopathy Syndrome: There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with RPLS, a rare neurologic disorder that can present with the following signs and symptoms (among others): seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Brain imaging is mandatory to confirm the diagnosis of RPLS. In patients who develop RPLS, treatment of specific symptoms, including control of hypertension, is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known (Glusker et al., 2006; Ozcan et al., 2006).

Congestive heart failure: In clinical trials CHF was observed in all cancer indications studied to date, but predominantly in patients with metastatic breast cancer. In the Phase III clinical trial of metastatic breast cancer (AVF2119g), 7 (3%) bevacizumab-treated patients experienced CHF, compared with two (1%) control arm patients. These events varied in severity from asymptomatic declines in left ventricular ejection fraction (LVEF) to symptomatic CHF requiring hospitalization and treatment. All the patients treated with bevacizumab were previously treated with anthracyclines (doxorubicin cumulative dose of 240–360 mg/m²). Many of these patients also had prior radiotherapy to the left chest wall. Most of these patients showed improved symptoms and/or left ventricular function following appropriate medical therapy (Miller et al., 2005).

In a randomized, Phase III trial of patients with previously untreated metastatic breast cancer (E2100), the incidence of LVEF decrease (defined as NCI-CTC Grade 3 or 4) in the paclitaxel + bevacizumab arm was 0.3% versus 0% for the paclitaxel alone arm

No information is available on patients with preexisting CHF of New York Heart Association (NYHA) Class II–IV at the time of initiating bevacizumab therapy, as these patients were excluded from clinical trials.

Prior anthracyclines exposure and/or prior radiotherapy to the chest wall may be possible risk factors for the development of CHF. Caution should be exercised before initiating bevacizumab therapy in patients with these risk factors.

A Phase II trial in patients with refractory acute myelogenous leukemia reported 5 cases of cardiac dysfunction (CHF or LVEF decrease to < 40%) among 48 patients treated with sequential cytarabine, mitoxantrone, and bevacizumab. All but one of these patients had significant prior exposure to anthracyclines as well (Karp et al., 2004).

Other studies in patients with various tumor types and either a history of anthracycline exposure or concomitant use with bevacizumab are ongoing.

Patients receiving concomitant anthracyclines or with prior exposure to anthracyclines should have a baseline MUGA scans or echocardiograms (ECHOs) with a normal LVEF.

Neutropenia: Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone (Sandler et al. 2006).

Additional Adverse Events: See the bevacizumab Investigator Brochure for additional details regarding the safety experience with bevacizumab.

2.3 Vorinostat clinical experience

As of 07-May-2008, vorinostat has been orally administered to more than 1899 patients in Ph I, II and III clinical studies. These studies were sponsored by either Merck, Sharp and Dohme Corp. the US National Cancer Institute (NCI) or the Merck Investigator initiated studies program (IISP). The clinical development program being conducted by Merck, Sharp and Dohme Corp. for vorinostat includes: Seventeen (Mastronardi et al., 1998) Phase I, II and III studies conducted with vorinostat in monotherapy and eleven (Duvic et al., 2005) Phase I, II and III studies conducted with vorinostat in combination therapy.

Zolinza® (vorinostat) was approved by the U.S. Food and Drug Administration (FDA) on 06-Oct-2006 for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma who have progressive, persistent or recurrent disease on or following two systemic therapies. The efficacy of vorinostat in CTCL has been demonstrated in a pivotal Phase IIb and a supportive Phase IIa study. A total of 107 individual patients with CTCL, 89 of who had Stage IIB or higher disease, were treated in these studies. In this refractory population, the response rates for all patients treated with vorinostat at 400 mg orally once daily, the dose and schedule approved for clinical use in patients with CTCL, were 30.8% and 29.7% for the overall population in these two studies. For patients with Stage IIB and higher CTCL, the response rates were 36.4% and 29.5% respectively. For patients with Sezary syndrome, the response rate was 33.3% in both studies. More information can be found in the prescribing information for vorinostat.

Phase I and II clinical studies of vorinostat sponsored by Merck, Sharp and Dohme, Corp. and the NCI have demonstrated confirmed anti-tumor activity in patients with acute myeloid leukemia (AML), advanced multiple myeloma, B-cell non-Hodgkin's lymphoma, squamous cell laryngeal carcinoma, thyroid carcinoma, breast carcinoma, non-small cell lung carcinoma, glioblastoma multiforme and myelodysplastic syndrome. Studies are ongoing to further evaluate whether these observations translate into clinical benefit.

a. Safety Profile

The total daily oral dose of vorinostat administered in these studies ranges from 200 mg to 900 mg. The tolerability of oral vorinostat appears to be determined by total daily dose and the length of consecutive days of dosing. The maximum tolerated dose (MTD) for continuous daily dosing without a rest period is 400 mg once a day or 200 mg twice a day (200 mg b.i.d.). The MTD for intermittent dosing is 300 mg b.i.d. x 3 consecutive days per week or 250 mg t.i.d. x 14 consecutive days followed by a 7-day rest. Dose-limiting toxicities (DLTs) are mainly non-hematologic (anorexia, dehydration, diarrhea and weight loss). Hematologic

toxicities were primarily anemia and thrombocytopenia, most of which were mild to moderate in intensity. The majority of DLTs occurred within the first month on oral vorinostat. The DLTs were manageable because these toxicities resolved quickly after drug administration was interrupted. The optimal dose, dose frequency, and dose duration remains under active investigation.

Adverse experiences considered by the Investigators to be at least possibly related to vorinostat reported as of 07-May-2008 by $\geq 10\%$ of patients across all Merck, Sharp and Dohme Corp.& Co., Inc. sponsored vorinostat clinical studies are summarized below by medical dictionary for regulatory activities (MedDRA), system organ class (SOC) and preferred term:

SOC	Reported Possible Related Adverse Experiences in $\geq 10\%$ Overall Patients
Blood and Lymphatic System Disorders	Thrombocytopenia, anemia
Gastrointestinal disorders	Nausea diarrhea, vomiting, constipation
General disorders and Administration Site Conditions	Fatigue
Investigations	Blood creatinine increased, weight decreased, hemoglobin decreased
Metabolism and Nutritional Disorders	Anorexia, dehydration, hyperglycemia
Nervous System Disorders	Dysgeusia

The types of adverse experiences observed in clinical trials of vorinostat were those usually associated with chemotherapy. No new or unique adverse experiences were commonly observed. The three major clinical categories of adverse experiences attributable to vorinostat include a constellation of gastrointestinal symptoms, constitutional complaints, and cytopenias. Most of the adverse experiences were manageable. In fact, most of the very common adverse experiences were reversible and could be managed using conventional supportive care for chemotherapy. There does not seem to be an increased incidence of venous thromboembolic disease in patients treated with vorinostat. There are no statistically significant data to suggest that vorinostat increases the QTc to > 500 ms or induces a change from baseline of > 30 msec. Taking these data together, administration of oral vorinostat was well tolerated in clinical studies. A study specifically designed to assess the effect of a single dose of vorinostat on the QTc interval in patients with advanced cancer was completed and showed a single suprathreshold dose of vorinostat was not associated with prolongation of the QTc interval. (Munster et al., 2009)

Vorinostat should be taken approximately 30 minutes after a meal whenever possible. Altered taste and decreased food and liquid intake are associated with vorinostat administration. These toxicities can be managed with fluid management and nutritional consultation.

To prevent dehydration, patients should consume at least 2 liters of fluid orally, daily. If patients are experiencing dysgeusia, popsicles or electrolyte fluid replacement drinks may be recommended. If diarrhea occurs it should be managed with loperamide according to

institutional guidelines. It is advisable that patients should receive appropriate anti-emetic therapy. In accordance with ASCO, NCCN, MASCC or ESMO guidelines, it is recommended that management of CINV should include a 5HT3 receptor antagonist, a corticosteroid and fosaprepitant and/or aprepitant in compliance with local prescribing information/therapeutic indication for each compound.

Vorinostat should not be administered concomitantly with other HDAC inhibitors (e.g., valproic acid) as class-specific adverse reactions may be additive. Severe (Grade 4) thrombocytopenia with associated gastrointestinal bleeding and anemia has been reported with the concomitant use of vorinostat and valproic acid.

b. HDAC inhibitors and gliomas

HDAC inhibitors have shown preclinical inhibition of glioma cell lines *in vitro* and *in vivo*. In particular, vorinostat upregulates p21, decreases VEGF levels and increases apoptosis in various glioma cell lines. Also, *in vivo* glioma xenograft studies demonstrate an increased survival time in rats treated with vorinostat. Other HDAC inhibitors, such as trichostatin A, FK228 and sodium butyrate, show similar effects *in vitro*. Ugur et al showed that intracranial administration of vorinostat inhibits tumor growth in a orthotopic glioma model; more relevant to this study, they also demonstrated that vorinostat significantly inhibited vessel formation in a endothelial cell tube forming matrigel assay. In addition, a 30% decrease in microvessel density was noted in addition to direct antitumor effects in glioma xenografts isolated from vorinostat treated animals resulting in increased survival of the animals (Ugur et al, 2007). Ongoing clinical studies are testing anti-tumor activity of vorinostat either as a single agent or in combination with temozolomide in gliomas. Final results of a phase II trial of vorinostat as a single agent against recurrent glioblastoma were reported (Galanis et al. 2009) and showed that in a cohort of 66 patients, 9 of the 52 evaluable patients were progression free at 6 months. From an intent to treat analysis, 15.2% of patients were alive and progression free at 6 months which was considered superior to historical controls and thus met the trial's primary efficacy endpoint. The study also showed upregulation of E-cadherin in a subgroup who received vorinostat prior to surgery, indicating a biologic effect of the HDAC inhibitor on the glioblastoma tumors.

2.4 Study Rationale

a) Angiogenesis, a critical biological feature of GBM

Since the notion of tumor angiogenesis was brought by Dr. Folkman in 1971 (Folkman, 1971), angiogenesis has been studied widely. Most solid tumors are angiogenesis-dependent (Folkman, 2006) and angiogenesis is the key feature in GBM (Jain et al., 2007). A mesenchymal/angiogenic gene expression signature was found in poor prognosis subclass of GBM patients by several gene profiling studies (Phillips et al., 2006; Tso et al., 2006). GBM frequently shift to mesenchymal phenotype at the time of their recurrence. A robust 38-gene profile, which is associated with mesenchymal/angiogenesis genes, was identified to predict survival in GBM (Colman et al., 2007, 2009). This gene set was subsequently narrowed down to a 9-gene set which when expressed as a metagene score was confirmed to be independent predictor of outcome in GBM. Because the proposed trial is expected to modify the angiogenic phenotype, analysis of improved outcome in patients with a poor metagene score

(from the 9-gene signature) could potentially indicate efficacy of the treatment proposed in our study.

b) Anti-angiogenic therapy in GBM

Given the importance of angiogenesis in GBM, anti-angiogenic therapy is a promising strategy in recurrent GBM. Bevacizumab, the first angiogenesis inhibitor approved against cancer by FDA based on improved survival of advanced colon cancer patient, has recently been studied in the GBM. In a prospective phase II trial, 35 patients with recurrent GBM were treated with bevacizumab and Irinotecan. The response rate was 57%, PFS 6 was 43%, 2 year OS 15% (Vredenburg et al., 2007). A subsequent Phase II, open-label, multicenter, randomized, non-comparative study (AVF3708g, BRAIN), evaluated the efficacy and safety of Bevacizumab alone, or in combination with irinotecan in 167 glioblastoma (GBM) patients with progressive disease following prior therapy. For single-agent Bevacizumab (n=85), ORR was 28.2% and median duration of response was 5.6 months. Six-month PFS and median overall survival (OS) were 42.6% and 9.2 months, respectively; Median PFS for the bevacizumab alone arm was 4.2 months. Based on these data, Bevacizumab, as a single agent, was approved by the FDA for the treatment of glioblastoma with progressive disease following prior therapy.

However, it has become evident recently despite the radiological response to bevacizumab, there is an increased risk of tumor infiltration on brain MRI suggesting development of resistance and leading to treatment failure; (Norden et al., 2008); Zuniga et al. 2008; Lassman et al., 2008).

c) Resistance to anti-VEGF therapy

The pattern of tumor stasis and then tumor growth seen in the clinical trials with bevacizumab as monotherapy or in combination with other cytotoxic agents highly suggests development of resistance to anti-VEGF therapy. Studies in animal models provide evidence that tumor cells develop the capability to re-grow in the face of VEGF/VEGFR blockade (Casanovas et al., 2005). Both intrinsic and adaptive resistance have been proposed as mechanisms for resistance to anti-angiogenic agents (Bergers and Hanahan, 2008). After the initial response to anti-VEGF therapy denoted by tumor stasis and reduction in tumor vascularity, alternative pro-angiogenic factors/signaling pathways are activated, such as fibroblast growth factor (FGF), angiopoietin, platelet-derived growth factor (PDGF), VEGF and placenta growth factor (PIGF) (Batchelor et al., 2007; Casanovas et al., 2005; Fernando et al., 2008). The upregulation and activation of these pro-angiogenic signaling pathways can further cause revascularization and tumor progression. Further, various bone marrow derived cells (BMDC) that consists of vascular progenitor cells and vascular modulator cells can be recruited secondary to the hypoxia which was induced by anti-VEGF therapy (Du et al., 2008). HIF-1 α , upregulated under such hypoxic condition is the key factor by recruiting pro-angiogenic BMDCs via stromal cell-derived factor (SDF) 1 α to facilitate revascularization (Du et al., 2008). In addition, many pericytes can survive the anti-VEGF therapy and support the endothelial cell survival as well (Bergers et al., 2003; Mancuso et al., 2006). Finally, tumor cells escape from their inability to induce neoangiogenesis in the face of initial anti-VEGF therapy by becoming more invasive by vessel cooption (Lamszus et al., 2003). Therefore, resistance to anti-VEGF therapy is complex multi-step process. An agent targeting

these multiple pathways of resistance will potentiate the effects of anti-VEGF therapy and repress mechanisms that attempt to bypass VEGF targeted angiogenesis inhibition.

d) Rationale of combining HDAC inhibitors and bevacizumab

HDAC inhibitors are known to impact several pathways related to angiogenesis. HDAC are enzymes responsible for regulation DNA transcription via deacetylation of the lysine tails of histones. As transcriptional repressors, there is increasing evidence that HDAC activity is altered in many cancers, including gliomas (Marks et al., 2004). Since epigenetic alterations in cancer cells affect virtually all cellular pathways that have been associated to tumorigenesis, it is not surprising that as epigenetic agents, HDAC inhibitors display pleiotropic activities. The anti-angiogenic properties of HDAC inhibitors have been associated with decreased expression of pro-angiogenic genes, such as VEGF, bFGF, angiopoietin and tunica intima endothelial kinase 2 (TIE2) (Bolden et al., 2006). More importantly, it also has been shown to regulate HIF 1 α transcriptional activity (Kim et al., 2001; Mahon et al., 2001), which is a key factor in mediating anti-VEGF resistance. HDAC inhibitors can largely down-regulate HIF-1 α expression in both tumor cells and endothelial cells. HDAC not only upregulate HIF-1 α through down-regulating p53 and VHL suppressor gene, but also directly regulate the stability and transcription activity via interaction with oxygen-dependent degradation domain (ODDD) of HIF-1 α (Kim et al., 2007). There is also evidence of HDAC inhibitor decrease chemokine receptor 4 (CXCR4) expression in human endothelial cells (Qian et al., 2004). HDAC inhibition also reported to resulted in impaired endothelial progenitor cell differentiation (Rossig et al., 2005). Resistance to bevacizumab is thought to be related to escape of tumor endothelium from dependency on VEGF. Glioma xenografts from animals treated with bevacizumab show increased expression of HIF-1 alpha. The combination of bevacizumab and HIF-1 alpha inhibition results in better antitumor effect than bevacizumab alone (Rapisarda et al). Thus combining a strategy that using vorinostat to inhibit HIF-1 alpha and bevacizumab to inhibit VEGF not only provided the potential of the independent effects of both agents but also the potential for synergy based on data provide above. In summary, among many anti-angiogenic effects, HDAC inhibitor is able to interfere with the endothelial function and down regulate most of the pro-angiogenic signals that contribute to evasion resistance of anti-VEGF therapy. It down regulates HIF-1 α , the factor helps recruiting the pro-angiogenic BMDCs, and further block the revascularization. It may overcome the evasive resistance and improve the anti-angiogenic therapy. This lead us to propose the present study which aim to determine the potential of vorinostat, an HDAC inhibitor plus bevacizumab, versus bevacizumab alone, in an attempt to increase the anti-angiogenic effects of VEGF by blocking the evasive resistance by combination with vorinostat.

e) Rationale for dosing schedule

Induction of hypoxia has been described in tumors which have been treated a variety of angiogenesis inhibitors (Yu et al., 2002). A study by Casanovas showed that tumor growth resulted in triggering of the angiogenic switch and that inhibition of this process with angiogenic inhibitors resulted in hypoxia (as detected by pimonidazole); however, this rapidly induced hypoxia was short term and appeared to trigger the expression of several angiogenic factors other than VEGF; the authors suggested that persistent subtle hypoxia may be the factor that maintain the VEGF independent angiogenic stimulus.(Casanovas et al.,

2005) Therefore, we hypothesize that the HIF 1 induced upregulation of other pro-angiogenic factors such as FGF, SDF, PDGF, PIGF and angiopoietin is largely dependent on the relatively transient increased upregulation of HIF 1 and likely the low level persistent hypoxia which can be abrogated by treatment with vorinostat. Based on these facts, we schedule bevacizumab infusion on day 1 and administer vorinostat on days 1- 7. Again, the second infusion of bevacizumab of the same cycle on day 15 will be followed by 7 days of vorinostat. This dosing schedule is designed to block the upstream of the cascade of evasive mechanism of resistance to anti-angiogenic therapy.

f) Rationale for obtaining exploratory data

Identification of markers that are associated with tumor during anti angiogenic therapy alone or in combination with other therapies will help understand the mechanism of the resistance and help identified the key molecules involving this mechanism. A big challenge in bevacizumab therapy is lack of identified and validated biomarkers during the treatment. HIF1 α has been found to stimulate neovascularization by producing a variety of pro-angiogenic factors, such as VEGF, VEGFR, PDGF, FGF and angiopoietin (Calvani et al., 2006; Holash et al., 1999; Okuyama et al., 2006). Neo-angiogenesis depends on the recruitment of BMDC cells, which includes endothelial progenitor cells and pericyte progenitor cells (Kopp et al., 2006).The most important factors in helping the recruitment of BMDC cells are HIF1 α , SDF and VEGF (Ceradini et al., 2004; Petit et al., 2007). To study these important biomarker during bevacizumab treatment, we propose to measure level of VEGF, PIGF, bFGF, SDF1 α , angiopoietin 1 and 2 by ELISA on cycle 1 pretreatment, cycle 1 day 2, day 15 (pre- and post-infusion) and cycle 2 (pre-infusion) in both treatment arms, bevacizumab alone and bevacizumab with vorinostat. Level of circulating endothelial cells (CEC) and circulating endothelial progenitor cells (CEPC) will also be measured at the same time.

MR imaging study is one of the most commonly used techniques for monitoring tumor growth. Analysis of MRI studies at different stages of therapy could potentially be used for correlation between disease prognosis and treatment response. Ultimately the goal would be that MRI could be used as an imaging correlate to predict the disease prognosis. To do that, we propose to use unique MRI sequences in addition to conventional contrast-enhanced (CE) MRI to evaluate the tumor response to bevacizumab with and without vorinostat. In this context, increased cell density, vascular proliferation and necrosis are the key features of higher grade malignant gliomas. Traditional CE-MRI does not adequately reflect the complex biology of the malignant glioma. Angiogenesis, the major mean for tumor to survival and proliferate, gives dilated, tortuous and hyperpermeable vessels. Anti-angiogenic therapy leads to decreased permeability and vascular regression. The traditional CE-MRI is dependent on blood brain barrier permeability to the MR contrast agent used as well as on tumor vascular density. Thus the amount of contrast entering the tumor decreases in the setting of antiangiogenic treatment regardless of changes in the tumor itself. This makes CE-MRI unreliable in evaluating tumor growth in the setting of anti-angiogenic therapy. This trial will use DCE-MRI to measure permeability, DSC-MRI measure the CBV and CBF, and DWI to measure the cell density with ADC maps and DTI to supplement this information. We expect that this will overcome the limitation of the traditional CE-MRI in evaluating the tumor growth. It will improve the understanding of the imaging changes related to anti-angiogenic

therapy and provide preliminary data to support the use of advanced MRI as a noninvasive tool to predict the tumor progression and disease prognosis.

3.0 **DRUG INFORMATION**

3.1 **BEVACIZUMAB DRUG INFORMATION**

3.1.1 Drug Name: Bevacizumab or Avastin

3.1.2 Appearance: Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution for intravenous (IV) infusion.

3.1.3 How supplied: Bevacizumab will be supplied by Genentech in 20-cc (400-mg) glass vials containing 16 mL bevacizumab (25 mg/mL). Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection (SWFI), USP. Vials contain no preservative and are suitable for single use only.

For further details, see the bevacizumab Investigator Brochure.

3.1.4 Storage and Stability: Upon receipt of the study drug, vials are to be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. Vials should be protected from light.

Opened vials must be used within 8 hours. VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 subject may not be used for any other subject. Once study drug has been added to a bag of sterile saline, the solution must be administered within 8 hours.

3.1.5 Human Toxicity:

Likely (occurring in more than 20% of patients)

high blood pressure pain headache dizziness hair loss abdominal pain vomiting	loss of appetite constipation diarrhea sores in the mouth bleeding in the digestive system upset stomach	taste disorder failure of the ovaries to produce hormones, which may be permanent (possible stopped menstrual cycle) weakness increased proteins in the urine (possible kidney damage) airway infection nosebleeds difficulty breathing
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Bevacizumab may likely cause low white blood cell counts. This means that while you take the drug, there is more of a chance of getting an infection, including pneumonia.

Common (occurring in 3-20% of patients)

low blood pressure fatigue nerve damage (possible numbness, tingling, and/or burning) confusion unusual manner of walking dry skin shedding and scaling of the skin (possible fatal loss of bodily fluids) skin discoloration nail disorder fainting low potassium blood levels (possible weakness)	low sodium blood levels (possible headache, confusion, seizures, and/or coma) gas weight loss nausea dry mouth inflammation of the intestines decreased intestinal function (possible vomiting, swelling, and/or pain) dehydration frequent urination	strong need to urinate vaginal bleeding fever, infection, and low white blood cell counts bleeding high levels of bile in the blood muscle and/or bone pain teary eyes voice changes lung inflammation build-up in the lung tissues infection infusion reactions
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Bevacizumab may commonly cause low blood cell counts (red blood cells and platelets). You may become anemic and/or have problems with bleeding, bruising, fatigue, and/or shortness of breath. You may need a blood transfusion.

Bevacizumab may commonly cause blood clots. The clots can occur in the veins or arteries that supply blood to the brain, heart, lungs, or other organs, which may cause stroke and/or heart attack.

Bevacizumab may commonly cause the development of a hole through the entire thickness of the wall of the stomach, small intestine or large intestine, which can cause leakage of the contents of these organs and lead to infection.

Rare but serious (occurring in fewer than 3% of patients)

heart failure heart attack chest pain due to heart trouble severe increase in blood pressure bleeding in the brain, causing stroke stroke bleeding in the space surrounding the brain bleeding gums	pockets of infected fluid in the abdomen death of tissue in the intestines intestinal blockage vein blockage in the abdomen destruction of the jaw bone eye infection blurry vision kidney damage hole between the nostrils coughing up blood	bleeding in the lung increased pressure in the blood vessel that leads to the lungs (possible shortness of breath) opening of a healed wound sudden, rapid loss of a skin graft (a patch of transplanted skin tissue) or other grafted tissue wound healing problems
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Bevacizumab may rarely cause brain damage (encephalopathy), including reversible posterior leukoencephalopathy syndrome, a medical condition related to leakiness of blood vessels in the brain, which can cause confusion, blindness or vision changes, seizure, changes in brain scans, and/or other symptoms. Leukoencephalopathy may occur up to 18 months after the last dose of study drug.

Bevacizumab may rarely cause an abnormal opening that develops between one area of the body and another (for example, an abnormal connection and opening in one or more places between the trachea [breathing tube] and esophagus, which may interfere with swallowing, digestion, and/or choking). This may result in death.

Other Information about Bevacizumab

Rarely (in about 1-2% of patients), bevacizumab may cause bleeding in the brain in patients who have received bevacizumab for the treatment of primary brain tumors. You will be monitored for this complication and removed from the study if this were to occur.

In most patients, blood pressure can be controlled with routine medications taken by mouth while bevacizumab is continued. However, uncontrolled high blood pressure and high blood pressure resulting in disturbance of organ function may occur.

Bevacizumab may also worsen any pre-existing heart or cerebrovascular disease (abnormality of the brain resulting from blood vessel problems).

The impact of bevacizumab on future fertility is currently unknown. However, it is possible that treatment with bevacizumab may affect fertility and decrease the likelihood of becoming pregnant in the future.

If you are older than 65, you may have an increased risk of blood vessel problems such as stroke and/or heart attack. You also may have a higher chance of low white blood cell, low platelet counts, diarrhea, nausea, headache, and/or fatigue.

If you are taking Coumadin (warfarin) or other blood-thinning drugs, you may be at higher risk of blood clots and/or bleeding.

3.1.6 Administration:

Bevacizumab 10mg/kg will be administered on day 1 and 15 intravenously on a 28 day cycle in both arms. Dilute bevacizumab according to the manufacturer package insert and/or institutional standards regarding bevacizumab storage, handling, dose preparation, and administration. Administration will be as a continuous IV infusion. Anaphylaxis precautions should be observed during study drug administration. It is not necessary to correct dosing based on ideal weight. .

The initial dose will be delivered over 90±15 minutes. If the first infusion is tolerated without infusion-associated adverse events (fever and/or chills), the second infusion may be delivered over 60±10 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30±10 minutes.

If a subject experiences an infusion-associated adverse event, he or she may be pre-medicated for the next study drug infusion; however, the infusion time may not be decreased for the subsequent infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30±10 minutes as long as the subject continues to be pre-medicated. If a subject experiences an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90±15 minutes. Similarly, if a subject experiences an infusion-associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60±10 minutes.

3.1.7 Supplier: Bevacizumab is supplied by Genentech Pharmaceuticals

3.2 VORINOSTAT DRUG INFORMATION

3.2.1 Drug Name: Vorinostat (Zolinza®)

3.2.2 Appearance: Vorinostat is supplied as a white, opaque gelatin, size 3 capsule, containing 100 mg of vorinostat.

3.2.3 How supplied: Vorinostat is supplied as a white, opaque gelatin, size 3 capsule, containing 100 mg of vorinostat. The inactive ingredients contained in each capsule are microcrystalline cellulose, sodium croscarmellose, and magnesium stearate. Vorinostat will be supplied in the marketed package (Zolinza®).

3.2.4 Storage and Stability: Vorinostat capsules should be stored at room temperature (do not store above 30°C) in a dry, limited-access area. Care should be taken to maintain acceptable storage temperature. Vorinostat capsules should not be opened or crushed and must be administered whole.

The shelf-life of the 100 mg capsule is 2 years.

3.2.5 Human Toxicity:

Likely (occurring in more than 20% of patients)

fatigue high blood sugar (possible diabetes) diarrhea nausea changes in taste	dry mouth weight loss loss of appetite decreased appetite vomiting difficulty breathing	increased proteins in the urine (possible kidney damage) increased creatinine blood level (possible kidney problems)
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Vorinostat may likely cause low platelet counts. You may become anemic and/or have problems with bleeding, bruising, fatigue, and/or shortness of breath. You may need a blood transfusion if a problem with bleeding occurs.

Common (occurring in 3-20% of patients)

arm and/or leg swelling irregular heartbeat chills dizziness headache	fever hair loss itching dehydration constipation	muscle spasm cough airway infection blood clots in the lung squamous cell carcinoma (skin cancer)
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Vorinostat may commonly cause low red blood cell counts. You may become anemic, fatigued, and/or short of breath. You may need a blood transfusion.

Rare but serious (occurring in fewer than 3% of patients)

chest pain blood clots in a vein high blood pressure heart attack stroke fainting swelling shedding and scaling of the skin (possible fatal loss of bodily fluids) low blood levels of calcium (possible weakness and/or cramping)	low blood levels of sodium (possible headache, confusion, seizures, and/or coma) low blood levels of potassium (possible weakness) bleeding in the digestive system inflammation of the gallbladder blockage in the tubes that drain urine from the kidneys inability to urinate	severe blood infection bacterial infection in the bloodstream blood vessel inflammation (possible fever and/or fatigue) spinal cord injury blurred vision kidney failure coughing up blood pneumonia infection tumor bleeding T-cell lymphoma (cancer of the lymph nodes)
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Vorinostat may rarely cause low white blood cell counts. This means that while you take the drug, there is more of a chance of getting an infection, including pneumonia.

Vorinostat can interact with many drugs. Be sure to tell your study doctor or nurse about all drugs that you are currently taking, including any over-the-counter or herbal products. While on study, please check with your study doctor or nurse before you start any new prescription drugs or over-the-counter or herbal products.

3.2.6 Administration: Vorinostat 400mg/day will be administered on day 1 to 7 and day 15 to 21 orally on a 28 day cycle in the arm with combination of vorinostat and bevacizumab.

Vorinostat will be administered orally. Vorinostat capsules should not be opened or crushed and must be administered whole. It is recommended that Vorinostat be administered with food, but not high fat meal. A pill count will be performed at each clinic visit to ensure that the medication is taken appropriately.

Special Handling Requirements: Vorinostat is an anticancer drug. Spills of powder from vorinostat capsules due to damaged or broken capsules should be cleaned up carefully to minimize inhalation of vorinostat. The affected area must be washed at least 3 times with ethyl alcohol, followed by water. Direct contact of the powder in vorinostat capsules with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly. Vorinostat capsules should be stored at room temperature (do not store above 30°C) in a dry, limited-access area. Care should be taken to maintain acceptable storage temperature. Vorinostat capsules should not be opened or crushed and must be administered whole.

For further details and molecule characterization, see the vorinostat Investigator Brochure.

3.2.7 Supplier: Vorinostat is supplied by Merck, Sharp and Dohme Corp.

3.3 Study Agent Distribution (for the Phase II Multi-Center component):

3.3.1 Ordering Study Agent/s:

Bevacizumab and vorinostat may be requested by the Principal Investigator (or their authorized designees) at each participating institution.

All regulatory document requirements (including a Pharmacy Initiation Worksheet), as described in the BTTC Operations Manual, must be current and up to date in the BTTC Coordinating Center. The participating institution must have received an Activation memo from the OMCR prior to requesting study agents. A Study Drug Order form and Pharmacy Initiation Worksheet will be provided to the sites by OMCR.

Signed and Dated Drug requests should be emailed to:

Uintavision

Attn: Michelle DuBois

Email: mdubois@uintavision.com

When a number of investigators are participating on a clinical study at the same institution, one investigator should be considered or designated the principal or lead investigator under whom all investigational agents for that protocol should be ordered.

3.3.2 Agent Storage and Accountability:

The investigator is responsible for the proper and secure physical storage and record keeping of investigational agents received for BTTC protocols. Specifically, the investigator must:

- Maintain a careful record of the receipt, use and final disposition of all investigational agents received, using the NCI Agent Accountability Record Form (DARF), <http://ctep.cancer.gov/forms/index.html>.
- Store the agent in a secure location, accessible to only authorized personnel, preferably in the pharmacy.
- Maintain appropriate storage of the investigational agent to ensure the stability and integrity of the agent.
- Return or destroy any unused investigational agents at the completion of the study or upon notification that an agent is being withdrawn.

The intent of the agent accountability procedures described in this section is to assist the investigator in making certain that agents received from BTTC are used only for patients entered onto an approved protocol. The record keeping described in this section is required under FDA regulation. Investigators are responsible for the use of investigational agents shipped in their name. Even if a pharmacist or chemotherapy nurse has the actual task of handling these agents upon receipt, the investigator is the responsible individual and has agreed to accept this responsibility by signing the FDA 1572, <http://www.fda.gov/opacom/morechoices/fdaforms/FDA-1572.doc>.

3.3.3 Returning or destroying unused and/or defective Agent:

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Investigators/Designees should make every effort to minimize the amount of agent ordered and returned unused, (e.g. limit inventories to an 8 week supply or less). The BTTC Operations Manual describes a generic Policy for returning or destroying supplied study agents. Procedures specific to this study are described here.

Agent Return/Destruction Procedure

All unused or expired investigational drug should be destroyed in accordance with the local institutional policies and procedures. The on site destruction of unused or expired product should be documented in the DARF, and forwarded to BTTC Coordinating center which in turn will notify Genentech and Merck Sharp and Dohme along with documentation of lot numbers and number of vials destroyed.

Destroy opened, partially used or unused vials/bottles. Do **NOT** return opened or partially used vials/bottles unless specifically requested otherwise in the protocol.

4.0 ELIGIBILITY CRITERIA

Subject Selection

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. Males and females will be recruited with no preference to gender. No exclusion to this study will be based on race. Minorities will actively be recruited to participate.

All patients who meet the following eligibility criteria must be registered with the Brain Tumor Trials Collaborative via the Office of Multicenter Clinical Research (MD ANDERSON CANCER CENTER OMCR) at the University of Texas, MD Anderson Cancer Center prior to receiving treatment with study drug. The OMCR's registration procedures are described in the Multicenter Procedures section of this protocol. **Patients must initiate study treatment within 96 hours after registration.**

Inclusion Criteria

Patients will be included in the study based on the following criteria.

- 4.1 Patients must have histologically proven glioblastoma, gliosarcoma or anaplastic glioma to be eligible for the **Phase I** component of this protocol. Anaplastic gliomas include anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), anaplastic mixed oligoastrocytoma (AMO), or malignant glioma NOS (not otherwise specified). Patients will be eligible if the original histology was low-grade glioma and a subsequent histological diagnosis of a malignant glioma is made. Only patients with histologically proven or imaging proven recurrent glioblastoma or gliosarcoma will be eligible for the **Phase II** component. Wafer acceptable if recurrence is confirmed.

- 4.2 All patients must sign an informed consent indicating their awareness of the investigational nature of this study. Patients must have signed an authorization for the release of their protected health information.
- 4.3 Patients must be 18 years old or older.
- 4.4 Patients must have a Karnofsky performance status (KPS) equal or greater than 60 (See Appendix 18.2).
- 4.5 At the time of registration:
- 4.5.1 Patients must have recovered from the toxic effects of prior therapy to < grade 2 toxicity per CTC version 4 (except deep vein thrombosis – see section 6.1.4
- 28 days from any investigational **agent**,
 - 4 weeks (28 days) from prior cytotoxic therapy,
 - 2 weeks (14 days) from vincristine,
 - 6 weeks (42 days) from nitrosoureas,
 - 3 weeks (21 days) from procarbazine administration,
 - ≥ 1 week (7 days) for non-cytotoxic agents, e.g., interferon, tamoxifen, thalidomide, cis-retinoic acid, etc. (radiosensitizer does not count).
- 4.5.2 Patients who receive anticancer agents for non-therapeutic purposes unrelated to this study (such as presurgically for obtaining pharmacology data for the agent) will be eligible to enter the study provided they have recovered from the toxic effects of the agent if any. Any questions related to the definition of non-cytotoxic agents should be directed to the Study Chair.
- 4.6 Patients must have adequate bone marrow function ($ANC \geq 1,500/mm^3$, platelet count of $\geq 100,000/mm^3$), adequate liver function ($SGPT \leq 3$ times upper limit normal and alkaline phosphatase ≤ 2 times upper limit normal, total bilirubin $\leq 1.5mg/dl$, “Patients with high bilirubin levels related to known diagnosis of benign hyperbilirubinemia (Gilbert’s syndrome) will be eligible “., and adequate renal function ($BUN \leq 1.5$ times institutional normal and Creatinine < 1.5 mg/dl) prior to registration. These tests must be performed within 14 days prior to registration.
- 4.7 Patients must have shown unequivocal evidence for tumor progression as determined by an MRI scan done prior to study entry which will be reviewed by the treating physician to confirm and document recurrence.
- Patients with prior therapy that included interstitial brachytherapy or stereotactic radiosurgery must have confirmation of true progressive disease rather than radiation necrosis using the local institutional standards for such determination including advanced imaging or surgery.
- 4.8 The baseline on-study MRI scan should be performed within 14 days (+ 3 working days) prior to registration but before starting treatment and on a steroid dose that has been stable or decreasing for at least 5 days. If the steroid dose is increased between the date of imaging and registration (or at that time), a new baseline MRI is required. The same type of scan, i.e., MRI must be used throughout the period of protocol treatment for tumor measurement.

- 4.9 Patients having undergone recent resection of recurrent or progressive tumor will be eligible as long as all of the following conditions apply:
- a) At least 4 weeks (28 days) have elapsed from the date of surgery and the patients have recovered from the effects of surgery.
 - b) Evaluable or measureable disease following resection of recurrent Malignant Glioma is not mandated for eligibility into the study.
 - c) To best assess the extent of residual disease post-operatively, a MRI should be done no later than 96 hours in the immediate post-operative period or at least 4 weeks post-operatively, within 14 days prior to registration. If the 96-hour scan is more than 14 days before registration, the scan needs to be repeated. If the steroid dose is increased between the date of imaging and registration, a new baseline MRI is required on a stable steroid dosage for at least 5 days.
- 4.10 Patients must have failed prior radiation therapy and must have an interval of greater than or equal to 12 weeks (84 days) from the completion of radiation therapy to study entry except if there is unequivocal evidence for tumor recurrence (such as histological confirmation or advanced imaging data such as PET scan) in which case at least 4 weeks (28 days) from completion of radiation therapy will suffice (Note: for patients who have undergone surgery to confirm recurrence after radiation therapy, guidelines in 4.9a should be followed).
- 4.11 Patients with prior therapy that included interstitial brachytherapy or stereotactic radiosurgery must have confirmation of true progressive disease rather than radiation necrosis based upon either PET or Thallium scanning, MR spectroscopy or surgical/pathological documentation of disease.
- 4.12 Women of childbearing potential must have a negative B-HCG pregnancy test documented within 14 days prior to registration. Women of childbearing potential must not be pregnant, must not be breast-feeding, and must practice adequate contraception (please refer to Appendix 18.11 for details and definitions – woman of childbearing potential; adequate methods of contraception) for the duration of the study, and for 30 days after the last dose of study medication. Patients must not be pregnant because animal studies show that bevacizumab and Vorinostat are teratogenic.
- 4.13 Male patients on treatment with Vorinostat must agree to use an adequate method of contraception for the duration of the study, and for 30 days after the last dose of study medication (please refer to Appendix 18.11 for definition of adequate methods of contraception).
- 4.14 Patient must be able to tolerate the procedures required in this study including periodic blood sampling, study related assessments, and management at the treating institution for the duration of the study.

- 4.15 Patients receiving treatment with any antiepileptic medications except Valproic acid (because of its HDAC inhibitory activity) can be included in the study. Vorinostat is not metabolized by Cytochrome P450 3A4 (CYP 3A4); however, Vorinostat may potentially suppress CYP 3A4 activity. Therefore, patients should preferably be treated with non-enzyme inducing anti-epileptic medications although this is not mandatory. If enzyme-inducing antiepileptic drugs are used, monitoring of these drug levels should be considered, as considered clinically appropriate by the treating physician (See Appendix 18.3).
- 4.16. For the Phase II portion of the study, patients may have had treatment for no more than 2 prior relapses. There is no limit to the number of relapses for the phase I portion of the study provided the functional status and other eligibility criteria for enrollment are met. Relapse is defined as progression following initial therapy (i.e. radiation+/- chemo if that was used as initial therapy). The intent therefore is that patients had no more than 3 prior therapies (initial and treatment for 2 relapses). If the patient had a surgical resection for relapsed disease and no anti-cancer therapy was instituted for up to 12 weeks, and the patient undergoes another surgical resection, this is considered as 1 relapse. For patients who had prior therapy for a low-grade glioma, the surgical diagnosis of a high-grade glioma will be considered the first relapse

General Exclusion Criteria

- 4.17 Inability to comply with protocol or study procedures (for example, an inability to swallow tablets).
- 4.18 Prior treatment with bevacizumab or Vorinostat.
- 4.19 Patients receiving valproic acid (VPA), an anticonvulsant drug with HDAC inhibitor properties, will be excluded, unless they are switched to an alternative agent prior to treatment initiation. A 5-day wash out period is required. Patients who have failed prior treatment with other histone deacetylase inhibitors will be excluded.
- 4.20 Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from providing informed consent.
- 4.21 Any condition, including the presence of clinically significant laboratory abnormalities, which places the patient at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study. These would include
- a) Active infection (including persistent fever) including known AIDS or Hepatitis C infection
 - b) Diseases or conditions that obscure toxicity or dangerously alter drug metabolism
 - c) Serious intercurrent medical illness (e.g. symptomatic congestive heart failure).
- 4.22 Current, recent (within 4 weeks (28 days) of the first infusion of this study, or planned participation in an experimental antitumor drug study (other than the current one).

- 4.23 Patients with a history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix or bladder), unless in complete remission and off of all therapy for that disease for a minimum of 3 years are ineligible.
- 4.24 Patients with spinal disease (metastasis) and/or leptomeningeal disease will not be allowed in the study.

Bevacizumab-Specific Exclusion Criteria

- 4.25 Inadequately controlled hypertension (defined as systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg).
- 4.26 Prior history of hypertensive encephalopathy.
- 4.27 New York Heart Association (NYHA) Grade II or greater congestive heart failure (see Appendix 18.9).
- 4.28 History of myocardial infarction or unstable angina within 6 months prior to Day 1.
- 4.29 History of stroke or transient ischemic attack within 6 months prior to Day 1.
- 4.30 Significant vascular disease (e.g., aortic aneurysm, requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1.
- 4.31 History of hemoptysis (\geq 1/2 teaspoon of bright red blood per episode) within 1 month prior to Day 1.
- 4.32 Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation).
- 4.33 Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 1 or anticipation of need for major surgical procedure during the course of the study. “Patients with recent resection will be eligible for entry into the surgical arm of the study but will follow guidelines as in section 4.9”.
- 4.34 Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to Day 1.
- 4.35 History of abdominal fistula or gastrointestinal perforation within 6 months prior to Day 1.
- 4.36 Serious, non-healing wound, active ulcer, or untreated bone fracture.
- 4.37 Proteinuria as demonstrated by:
 - Urine protein: creatinine (UPC) ratio \geq 1.0 (Appendix 18.10) at screening OR

- Urine dipstick for proteinuria $\geq 2+$ (patients discovered to have $\geq 2+$ proteinuria on dipstick urinalysis at baseline should undergo a 24 hour urine collection and must demonstrate $\leq 1g$ of protein in 24 hours to be eligible).

4.38 Known hypersensitivity to any component of bevacizumab.

4.39 Pregnancy (positive pregnancy test) or lactation. Use of effective means of contraception (men and women) in subjects of child-bearing potential is required for study treatment.

5.0 STRATIFICATION/DESCRIPTIVE FACTORS

See section 11.0 Statistical Considerations.

6.0 TREATMENT PLAN

6.1 General

All patients who meet eligibility criteria must be registered with the Brain Tumor Trials Collaborative Office of Multicenter Clinical Research (MD ANDERSON CANCER CENTER OMCR) at the University of Texas, MD Anderson Cancer Center (UT MD ANDERSON CANCER CENTER). Patients must initiate study treatment within 96 hours after registration.

6.1.1 Patients will be monitored for hematologic or serologic evidence of myelosuppression, hepatic injury, renal injury, and electrolyte disturbances and for clinical evidence of other toxicity as is described in section 8.0.

6.1.2 G-CSF Administration

G-CSF and erythropoietin administration: Routine prophylactic use is not permitted. However, therapeutic use in patients with complications (severe neutropenia with fever or anemia), may be considered at the investigator's discretion.

6.1.3 Supportive Care

a. Corticosteroids should be used in the smallest dose to control symptoms of cerebral edema and mass effect, and discontinued if possible.

b. Anti-seizure medications should be used as indicated. Treatment with valproic acid is not allowed. Patients should preferably be treated with non-enzyme inducing antiepileptic medications to avoid any potential interactions with vorinostat. For patients on treatment with enzyme-inducing antiepileptic drugs, clinically relevant monitoring of drug levels is recommended, as considered appropriate by the treating physician

c. Febrile neutropenia may be managed according to the local institution's Infectious Disease guidelines. Measures may include appropriate laboratory testing, including

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blood and urine cultures and the institution of broad-spectrum antibiotics. If a source for the fever is not identified or the fever resolves when the neutrophil count recovers, antibiotics may be discontinued and the patient observed.

d. Antiemetics: prophylactic and therapeutic use is allowed.

e. Other Concomitant Medications

Therapies considered necessary for the well-being of the patient may be given at the discretion of the treating physician. All concomitant medications must be recorded.

f. Other Anticancer or Experimental Therapies

No other anticancer therapy (including chemotherapy, radiation, hormonal treatment or immunotherapy) of any kind is permitted during the study period. No other antitumor drugs under investigation may be used concomitantly with the study drug.

g. Surgery

If neurosurgical management is required for reasons not due to tumor progression, these procedures must be documented, including the indications for surgery, the surgical operative note and pathology report.

6.1.4 Definition of dose limiting toxicities (DLT) (Phase I portion)

All patients in the phase I study will be evaluable for assessment of toxicity in order to define DLT. Toxicities will be graded according to the Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. If multiple toxicities are seen, the presence of DLT should be based on the most severe toxicity experienced. DLT will be defined as any of the following events occurring in the first cycle of treatment (4 weeks) and attributable to the study drugs:

- Any grade 4 hematological toxicity except neutropenia and thrombocytopenia, as indicated below
 - febrile neutropenia defined as grade 3-4 neutropenia with fever $\geq 38.5^{\circ}\text{C}$ and/or infection requiring antibiotic or antifungal treatment OR any grade 4 neutropenia lasting 5 days or more is considered a DLT
 - Grade 4 thrombocytopenia OR platelet count $< 25,000/\text{ul}$ of any duration is considered a DLT;
- Any non-hematologic grade 3 or 4 toxicity, except the following
 - nausea or vomiting that responds to symptomatic therapy
 - fatigue that responds to symptomatic therapy
 - alopecia
 - lymphopenia,
 - weight gain (in patients on steroids),
 - venous thromboembolic disease*.

- In case of isolated laboratory abnormalities that may not reach clinical significance, a determination will be made in consultation with the IRB on a case by case basis to determine if DLT needs to be declared.
- Failure to recover from treatment related toxicities to be eligible for re-treatment within 4 weeks of the last dose of the drugs.

***Non-Relevant Toxicities for Brain Tumor Protocols**

Lymphopenia is a common finding among patients with primary brain tumors and is directly attributable to concurrent use of corticosteroids. To date, even Grade III lymphopenia has not been associated with a worsening of clinical outcome. Therefore, we will not consider this parameter in the determination of optimal dosing of drugs.

Weight gain is a common finding among patients with primary brain tumors. This too is directly attributed to the concurrent use of corticosteroids. Doses of steroids or study agents will not be modified as a consequence of weight gain. Corticosteroid dosage will be based on maintenance of control of edema in the brain and the standard clinical practice to use the minimal effective dose of corticosteroids will be employed.

Alopecia is a common occurrence in patients with brain tumors as a consequence of cranial radiotherapy. Alopecia will not be recorded or graded as toxicity.

Venous thromboembolic disease is a common complication occurring in up to 30% of patients with malignant gliomas (Wen and Marks, 2002; Semrad et al., 2006). In this study, patients who develop deep vein thrombosis may receive anticoagulation and resume therapy once they are stable on anticoagulation. Grade III deep vein thrombosis will not be considered a DLT for the phase I portion.

The routine use of filgrastim or other white cell growth factors is not permitted during cycle 1 of the Phase I portion unless clinically indicated (see section 6.1.2), but it may be used beyond this period or once the assessment of DLT has been completed.

6.2 Phase I Treatment Plan

The Phase I study has been completed in MDACC. The Phase II dose has been determined. Brief details of the phase I study are included in this section to indicate the doses explored and the final phase II dose identified.

6.2.1 Drug Dose/s:

In this component, the combination treatment arm was tested and several dose levels planned. The starting dose was bevacizumab 10mg/kg administered on day 1 and 15 intravenously and vorinostat at 400 mg/day orally on days 1 to 7 and days 15 to 21. This dose of vorinostat is also the recommended dose for combination trials based on other ongoing studies.

6.2.2 Dose Escalations and definition of maximum tolerated dose (MTD):

A conventional Phase 1 design was used with 3 patients enrolled into level 0 and monitored for 4 weeks. Dose-limiting toxicity was as defined in section 6.1.4. If no DLT was seen in the first cohort, the next 3 patients would be enrolled to level 1. If no DLT was noticed after dose escalation to level 1, this dose was to be used for Phase II component of the study. If 1/3 of the patients experience DLT, the cohort was to be expanded to 3 more patients; if 1/6 patients experience DLT, the MTD was to be considered reached and this dose would be used for the phase II part of the study. If 2/6 patients experience DLT, the MTD was considered exceeded and the previous dosage level would be declared as MTD of vorinostat in combination of bevacizumab.

6.2.3 Results of the Phase I Study

The Phase I study enrolled 3 patients in the first cohort at 400 mg/daily of vorinostat and 10 mg/kg of bevacizumab. One patient experienced a grade 3 ALT elevation and grade 3 hyperglycemia which were designated as possibly related to vorinostat – these toxicities constituted a DLT for this dose level. The cohort was hence expanded by 3 more patients. None of these patients experienced a DLT in the first cycle. Per protocol guidelines as noted in section 6.2.2, given that 1/6 patients experienced DLT at the starting dose level and because this dose level was also the recommended dose for combination studies based on other ongoing trials, the starting dose level of bevacizumab and vorinostat was declared the Phase II dose.

6.3 Phase II Treatment Plan

6.3.1 Drug Dose/s:

The dose for phase II study of the combination has been identified as follows: bevacizumab 10mg/kg administered on day 1 and 15 intravenously and vorinostat at 400 mg/day orally on days 1 to 7 and days 15 to 21. On cycle 1 day 1, vorinostat should be taken prior to the bevacizumab infusion.

6.3.2 Non- Surgical Arm:

In this component, patients will be randomized between two competing treatment arms: Vorinostat + bevacizumab versus bevacizumab alone using an adaptive randomization design (see Statistical Section). The dosage for the vorinostat + bevacizumab arm as derived from the MTD of the combination determined in the phase I component of the study is as described in section 6.3.1. The treatment schedule will be identical to that described above in the phase I component, with each course comprising 28 days. Patients will continue treatment until tumor progression or unacceptable toxicity occurs.

6.3.3 Surgical Arm:

Patients who need a surgical resection for their recurrent tumors are eligible for this part of the study. These patients will be primarily accrued in MD Anderson Cancer Center.

Other interested sites may participate on the surgical arm provided there are available local resources for appropriate sample collection and shipment. This will be decided on an institution specific manner after discussion with the Study Chair. Such participating institutions are expected to ensure that participation of such subjects as well as shipment of tissue to MDACC are in compliance with institutional and federal human subjects protection guidelines. Based on prior experience with such accrual it is anticipated that no more than 10 patients will be accrued into this portion of the study. Tumor tissue from the resection will be sent for qRT-PCR assessment of a prognostic 9 gene profile (Aldape and Colman, unpublished data). This profile distinguishes between an angiogenic (poor prognosis) mesenchymal group and a proneural (good prognosis) group. We hypothesize that the current treatment can modify the poor prognosis of the mesenchymal subgroup and improve their PFS and OS; this will be preliminarily tested in this study. Patients on this arm will be eligible after surgery to be randomized to two treatment arms (as described above in section 6.3.2) using a Bayesian adaptive algorithm after a **4 week recovery period**. PFS in patients in the surgical arm will be determined from the date of randomized to the treatment arms and not from the date of registration in the trial. Tissue will also be collected from all patients (including from the nonsurgical arm) from their original or most recent resection for this assessment.

6.3.3.1 Pre and Post-operative evaluations as a result of this part of the study will consist of history and physical examination, laboratory studies, baseline toxicity assessments and postsurgical symptoms assessment as described in sections 7.0 and 8.0.

6.3.3.2 Once patients have recovered from the effects of surgery, they will embark upon the phase II component of the study. Patients are not required to have residual disease to continue onto the phase II component.

6.3.3.3 Following surgery, a MRI scan should be done no later than 96 hours after surgery; given that patients are required to be at least 4 weeks after surgery to begin treatment in the adaptive randomized portion of the trial, the MRI should be repeated prior to initiation of treatment and on a steroid dose that is stable or decreasing. Treatment with bevacizumab or bevacizumab+vorinostat post-operatively should start no later than 14 days after the scan.

6.4 Dose Modifications:

Treatment cycles are 28 days (+3 days if needed for scheduling around holidays); treatment will be continued if there is no tumor progression and patients recovered from treatment-related adverse events associated with the prior cycle. Recovery has occurred once all the following conditions have been met:

1. ANC > 1000/ml;
2. Platelet > 100,000/ml;
3. All drug associated non- hematological toxicity have recovered to grade 0 or 1 (except for DVT as below).

If recovery has not occurred by **Day 28** (+ 3 days), the subsequent cycle will be delayed until these criteria have been met. If the patient has not recovered within 4 weeks of rest, he/she will be

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taken off treatment. However, if the patient develops a lower extremity deep venous thrombosis and requires anticoagulation or intervention (grade 3 toxicity), treatment may be restarted after a 2 week rest period if the patient is stably anticoagulated and is judged medically stable to begin chemotherapy, in the opinion of the treating physician. (Please note: DVT is graded in the CTC version 4.0 as grade 1= superficial thrombosis, grade 2= DVT, medical intervention indicated, grade 3= uncomplicated pulmonary embolism, medical intervention indicated, grade 4=life-threatening pulmonary embolism, cerebrovascular event, arterial insufficiency, urgent intervention indicated).

The dose of Vorinostat will be initiated at MTD dose from the phase I part of the trial. The same dose will be continued unless $>$ or $=$ grade 3 drug related toxicity occurs; treatment will be held until toxicity resolves to less than grade 2. The dose for next cycle will be reduced to one level below the dose that caused the grade 3 toxicity. If grade 3 toxicity occurs again at lower dose, the dose will be further reduced to the next lower level. A maximum of 2 dose reductions will be allowed for vorinostat.

There is no dose reduction for bevacizumab. If any drug related adverse event occurs that necessitate holding bevacizumab, the dose will remain unchanged once treatment resumes. The maximum allowable length of treatment interruption is 4 weeks.

6.4.1 Bevacizumab Dose Modification and Toxicity Management

There are no reductions in the bevacizumab dose. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes provided these events do not require discontinuation of the agent (Table 1).

Any toxicity associated or possibly associated with bevacizumab treatment should be managed according to standard medical practice. Discontinuation of bevacizumab will have no immediate therapeutic effect. Bevacizumab has a terminal half-life of 21 days; therefore, its discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab.

Subjects should be assessed clinically for toxicity prior to, during, and after each infusion. Blood pressure should be checked prior to each bevacizumab infusion and **standard practice guidelines followed for determining initiation and continued infusion of Bevacizumab** If resting systolic blood pressure is >140 and or resting diastolic blood pressure >90 mmHg on two separate measurements at least 5 minutes apart, Bevacizumab should be deferred until the hypertension is managed with appropriate antihypertensive medication. Treatment may be initiated once the criteria for blood pressure outlined above are met. If unmanageable toxicity including events such as medically uncontrolled hypertension or hypertensive encephalopathy occurs because of bevacizumab at any time during the study, treatment with bevacizumab should be discontinued.

Infusion Reaction: Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. Subjects who experience a NCI CTCAE v. 4.0 Grade 3 or 4 allergic reaction / hypersensitivity, adult respiratory distress

syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment.

The infusion should be slowed to 50% or less or interrupted for subjects who experience any infusion-associated symptoms not specified above. When the subject's symptoms have completely resolved, the infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle.

Adverse events requiring delays or permanent discontinuation of bevacizumab are listed in Table 1.

Regardless of the reason for holding study drug treatment, the maximum allowable length of treatment interruption is 4 weeks.

**Table 1:
Bevacizumab Dose Management Due to Adverse Events**

Event	Action to be Taken
Hypertension	
No dose modifications for grade 1/2 events	
Grade 3	If not controlled to 140/90 mmHg with medication, discontinue bevacizumab.
Grade 4 (including hypertensive encephalopathy)	Discontinue bevacizumab.
Hemorrhage	
No dose modifications for grade 1/2 non-pulmonary and non-CNS events	
Grade 3 Non-pulmonary and non-CNS hemorrhage	<p>Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab.</p> <p>All other subjects will have bevacizumab held until all of the following criteria are met:</p> <ul style="list-style-type: none"> • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. <p>Subjects who experience a repeat Grade 3 hemorrhagic event will be discontinued from receiving bevacizumab.</p>

Grade 4 non-pulmonary or non-CNS hemorrhage	Discontinue bevacizumab.
Grade 1 pulmonary or CNS hemorrhage	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab held until all of the following criteria are met: <ul style="list-style-type: none"> • The bleeding has resolved and hemoglobin is stable.as clinically determined • There is no bleeding diathesis that would increase the risk of therapy. There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.
Grade 2, 3, or 4 pulmonary or CNS hemorrhage	Discontinue bevacizumab
Venous Thrombosis No dose modifications for grade 1/2 events	
Grade 3 or 4	Hold study drug treatment. If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation if all of the following criteria are met: <ul style="list-style-type: none"> • The subject must have an in-range INR (usually between 2 and 3) if on warfarin; LMWH, warfarin, or other anticoagulant dosing must be stable prior to restarting bevacizumab treatment. • The subject must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation.
Arterial Thromboembolic event (New onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event) Any grade Discontinue bevacizumab.	
Congestive Heart Failure (Left ventricular systolic dysfunction) No dose modifications for grade 1/2 events	
Grade 3 Grade 4	Hold bevacizumab until resolution to Grade ≤ 1. Discontinue bevacizumab.

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Proteinuria	
No dose modifications for grade 1/2 events	
Grade 3 (UPC > 3.5, urine collection > 3.5 g/24 hr)	Hold bevacizumab treatment until ≤ Grade 2, as determined by either UPC ratio ≤ 3.5 or 24 hr collection ≤ 3.5 g
Grade 4 (nephritic syndrome)	Discontinue bevacizumab
GI Perforation	Discontinue bevacizumab.
Fistula	
Any grade (TE fistula)	Discontinue bevacizumab.
Grade 4 fistula	Discontinue bevacizumab.
Bowel Obstruction	
Grade 1	Continue patient on study for partial obstruction NOT requiring medical intervention.
Grade 2	Hold bevacizumab for partial obstruction requiring medical intervention. Patient may restart upon complete resolution.
Grade 3/4	Hold bevacizumab for complete obstruction. If surgery is necessary, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion.
Wound dehiscence Any grade (requiring medical or surgical therapy)	Discontinue bevacizumab.
Reversible Posterior Leukoencephalopathy	
Any grade (confirmed by MRI)	Discontinue bevacizumab.
Other Unspecified Bevacizumab-Related Adverse Events	
Grade 3	Hold bevacizumab until recovery to ≤ Grade 1
Grade 4	Discontinue bevacizumab.

6.4.2 Vorinostat Dose Modification and Toxicity Management

Vorinostat will be administered from day 1 to day 7 and day 15 to day 21 in each 28-day cycle in arm receiving vorinostat and bevacizumab. Treatment will be initiated at the MTD dose determined in the phase I component of the trial. This dose will be maintained as long as there are no vorinostat related toxicities \geq grade 2. For grade 2 vorinostat related toxicities, treatment will be withheld and the patients will be monitored until toxicities resolve to $<$ grade 2 (except for deep venous thrombosis as noted in section 5.3). For subsequent treatment the dose will be unchanged provided the recovery occurs within 2 weeks of treatment hold; if it is longer than 2 weeks, the next cycle will be at one dose level below the one that caused the toxicity. If there is grade 3 or greater non-hematologic toxicity, a minimum of 2-week rest period will be required. Subsequently, patients will restart treatment at one dose level less than the one that resulted in the toxicity as indicated below after the toxicities resolve to $<$ grade 2 (except for deep venous thrombosis as noted in section 6.4).

Dose adjustments for the subsequent cycles: dose will be one level below the dose that produced toxicity of grade 3 or greater per dose schedule changes indicated below. If grade 3 or 4 toxicity recurs, patients will again discontinue the vorinostat until toxicity returns to grade 1 or less. The estimated dose levels below are shown for various MTD that may be determined in the phase I study.

Dose Level	-2	-1	0
Drug: Vorinostat	N/A	100 mg/day	200 mg/day
	100 mg/day	200 mg/day	300 mg/day
	200 mg/day	300 mg/day	400 mg/day
	300 mg/day	400 mg/day	500 mg/day

Only 2 dose reductions of vorinostat are permitted as above. If the patient experiences grade 3 or greater toxicity after 2 dose reductions, he/she will be taken off treatment. If starting dose is 200 mg once daily, only 1 dose reduction of vorinostat is allowed.

Regardless of the reason for holding study drug treatment, the maximum allowable length of treatment interruption is 4 weeks after which the patient will be taken off the study.

6.5 CONCOMITANT ASPIRIN

Low-dose aspirin (\leq 325 mg/d) may be continued in subjects at higher risk for arterial thromboembolic disease. Subjects developing signs of arterial ischemia or bleeding on study should be evaluated for possible bevacizumab discontinuation per Table 1, Bevacizumab Dose Management Due To Adverse Events.

- 6.6 For treatment or dose modification related questions, please contact the Study Chair or the MD ANDERSON CANCER CENTER OMCR at UT MD ANDERSON CANCER CENTER at (713) 792-8519 or OMCR_BTTC@mdanderson.org.

7.0 PRETREATMENT EVALUATION

General Requirements

- 7.1 A complete history and physical (including baseline blood pressure measurement) and neurological examination (include documentation of the patients height, weight and Karnofsky Performance Status), as well as documentation of measurable and/or evaluable disease shall be performed on all patients within 14 calendar days (+ 3 working days) of study entry.
- 7.2 The treating physician will review a contrast enhanced MRI scan done prior to study entry documenting progression. For non-surgical arm patients, a baseline scan should be performed within 14 calendar days (+ 3 working days) of registration, with day 0=registration date. The baseline on-study MRI should be performed on a steroid dosage that has been stable or decreasing for at least 5 days. If the steroid dose is increased between the date of imaging and the initiation of therapy (or at that time), a new baseline MRI is required.
- 7.3 Baseline pre and post contrast MRI scan (with T1, T2, DWI, and T2 FLAIR images sequences and when feasible, T2* and DTI sequences) will be done in all patients within 14 days of entry into the study. Optional studies including dynamic contrast enhanced (DCE) and dynamic susceptibility contrast (DSC) are preferred if individual sites can obtain the same but are not required. If DCE/DSC sequences can be obtained, it is important to obtain them at baseline and at each imaging follow-up.
- 7.4 Pre-treatment laboratory tests will include CBC, differential, platelets, , total protein, albumin, calcium, , , glucose, BUN, creatinine, sodium, potassium, total bilirubin, alkaline phosphatase, LDH, SGPT (ALT), SGOT (AST), Urine protein: Creatinine ratio or urine dipstick and a pregnancy test for women of child bearing potential. PT, PTT, INR, phosphorus, magnesium and uric acid will be done at the discretion of the treating physician. Blood tests must be performed within 14 calendar days (+ 3 working days) of registration, with day 0 = registration date. Pregnancy test must be obtained 14 calendar days (+ 3 working days) of registration before treatment starts. Patient's whose clinical condition has significantly changed between the time of these tests and the initiation of treatment in the judgment of the treating physician, will have a repeat chemistry panel prior to the start of treatment.
- 7.5 About 5 cc blood samples will be collected for testing levels of biomarkers including VEGF, PlGF, bFGF, SDF1 α , angiopoietin 1 and 2, at baseline before treatment in those patients that have consented to the optional procedures.
- 7.6 About 7 cc of blood for isolation of peripheral blood monocytes will be collected for circulating endothelial cells (CEC) and circulating endothelial progenitor cells (CEPC) analysis at baseline before starting treatment in those patients that have consented to the optional procedures..
- 7.7 If available, unstained paraffin tissue from surgical samples will be obtained. A representative paraffin tissue block (at least 5 mm x 5 mm) will be obtained from recent surgery to confirm the recurrence and original surgery, before entry into the clinical trial.

The tissue will be used to test the 9 gene signature expression profile using qRT-PCR. These will be correlated with response.

- 7.8 Documentation of tumor diagnosis by pathology report from the patient's initial or most recent surgery or biopsy
- 7.9 (*) Patients will complete a baseline MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT) (Appendix 18.12) after registration but before initiating treatment on the clinical trial (*). The MDASI-BT will be completed only by the patient, unless changes in vision or weakness make this difficult. If this occurs, then the caregiver or research assistant may read the questions to the patient or assist with marking the severity number or score as described by the patient. A patient caregiver may complete the questionnaires as a patient-preference proxy if the patient's deficits preclude self report.

* Note: 7.9 is an optional procedure, and will be obtained if the patient gives his or her informed consent.

8.0 EVALUATIONS DURING STUDY

General Requirements

- 8.1 Blood pressure monitoring every 2 weeks prior to bevacizumab infusion.
- 8.2 Proteinuria will be monitored by urine protein: creatinine (UPC) ratio or dipstick every 2 weeks in the first cycle then prior to every subsequent cycle.
- 8.3 CBC, differential and platelets will be performed every two weeks (\pm 3 days) during treatment and prior to each new cycle. In addition, all patients will have the following tests every 4 weeks (\pm 3 days) prior to each new cycle if no significant toxicities are noted: total protein, albumin, calcium, glucose, BUN, creatinine, sodium, potassium, total bilirubin, alkaline phosphatase, LDH, SGPT, SGOT, urine protein: creatinine. Patients may also be evaluated with labs at any time clinically indicated. PT, PTT, INR, phosphorus, magnesium, and uric acid will be done at the discretion of the treating physician.
- 8.4 A pre and post contrast MRI scan (with T1, T2, DWI, and T2 FLAIR images sequences and when feasible, T2* and DTI sequences) shall be done pretreatment, and subsequently after each 2 cycles of treatment. MRI scans may also be done at any time clinically indicated. Optional DCE/DSC MRI scans will be obtained at baseline, after cycle 2 (at week 8) and subsequently every 2 cycles prior to initiating the next cycle (or within 3 working days of starting the cycle).
- 8.5 About 5 cc of blood for measuring VEGF, PlGF, bFGF, SDF1 α , angiopoietin 1 and 2, will be drawn at baseline before treatment, cycle 1 day 2, day 15 (pre-infusion and post-infusion) and cycle 2 (pre-infusion) in those patients that have consented to the optional procedures. The post-infusion blood will be drawn between 12-24 hr after infusion.

- 8.6 About 7 cc of blood will be collected for CEC and CEPC analysis at baseline, on cycle 1 day 2 (post-infusion), and day 15 (pre-infusion and post-infusion) in those patients that have consented to the optional procedures. The post-infusion blood drawn between 12-24 hr after infusion. Subsequently, pretreatment samples will be drawn cycle 2.
- 8.7 Physical and neurologic examinations will be performed after each cycle for the first 2 cycles and subsequently after each 2 cycles of treatment prior to initiating the next cycle. Patients will also be evaluated anytime their clinical situation demands an assessment.
- 8.8 All relevant information regarding drug doses, concomitant medications, and doses, measurable lesions with measurements, tumor response, laboratory examinations, and treatment-related toxicities shall be documented in the patient's medical record and flow sheets.
- 8.9 Pregnancy testing for FCBP (Appendix 18.11)
- 8.10 (*)The patient will complete the MDASI-BT (Appendix 18.12) at the time of clinical evaluation with MRI as long as the clinical therapy is being administered, unless clinical deterioration makes self-report not possible before that time. The time when patients are unable to complete the self-report questionnaires will be used as part of the study analysis. The MDASI-BT will be completed only by the patient, unless changes in vision or weakness make this difficult. If this occurs, then the caregiver or research assistant may read the questions to the patient or assist with marking the severity number or score as described by the patient. A patient caregiver may complete the questionnaires as a patient-preference proxy if the patient's deficits preclude self-report.
- * Note: 8.10 is an optional procedure, and will be obtained if the patient gives his or her informed consent.
- 8.11 Phase II patients will be evaluated for adverse events after each cycle for the first two cycles and subsequently after each two cycles of treatment prior to initiating the next cycle. In addition all serious adverse events will be reported to the OMCR and the study chair as directed in section 15.7.
- 8.12 After treatment on protocol is discontinued patients will be followed for overall survival, when possible.
- a) Patients who discontinue treatment due to progression will be followed for survival every 3 months.
 - b) Patients who come off therapy for reasons other than progression will be followed every 2 months with an MRI until progression or institution of new anti-tumor therapy. They will then be followed for survival every three months.

9.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

- 9.1 The primary efficacy endpoint for BTTC studies will be progression free survival (PFS) at six months from patient registration. However, objective response status should be measured and recorded. For this and for all other time to event analyses that use registration date, if a patient is registered on the pre-operative portion of the study, the start date for calculation of time to event will be the date of first post-operative study drug administration.
- 9.2 Definitions of Response
- 9.2.1. Measurable Disease: Bidimensionally measurable lesions with clearly defined margins by MRI scan.
- 9.2.2. Evaluable Disease: Unidimensionally measurable lesions, masses with margins not clearly defined. Patients with only this kind of imaging will not be allowed to enter this study unless they have recently undergone surgery and have histologically proven recurrent disease.
- 9.2.3. Non-Evaluable Disease: Not Applicable for response evaluation.
- 9.2.4. Objective Status, To Be Recorded at Each Evaluation: If there are too many measurable lesions to measure at each evaluation, choose the largest two to be followed before a patient is entered on study. The remaining lesions will be considered evaluable for the purpose of objective status determination. Unless progression is observed, objective status can only be determined when ALL measurable and evaluable sites and lesions are assessed.

Response Criteria (Modified MacDonald Criteria)

- 9.2.4.1 Complete Response (CR): Complete disappearance of all measurable and evaluable disease. No new lesions. No evidence of non-evaluable disease. All measurable, evaluable and non-evaluable lesions and sites must be assessed using the same techniques as baseline. Patients must be on none or only physiologic doses of steroids.
- 9.2.4.2. Partial Response (PR): Greater than or equal to 50% decrease under baseline in the sum of products of perpendicular diameters of all measurable lesions. No progression of evaluable disease. No new lesions. All measurable and evaluable lesions and sites must be assessed using the same techniques as baseline. Responders must be on the same or decreasing doses of dexamethasone and have stable or improved neurological exams.
- 9.2.4.3. Partial Response, Non-Measurable (PRNM): Not applicable.

9.2.4.4. Stable/No Response: Does not qualify for CR, PR, or progression. All measurable and evaluable sites must be assessed using the same techniques as baseline. Responders must be on the same or decreasing doses of dexamethasone and have stable or improved neurological exams.

9.2.4.5. Progression: 25% increase in the sum of products of all measurable lesions over smallest sum observed (over baseline if no decrease) using the same techniques as baseline, OR clear worsening of any evaluable disease, OR appearance of any new lesion/site, OR failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer).

9.2.4.6. Unknown: Progression has not been documented and one or more measurable or evaluable sites have not been assessed

9.3 Best Response: This will be calculated from the sequence of objective statuses.

For patients with all disease sites assessed every evaluation period, the best response will be defined as the best objective status as measured according to Section 9.3. If the response does not persist at the next regular scheduled MRI, the response will still be recorded based on the prior scan, but will be designated as a non-sustained response. If the response is sustained, e. g. still present on the subsequent MRI, it will be recorded as a sustained response, lasting until the time of tumor progression. Best response is unknown if the patient does not qualify for a best response or increasing disease and if all objective status determinations before progression are unknown.

9.4 Neurological Exam: Although not used for determining response, it is useful to evaluate improvement in the neurologic exam, (as compared to the baseline assessment), that should coincide with objective measurement of tumor size.

+2 Definitely Better
 +1 Possibly Better
 0 Unchanged
 -1 Possibly Worse
 -2 Definitely Worse

9.5 Performance Status: Patients will be graded according to Karnofsky Performance Status (see Appendix 18.2).

- 9.6 Time to Treatment Failure: From date of registration to the date of first observation of progressive disease (as defined in Section 9.3), non-reversible neurologic progression or permanently increased steroid requirement (applies to stable disease only), death due to any cause, or early discontinuation of treatment. If a patient is registered on the pre-operative portion of the study, the start date for calculation of time to event will be the date of first post-operative study drug administration.
- 9.7 Time to Death: From date of registration to date of death due to any cause.
- 9.8 Documenting FLAIR: Although not part of Macdonald criteria, investigators will be asked to measure tumor related changes on FLAIR sequence as best as possible, as non-enhancing patterns of recurrence can occur. If this occurs within the setting of clinical decline, the patient will be considered to have progressive disease. Investigators will also be asked to document if recurrence of disease is multifocal.

10.0 SUBJECT DISCONTINUATION

10.1 Criteria for Removal from Protocol Treatment:

- a. After administration of 12 cycles (unless there is clear evidence of clinical benefit to justify continuation of treatment) .
- b. Progression of disease as defined in Section 9.3, after 1 cycle of treatment.
- c. Unacceptable toxicity (**including the following**).
 - Grade 4 hypertension or Grade 3 hypertension not controlled with medication
 - Nephrotic syndrome
 - Grade ≥ 2 pulmonary or CNS hemorrhage; any Grade 4 hemorrhage
 - Symptomatic Grade 4 venous thromboembolic event
 - Any grade arterial thromboembolic event
 - Grade 4 congestive heart failure
 - Gastrointestinal perforation
 - Tracheoesophageal fistula (any grade) or Grade 4 fistula
 - Grade ≥ 2 bowel obstruction that has not fully recovered despite medical or surgical intervention
 - Wound dehiscence requiring medical or surgical intervention
 - Determination by the investigator that it is no longer safe for the subject to continue therapy
 - Grade 4 events thought to be related to bevacizumab by the investigator
- d. The patient may withdraw from the study at any time for any reason.
- e. Medical or psychiatric illness which in the investigator's judgement renders the patient incapable of further therapy.

- f. Treatment related adverse events not resolved within a 4 weeks rest period or requiring more than two dose de-escalations of any drug whichever is earlier.
- g. Pregnancy

Patients who have an ongoing bevacizumab related Grade 4 or serious adverse event at the time of discontinuation from study treatment will continue to be followed until resolution of the event or until the event is considered irreversible.

Patients may remain on treatment as long as disease progression is not observed and the patient is not experiencing unacceptable toxicity (see Section 10.1). Although therapy is planned for one year, the patient may remain on treatment beyond this time if both the patient and physician agree that further therapy is in the patient's best interests.

10.2 Criteria from Removal from the Study

- Protocol Defined Follow-up Completed
- Patient Lost to Follow-up
- Patient Refused Follow-up
- Death

10.3 All reasons for discontinuation of treatment and/or removal from the study must be documented in the source records and the BTTC study database.

11.0 STATISTICAL CONSIDERATIONS

All statistical components of the study will be analyzed in collaboration with Dr. Ying Yuan, Department of Biostatistics at MD Anderson Cancer Center.

11.1 Statistical Analysis

11.1.1 Phase I component: The phase I component will assess the MTD of Vorinostat in combination with Bevacizumab as shown in the table. A conventional phase I design will be used and the MTD will be selected using a 3+3 accrual design at each dose level until MTD is determined. A maximum of 18 patients will be recruited to this component of the study.

11.1.2 Phase II component: This is a randomized phase II trial to Bevacizumab to Vorinostat+ Bevacizumab in patients with recurrent GBM. The primary outcome is progression free survival. Patients will be randomized between the two arms using a Bayesian adaptive algorithm. Patients will be randomized fairly between the two arms at the start of the trial (for the first 20 patients). Thereafter, as the trial progresses and data accrue, the randomization will become unbalanced in favor of the treatment that, on average, has better results in terms of failure time. Therefore, each successive patient is more likely to receive the treatment with better results, on average. A minimum of 20 and a maximum of 90 patients will be accrued. Based on an anticipated accrual

rate between 3 and 5 patients per month, the maximum trial accrual period will be between 12 and 24 months.

The table given below summarizes the operating characteristics of the design. The historical median progression free survival is 4 months. The tables below assume an accrual rate of either 3 or 5 patients per month. The trial will be stopped early and a treatment selected as being “better” if the probability that one treatment’s median PFS is larger than the other’s PFS exceeds 0.995. If the trial does not stop early and the maximum 90 patients are accrued, a treatment is selected as being “better” if the probability that one treatment’s median PFS is larger than the other’s PFS exceeds 0.975. A treatment arm will be dropped at any point during the trial if the probability that the treatment’s median PFS is larger than 4 months is less than 0.01. The “# of patients treated” row is the average number of patients treated on a given arm under the given scenario. When the medians are equal, the probability of selecting either of the two arms (i.e., a false positive result) is 8% for both accrual rates. The probability of selecting the better treatment (i.e., a true positive result) for a doubling in the median PFS is 82% for 3 per month and 80% for 5 per month.

Accrual Rate: 3 Per Month			Accrual Rate: 5 Per Month		
	Treatment			Treatment	
	BEV	BEV+V		BEV	BEV+V
True Median PFS	4*	4	True Median PFS	4	4
# Patients Treated	42.3	41.6	# Patients Treated	41.4	41.6
Pr(Selected)	0.04	0.04	Pr(Selected)	0.04	0.04
Pr(Selected Early)	0.02	0.01	Pr(Selected Early)	0.01	0.02
True Median PFS	4	6	True Median PFS	4	6
# Patients Treated	25.7	53.9	# Patients Treated	27.5	54.1
Pr(Selected)	0.00	0.42	Pr(Selected)	0.00	0.42
Pr(Selected Early)	0.00	0.23	Pr(Selected Early)	0.00	0.20
True Median PFS	4	8	True Median PFS	4	8
# Patients Treated	18.8	47.4	# Patients Treated	20.9	51.2
Pr(Selected)	0.00	0.82	Pr(Selected)	0.00	0.80
Pr(Selected Early)	0.00	0.60	Pr(Selected Early)	0.00	0.50

*True median failure times are given in month; V: vorinostat; BEV: bevacizumab

At each evaluation when a new patient comes in the study, the data for patients who have been followed till that time and not yet progressed are accounted in the analysis. The trial will be conducted using a web based program developed by the Department of Biostatistics and Applied Bevacizumab + Vorinostat Protocol

Mathematics at MD Anderson Cancer Center. Through the website interface, the Clinical Trial Conduct site, the users will have the ability to randomize patients, update the current patients' status. The results of randomization are displayed for user to review. When a patient is randomized the calculations are based on all available data entered into the website. The results of the randomization are displayed to the screen for the user to view. All data is stored in a secure SQL server database.

Time-to-event outcomes, including PFS and OS will be estimated using Kaplan-Meier method. The log rank test will be performed to test the difference in time-to-event distributions between two groups. Cox proportional hazards model will be utilized as regression technique to adjust the covariates in the time-to-event analysis.

11.1.3 Correlative studies:

11.1.3.1 Gene Profile analysis: Tumor tissue will be collected for qRT-PCR analysis to determine the established 9 gene profile and identify the presence of mesenchyme/angiogenic (poor prognosis) genotype versus the proneural (good prognosis) genotype. The response for each of the treatment arms will be correlated with the two expected genotypic prognostic groups of patients. Because this is an optional procedure and the trial is powered to detect differences in clinical outcome and not for biomarker analysis, these data will be used to generate preliminary data regarding identification of specific patient populations who may benefit from the treatments and for a future genomic-profile driven personalization of treatment in future studies.

11.1.3.2 Biomarker analysis: measurement of plasma angiogenic proteins including VEGF, PlGF, bFGF, SDF1 α , angiopoietin 1 and 2 by ELISA on cycle 1 pretreatment, cycle 1 day 2, day 15 (pre- and post-infusion) and cycle 2 (pre-infusion).

11.1.3.3 Blood circulating cells study: blood cells experiment will be enumerated by flow cytometric analyses of CD31, CD 34, CD 45 and CD 133 using fluorescence-labeled monoclonal antibodies (Duda et al., 2006, 2007). Cell concentration will be calculated as percentage of total number of mononuclear cells. The quantitative analyses end point will be the change in fraction of CD31+ CD34+CD45- and CD133+CD34+ within the mononuclear blood cell population in patients receiving treatment. Percent value will be obtained at baseline prior to every treatment cycle, and in addition on cycle 1 day 2 (post-infusion), and day 15 (pre- and post-infusion). Subsequently, pretreatment samples will be drawn on cycle 2. Post-treatment values in cycle 1 will be compared with pretreatment value in each individual using Wilcoxon signed rank test.

11.1.3.4 Imaging study (for MDACC patients: other sites may participate if interested and able to): Imaging parameter analysis and statistical analysis, based on the published study by Batchelor et al. (Batchelor et al., 2007), will be conducted in collaboration with Dr. Ed Jackson, imaging physicist.

-Volumetrics: Enhancing lesion and areas of T2 abnormality on FLAIR imaging will be quantified by a neuroradiologist. The lesions will be outlined by using a volumetric approach (Sorensen et al., 2001).

-Diffusion imaging assessment: Apparent diffusion coefficient are created from high and low b value image using the standard Stejskal-Tanner diffusion approximation (Oh et al., 2005). This

provides an estimate of relative water motility on a voxel-by-voxel basis. The units of the map are in area/time, mm²/s.

- Permeability: DCE-MRI data will be processed following published approach, including K^{trans} (Tofts et al., 1999) and V_e (extracellular-extravascular volume fraction).

- Statistical analysis: The comparison between the MRI parameters, protein level and cell counts that measured on the different days will be performed with a two tailed paired Wilcoxon test (Hollander and Wolfe, 1973).

11.2 Determination of Sample Size

11.2.1 Phase I component: The Phase I component will assess the MTD of vorinostat in combination with bevacizumab as shown in the table. A conventional phase I design will be used and the MTD will be selected using a 3+3 accrual design at each dose level until MTD is determined. A maximum of 18 patients will be recruited into this part of the study.

11.2.2 Phase II component: This is a randomized phase II trial to bevacizumab to vorinostat+ bevacizumab in patients with recurrent GBM. The primary outcome is progression free survival. Patients will be randomized between the two arms using a Bayesian adaptive algorithm. Patients will be randomized fairly between the two arms at the start of the trial (for the first 20 patients). Thereafter, as the trial progresses and data accrue, the randomization will become unbalanced in favor of the treatment that, on average, has better results in terms of failure time. Therefore, each successive patient is more likely to receive the treatment with better results, on average. A minimum of 20 and a maximum of 90 patients will be accrued. Based on an anticipated accrual rate between 3 and 5 patients per month, the maximum trial accrual period will be between 12 and 24 months.

The table given in Section 10 summarizes the operating characteristics of the design. The historical median time to progress is 4 months. The tables below assume an accrual rate of either 3 or 5 patients per month. The trial will be stopped early and a treatment selected as being “better” if the probability that one treatment’s median PFS is larger than the other’s PFS exceeds 0.995. If the trial does not stop early and the maximum 90 patients are accrued, a treatment is selected as being “better” if the probability that one treatment’s median PFS is larger than the other’s PFS exceeds 0.975. The number of patients treated row is the average number of patients treated on a given arm under the given scenario. When the medians are equal, the probability of selecting either of the two arms (i.e., a false positive result) is 9% for both accrual rates. The probability of selecting the better treatment (i.e., a true positive result) for a doubling in the median PFS is 85% for 3 per month and 83% for 5 per month. At each evaluation when a new patient comes in the study, the data for patients who have been followed till that time and not yet progressed are accounted in the analysis. The trial will be conducted using a web based program developed by the Department of Biostatistics and Applied Mathematics at MD Anderson Cancer Center. Through the website interface, the users will have the ability to randomize patients, update the current patients’ status. The results of randomization are displayed for user to review.

If the study reaches the total enrollment specified in section 11, allowance will be made for the enrollment of 10 or more additional patients in the phase II component to be treated in order to fulfill the minimal number for the pre-operative study for tissue correlates.

11.3 SAFETY PLAN

11.3.1 GENERAL PLAN TO MANAGE SAFETY

A number of measures will be taken to ensure the safety of patients participating in this trial. These measures will be addressed through exclusion criteria (see Section 4.0) and routine monitoring as follows.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements. Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study. Patients discontinued from the treatment phase of the study for any reason will be evaluated ~30 days (28–42 days) after the decision to discontinue treatment.

A. Bevacizumab-Specific

Specific monitoring procedures are as follows:

- Hypertension will be monitored through routine evaluation of blood pressure prior to each bevacizumab treatment. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.
- Proteinuria will be monitored by urine protein: creatinine (UPC) ratio or dipstick every 2 weeks in the first cycle then prior to every subsequent cycle.
- If patients on treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4-8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 4 weeks after that procedure (in the case of high risk procedures eg. liver resection, or thoracotomy, it is recommended that chemotherapy be restarted no earlier than 6 wk and bevacizumab no earlier than 8 wk after surgery).
- If the surgery is not due to tumor progression or due to adverse event attributable to study drugs, the patient may resume treatment once medically stable and per guidelines above. ***The provision to continue treatment after surgery will constitute an exception to the provision in section 6.4.1*** and permits the patient to continue on the study despite a 4 weeks or greater break from treatment if this is considered in the patient's best interest. A new baseline scan will be necessary before beginning such treatment. If the patient has disease progression on this scan, the date of this scan will be considered as the progression date for the purposes of PFS calculation.

B. Vorinostat-Specific

Specific monitoring procedures are as follows:

Anorexia and other constitutional symptoms, including weight loss, fatigue will be monitored through routine evaluation including body weight at every clinic follow up visit during the vorinostat treatment.

Cytopenia, especially thrombocytopenia will be monitored by CBC every 2 weeks.

Gastrointestinal symptoms, such as nausea, vomiting, diarrhea, constipation will be monitored through routine evaluation at week 4 then every 8 weeks during the treatment with vorinostat. Patients are also encouraged to communicate with the clinical nurse to report severe GI symptoms.

12.0 DISCIPLINE REVIEW

12.1 Pathology Review

Not Applicable .

12.2 Radiology Review

Not Applicable

13.0 PHARMACOKINETICS

N/A

14.0 LABORATORY CORRELATES

See Appendices 18.4 and 18.5

15.0 MULTICENTER PROCEDURES

15.1 General Procedures

The BTTC Operations Manual and Data Submission Forms, on file at all BTTC institutions, document the data management and quality assurance programs for this collaboration. BTTC institutions will follow the guidelines as addressed below and throughout this protocol.

15.2 Principal Investigators

Bevacizumab + Vorinostat Protocol

The principal investigator(s) will be responsible for the conduct of the study and monitoring its progress. The responsibility for all reports and forms required by BTTC will be that of the principal investigator(s).

15.3 Procedures for Patient Entry

15.3.1 Centralized Patient Registrations

Patients who are candidates for the study will first be evaluated for eligibility by the local investigator. All patients must be registered both locally and centrally with BTTC.

Before an institution may begin participating in a BTTC protocol, they must complete the following steps:

- Submit all required regulatory documents to the MD ANDERSON CANCER CENTER Office of Multicenter Clinical Research (OMCR) as outlined in the BTTC Operations Manual
- Participate in a site initiation visit, webcast, or conference call
- Receive training regarding study specific CRF's and/or databases
- Execute all relevant contractual agreements

After these requirements have been fulfilled, the participating institution will receive by fax, e-mail, or hard copy memo a Site Activation Notification. Once the Site Activation Notification has been received, the participating institution may begin to register patients to the protocol

15.3.2 Patient Registration Procedures

BTTC patients will be registered with the MD ANDERSON CANCER CENTER OMCR by fax & phone at UT MD ANDERSON CANCER CENTER. All eligibility requirements will be checked prior to registration. The status of all regulatory documents will be checked prior to registration. No patient will be entered on protocol if they do not satisfy all regulatory document and eligibility requirements. Generic MD ANDERSON CANCER CENTER OMCR registration procedures are also described in the BTTC Operations Manual.

Informed Consent/Authorization

Prior to protocol enrollment and initiation of treatment, subjects must sign and date an Institutional Review Board (IRB) approved consent form.

Patient Registration Procedures

Participating institutions must register patients via EDMS, fax, and phone with the MD ANDERSON CANCER CENTER Office of Multicenter Clinical Research at:

EDMS: <https://iview.mdanderson.org/>

Fax: (713) 794-1902

Phone: (713) 792-8519

Registration hours are 8:00 a.m. to 5:00 p.m. Central Standard Time, Monday through Friday, except holidays.

Registrations must be completed after the patient has signed the informed consent and has been determined to be eligible by the local investigator.

At the time of registration the following information will be requested by the MD ANDERSON CANCER CENTER Office of Multicenter Clinical Research (OMCR):

- A copy of a completed and signed, protocol specific, Eligibility Checklist form
- One copy of a Pathology report from the patient's most recent surgery or biopsy
- One copy of the signed and dated Informed Consent/Authorization.

The eligibility checklist form should be prepared and signed prior to sending to the MD ANDERSON CANCER CENTER OMCR. The submission should be followed by a phone call to the MD ANDERSON CANCER CENTER OMCR to verify receipt. If the patient fails eligibility screening do not proceed to the registration process.

Patient Number for Participating Institutions

Once eligibility has been established during Registration, the patient from the participating institution is assigned a six character MD ANDERSON CANCER CENTER OMCR patient ID number and a protocol specific Accession Number. The patient ID number is unique to the patient and, except for SAE reports, must be used for registrations onto subsequent protocols and written on all data and correspondence for the patient. The SAE reports must use the protocol specific Accession Number.

Verification of Registration

For participating institutions, a Registration Verification Letter for patients registered to BTTC protocols will be faxed or emailed to the registering institution within one working day after the registration is received. The OMCR must be notified in advance of patient cases that may require an expedited registration.

Initiation of Therapy

Treatment may not be initiated until the participating institution receives a faxed or emailed copy of the patient's Registration Verification Letter from the MD ANDERSON CANCER CENTER OMCR.

All Patients that are eligible to receive therapy must initiate treatment within 96 hours after the registration.

The MD ANDERSON CANCER CENTER OMCR must be notified in writing of any exceptions to this policy.

Eligibility Exceptions

Eligibility Exceptions will not be granted.

15.4 Data Management

All data will be entered into the computerized web accessible data management system located at the MD ANDERSON CANCER CENTER OMCR at MD ANDERSON CANCER CENTER. Designated research staff from the registering institution will enter the data. The protocol specific electronic forms are to be used by the participating sites. All investigators will utilize these forms for Baseline, Treatment, Tumor Evaluation, Off Treatment, Survival, and Off-study data.

Confidentiality

All documents, investigative reports, or information relating to the patient are strictly confidential. Any patient specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the MD ANDERSON CANCER CENTER OMCR must have the patient's full name & social security number "blacked out" and the assigned MD ANDERSON CANCER CENTER patient ID number, protocol number and event time point written on every page of the document. Patient initials may be included or retained for cross verification of identification.

15.5 Data Monitoring

All submitted data will be monitored by the MD ANDERSON CANCER CENTER Protocol Manager specifically assigned to this protocol. Requests for correction of data deficiencies will be sent via email to the Institutional Coordinator. Any major deficiencies will be corrected by telephone communication followed by amendments to the study documents. All data will be monitored for completeness. Key parameters such as drug dosages including attenuations and escalations, toxicity documentation and tumor measurements will be analyzed. All data deficiencies will be corrected within two weeks.

The schedule for data & source document submission is outlined as follows. Source document requirements are subject to increase for a given participating institution or

patient case in the event of questionable study conduct, data quality, and/or non-compliance with the following submission schedule.

Data Set / Source Documents	Schedule for Submission
Regulatory Documents (as described in the BTTC Operations Manual)	Prior to Patient Registration
Eligibility Checklist	Prior to Patient Registration
Copy of signed & dated Informed Consent w/ HIPAA Authorization	Prior to Patient Registration
Pathology Report (from the most recent pre-registration diagnostic biopsy or surgery)	Prior to registration
Baseline Data (To include prior disease/treatment history, and baseline clinical evaluation information)	Within 14 days after the registration date
Baseline Source Documents (To include all source documents that support all data reported on the Baseline form and Eligibility Checklist/s)	Within 14 days after the registration date
Baseline MDASI – BT Questionnaire	Within 14 days after the registration date
Treatment (Cycle) Data (To include treatment, AE, concurrent medications, and clinical evaluation information)	Within 38 days after the first day of each treatment cycle.
Treatment (Cycle) Source Documents (To include Infusion records, Physician Orders, Prescriptions, Patient Diaries, Pill Count records)	Within 38 days after the first day of each treatment cycle.
Disease Evaluation Data (To include response, measurements, and clinical evaluations used to determine the response)	Within 14 days after registration (for baseline) and then REAL TIME after each protocol defined on-therapy assessment time point.
Disease Evaluation Source Documents (To include MRI Scans or any other assessment used to determine the patients baseline status and/or response to protocol therapy)	Within 14 days after registration (for baseline) and then REAL TIME after each protocol defined assessment time point.
Off Treatment Data	REAL TIME after the last date of any modality of protocol treatment

Off Treatment Source Documents	Within 10 days after off treatment decision has been made.
Follow-up (Survival) Data	Within 40 days after the last treatment date and then every 90 days until Off Study (unless otherwise specified by the protocol)
Follow-up Source Documents	On Request
Non-Treatment Data (May include Quality of Life questionnaires (MDASI_BT), Specimen Tracking information, Pathology Specimen Submission, etc. when applicable)	Within 10 days after each scheduled assessment, event, or activity
Off Study Data	Within 10 days after the date the patient is removed from the study.
Off Study Source Documents	Within 10 days after the date the patient is removed from the study.

15.6 Safety Assessments and Toxicity Monitoring

All patients receiving study agents will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, CNS observations, physical examination findings, and spontaneous reports of adverse events reported to the investigator by patients. All toxicities encountered during the study will be evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and recorded prior to each course of therapy during the first two cycles and subsequently after each two cycles of treatment and prior to initiating the next cycle. Life-threatening toxicities that are unexpected and assessed to be possibly related to the study agent/s should be reported immediately to the study Coordinator, Institutional Review Board (IRB), and those that are unexpected and assessed to be possibly related to the study agents should also be reported to the FDA. **MD Anderson Cancer Center OMCR will notify Genentech Drug Safety and Merck Sharp and Dohme Corp Worldwide safety of ANY serious treatment emergent adverse event (STEA) as soon as possible.**

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the Adverse Event Case Report Form and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy) even if the event is not considered to be related to study drug.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form are recorded on the Baseline Evaluations_Adverse Events Case Report Form. Abnormal laboratory values or test results constitute adverse events

only if they induce clinical signs or symptoms or require therapy, and are also recorded on the Adverse Events Case Report Form.

Adverse events for Phase II patients will be reported prior to the beginning of each new cycle for the first two cycles, and subsequently after each two cycles of treatment prior to initiating the next cycle. In addition all serious adverse events will be reported to the study chair, and the MD ANDERSON CANCER CENTER OMCR as directed in section 15.7.

The study will be monitored by the Data Safety Monitoring Board (DSMB) of MD Anderson Cancer Center. All adverse events submitted to the IRB will also be reviewed by the DSMB. In addition, the principal investigator and the biostatistician will submit data relating to safety and efficacy to the DSMB annually.

Safety Monitoring and Early Stopping Rule

Patients will be monitored on an ongoing basis for development of grade 3 or higher drug related toxicities. Persistent toxicities that may affect treatment schedule and dose will also be monitored on an ongoing basis. In addition, we will have a review of the toxicities of all enrolled patients after the first 20 patients in the phase II portion have completed one cycle of treatment and subsequently for every 20 patients enrolled until study completion. This will ensure identification of any unexpected toxicities. If unexpected toxicities are seen in more than 30% of the patients at the time of any of the periodic reviews noted above, the trial will be placed on hold and the dosing and schedule of the treatment re-evaluated.

A serious adverse event is any adverse drug experience at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions in a patient who has never had seizure activity in the past that do not result in inpatient hospitalization, or the development of drug dependency or abuse.

Events *not* considered to be serious adverse events are hospitalizations for the purposes of this protocol and include:

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- Treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- Treatment on an emergency, outpatient basis for an event *not* fulfilling any of the definitions of serious given above and *not* resulting in hospital admission.

Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

The study will utilize the Cancer Therapy Evaluation Program (BTTC) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 for Toxicity and Adverse Event reporting. A copy of the CTCAE version 4.0 can be downloaded from the BTTC home page (<http://BTTC.cancer.gov/reporting/ctc.html>). All appropriate treatment areas should have access to either a hard copy of the CTCAE version 4.0 or the www version.

Serious Adverse Events will be reported via the BTTC SAE reporting process. **See section 15.7 for BTTC SAE reporting guidelines.**

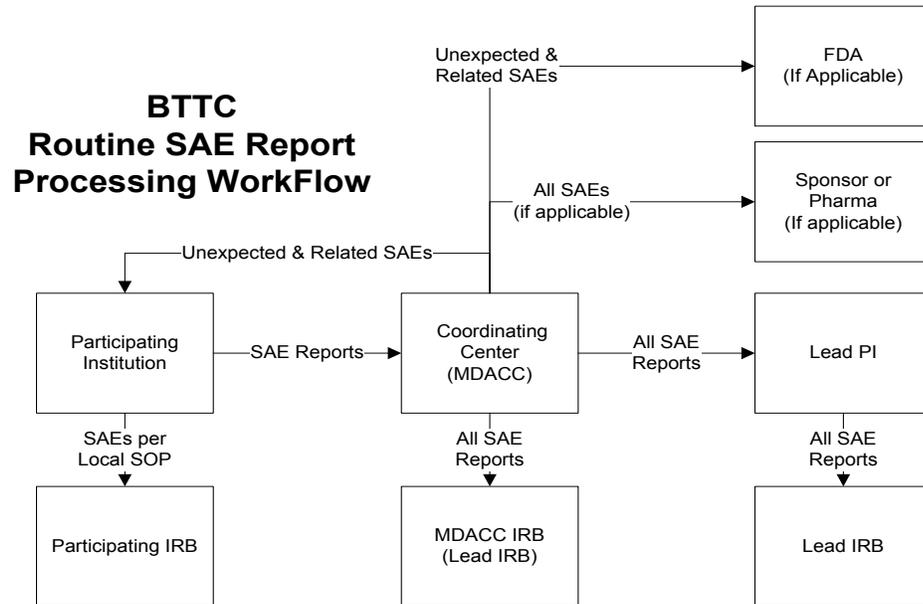
Notification of Investigators of Expedited Adverse Events Reported to the FDA

Safety Reports or Updates –Investigators will be sent a copy of expedited adverse events, which BTTC has sent to the FDA or that BTTC receives from the agent suppliers. BTTC will notify consortium investigators via the MD ANDERSON CANCER CENTER Office of Multicenter Clinical Research. Within 7 business days of receipt of the notification the MD ANDERSON CANCER CENTER OMCR will forward the reports to the participating members with protocol specific instructions for IRB submissions, patient notifications, etc. For routine IND Safety Reports BTTC does not generally require an immediate revision to the master protocol and/or model informed consent documents maintained at the MD ANDERSON CANCER CENTER Office of Multicenter Clinical Research. The investigators are to file a copy with their protocol file and send a copy to their IRB according to their local IRB’s policies and procedures.

IND AE Action Letters - These letters are issued by BTTC for those serious adverse events, which warrant an immediate change in the informed consent form and/or protocol. Investigators will be sent a copy of expedited adverse events, which BTTC has sent to the FDA or that BTTC has received from the agent supplier/s. BTTC will notify consortium investigators via the MD ANDERSON CANCER CENTER Office of Multicenter Clinical Research with the requirement that the model informed consent and or master protocol be amended to include the new event. Immediately upon receipt of the notification the MD ANDERSON CANCER CENTER OMCR will forward the letters to the participating members with protocol specific instructions for IRB submissions, patient notifications, etc. BTTC provides a time frame for which to submit the amendment to the BTTC Protocol and Information Office. The letter from BTTC will specify if accrual to the protocol is to be suspended until the revision is made and whether patients already on study require re-consenting.

15.7 Guidelines for Reporting Serious Adverse Events to BTTC

All patients receiving agents will be evaluated for safety. Both local IRB and BTTC SAE reporting procedures are to be followed by all Institutions.



BTTC SAE reporting requirements and time frames for reporting to the BTTC Coordinating Center are described below:

What to Report?	When to Report?	How to Report?
Serious Adverse Events (SAE's)		
1. All Deaths occurring from the time the consent is signed through 30 days after the last day of active treatment	Within 1 working day (24 hours) from the time the research team becomes aware of event	Unless otherwise specified in the protocol use the MD ANDERSON SAE Report Form for Multicenter Reporting (Multicenter Participants outside MD ANDERSON)
2. Other SAE's (that did not result in death) that are serious AND unexpected AND related occurring from the time the consent is signed through 30 days after the last day of active treatment	Within 5 working days from the time the research team becomes aware of event	Unless otherwise specified in the protocol use the MD ANDERSON SAE Report Form for Multicenter Reporting (Multicenter Participants outside MD ANDERSON)
3. Other SAE's (that did not result in death) that do not meet the above criteria occurring from the time the consent is signed through 30 days after the last day of active treatment (the SAE is unrelated)	Within 5 working days from the time the research team becomes aware of event	Unless otherwise specified in the protocol use the MD ANDERSON SAE Report Form for Multicenter Reporting (Multicenter Participants outside MD ANDERSON)

Serious Adverse Events are to be reported to the local IRB in accordance with local policy and procedures. However, all SAE's are to be reported to the OMCR in accordance with BTTC policy even when the local IRB does not require a report, or does not require a prompt report. In these cases a formal memo explaining the local policy must accompany the report that is submitted to the OMCR.

The BTTC Coordinating Center will maintain documentation of all Serious Adverse Events from each institution. The BTTC Coordinating Center will notify all investigators of any serious and unexpected adverse experiences that are possibly related to the study agent/s. The investigators are to file a copy with their protocol file and send a copy to their IRB according to their local IRB's policies and procedures.

All serious adverse events that are unexpected and assessed to be possibly related to the study agents must be reported to the FDA by the lead investigator (or their designee) as a

15-day post-marketing ‘Alert Report’. **An unexpected adverse event is one that is not already described in the study agent Investigator Brochure(s).** The lead principal investigator (or their designee) also has the obligation to report serious adverse events to their IRB, Genentech Drug Safety and Merck Sharp and Dohme Corp Worldwide safety.

The BTTC Coordinating Center will forward all SAE reports to the lead IRB via the lead investigator, FDA (when applicable), and , Genentech Drug Safety and Merck Sharp and Dohme Corp Worldwide safety.

Genentech Drug Safety and Merck Sharp and Dohme Corp Worldwide safety	FDA MedWatch 15-day Alert Report
<p>Genentech Drug Safety Fax: (650) 225-4682 or (650) 225-5288 (Using the safety reporting fax cover sheet attached to this document)</p> <p>Merck Sharpe and Dohme Corp. (Attn: Worldwide Product Safety)</p> <p>Fax: 215-993-1220</p> <p>AND:</p> <p>Study Coordination Center/Principal Investigator Contact Information and fax # (713) 792-2883 and (713) 794-4999</p>	<p>Phone: 1-800-FDA-1088</p> <p>FAX: 1-800-FDA-0178 or by mail to MedWatch</p> <p>Center for Biologics Evaluation and Research Food and Drug Administration Suite 200N 1401 Rockville Pike Rockville, MD 20852-1448</p> <p>FAX: 1-800-FDA-0178 or by mail to MedWatch, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857-9787</p>

SAEs should be recorded on a Multicenter Serious Adverse Event Form (Appendix 18.8). **The completed SAE form is to be imported or faxed to:**

MD ANDERSON CANCER CENTER Office of Multicenter Clinical Research
Attn: BTTC Project
EDMS: <https://iview.mdanderson.org/>
Fax: 713-794-1902

Follow-up information:

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original SAE report and submitting it as follow-up.
- Adding supplemental summary information and submitting it as follow-up with the original SAE report.

Occasionally BTTC may contact the reporter for additional information, clarification, or current status of the subject for whom an adverse event was reported.

Assessing Causality:

Investigators are required to assess whether there is a reasonable possibility that the study agent/s caused or contributed to an adverse event. The following general guidance may be used.

Yes: If the temporal relationship of the clinical event to the study agent/s administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No: If the temporal relationship of the clinical event to the study agent/s administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

15.8 Guidelines & Procedures for reporting Violations, Deviations and Unanticipated Problems

Neither the FDA nor the ICH GCP guidelines define the terms “protocol violation” or “protocol deviation.” The definition is often left to the Lead Institution IRB. Accordingly, since MD ANDERSON CANCER CENTER is the Coordinating Center and the Protocol Chair must adhere to those policies set by the MD ANDERSON CANCER CENTER IRB, the definitions for protocol violation and deviation as described by the MD ANDERSON CANCER CENTER IRB will be applied for reporting purposes for all institutions participating in the MD ANDERSON CANCER CENTER Multi-center Project. Definitions, reporting guidelines and procedures for reporting violations, deviations and/or unanticipated problems are described in the BTTC Operations Manual.

Protocol violations/deviations/unanticipated problems occurring at a participating institution will be submitted to that institution’s own IRB. A copy of the participating institution’s IRB violation/deviation/unanticipated problem report will be forwarded to the BTTC Coordinating Center by importing into EDMS or by faxing within 7 calendar days after the original submission.

MD ANDERSON CANCER CENTER Office of Multicenter Clinical Research

EDMS: <https://iview.mdanderson.org/>
Fax: 713-794-1902

BTTC Coordinating Center: Upon receipt of the violation/deviation/unanticipated problem report from the participating institution, the BTTC Coordinating Center will submit the report to the lead Protocol Chair for review. Subsequently, the participating

institution's IRB violation/deviation/unanticipated problem report will be submitted to the MD Anderson Cancer Center IRB for review.

15.9 Institutional Review

Each cooperating center will submit the protocol to its own IRB. Documentation of the IRB approval will be forwarded to the MD ANDERSON CANCER CENTER OMCR at UT MD ANDERSON CANCER CENTER before a patient from that institution can be registered on protocol. No changes in the protocol will be allowed unless approved by the principal investigator and BTTC.

15.10 Protocol Revisions and Closure

Non life-threatening revisions: BTTC investigators will receive written notification of protocol revisions regarding non life-threatening events.

Life-threatening revisions: BTTC investigators will receive telephone notification of life-threatening revisions with follow-up by fax and/or e-mail. Life-threatening protocol revisions will be implemented immediately.

Protocol closures and temporary holds: BTTC investigators will receive email notification of protocol closures and holds. Closures and holds will be effective immediately. Centers will be updated on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

15.11 Quality Assurance

The BTTC Quality Assurance procedures and reports are described in detail in the BTTC Operations Manual. However, an abbreviated description is provided below.

BTTC Quality assurance measures are provided by three mechanisms: ongoing in-house monitoring of protocol compliance, on-site audits, and response reviews. All data submitted to the MD ANDERSON CANCER CENTER OMCR at UT MD ANDERSON CANCER CENTER will be monitored in-house for timeliness of submission, completeness, and adherence to protocol requirements. Data monitoring will begin at the time of patient registration and will continue during protocol performance and completion. The MD ANDERSON CANCER CENTER Protocol Manager will perform the ongoing protocol compliance monitoring with the support of the BTTC study investigators.

In the absence of a sponsor monitoring requirement, or agency, institutions participating in BTTC Protocols may be subject to on-site auditing conducted by the MD ANDERSON CANCER CENTER OMCR as described in the MD ANDERSON CANCER CENTER OMCR's Multi-Center Audit Plan for the BTTC consortium. The Multi-Center Audit Plan does not replace the in-house monitoring described in this manual. On-Site auditing combined with the in-house monitoring are intended to enhance the reliability and validity of clinical trial data from BTTC institutions through the use of routine monitoring & auditing procedures.

15.12 Retention of Records

Retain all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for at least 2 years after the investigation is completed.

15.13 Data confidentiality Plan

The investigator will assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, patients will authorize the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The use of the samples for research will be done in accordance with the guidelines defined by the FDA document "Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable" (issued 25 April 2006). The subject's personal information will be removed before the research samples are used. The research samples will be de-identified by *setting a study code /initials*. If a subject requests destruction of their banked research tissue and blood samples, and the samples have not yet been de-identified, the investigator will destroy the samples as described in this FDA guidance.

16.0 PATIENT RELATED OUTCOMES MEASURES

This study seeks to establish effective therapies at recurrence and improve on current clinical results. We hypothesize that using a combination of vorinostat and bevacizumab will result in improved outcome compared to bevacizumab alone. However, given the intensive nature of this regimen, it will be important to determine whether if any determined survival benefit is associated with improvements in symptoms or does a worsening of these parameters offset the increase in survival.

Precedence for measuring "non-therapeutic" endpoints exists in oncology research. For example, Gemcitabine was approved by the FDA partially as a consequence of the decrease in pain reported in pancreatic patients who were treated, not on the basis of survival improvement which was modest, at best¹ (Carmichael, Fink et al. 1996). There have been efforts in neuro-oncology to evaluate secondary endpoints using validated instruments as an additional indicator of benefit.

The MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT) allows the self-reporting of symptom severity and interference with daily activities. The MDASI-BT has demonstrated reliability and validity in the adult primary brain tumor patient population² (Armstrong, Mendoza et al. 2006). This tool represents a modification of the widely used and validated MDASI, with particular attention to symptoms common in patients with brain tumors.

The availability of validated instruments provides an opportunity to prospectively assess the

impact of treatment, both positive and negative, on patients. This evaluation of symptom burden in this study will assist in finding the best possible treatment with the least toxicity.

16.1 Patient Related Outcome Objectives:

1. To evaluate longitudinal changes in symptom measures and determine the impact of the therapy on these parameters.
2. To measure symptom burden over the course of therapy to evaluate differences between patients individual symptom severity, overall mean symptom severity, and difference in scores on the interference items between responders and non-responders.
3. To describe the variability of symptom severity longitudinally over the treatment course and follow-up period.

16.2 Patient Related Outcome Methods:

16.2.1 Patient Related Outcome Instruments:

The MDASI-BT will be utilized for this portion of the study. Full instruments are provided in the appendix. In addition, information regarding demographics and treatment history will be collected as part of the larger study and used in this analysis.

The MDASI-BT consists of 23 symptoms rated on an 11-point scale (0 to 10) to indicate the presence and severity of the symptom, with 0 being “not present” and 10 being “as bad as you can imagine.” Each symptom is rated at its worst in the last 24 hours. Symptoms included on the instrument include those commonly associated with cancer therapies, those associated with increased intracranial pressure, and those related to focal deficits. The questionnaire also includes ratings of how much symptoms interfered with different aspects of a patient’s life in the last 24 hours. These interference items include: general activity, mood, work (includes both work outside the home and housework), relations with other people, walking, and enjoyment of life. The interference items are also measured on 0 - 10 scales. The average time to complete these instruments is 5 minutes. The MDASI-BT has been translated into 18 languages (Armstrong, Mendoza et al. 2006).

16.2.2 Patient Related Outcome Data collection:

After enrollment on the clinical trial, patients will complete as baseline measures the MDASI-BT. The patient will continue to complete the MDASI-BT at the time of clinical evaluation with MRI as long as the clinical therapy is being administered, unless clinical deterioration makes self-report not possible before that time. The time when patients are unable to complete the self-report questionnaires will be used as part of the study analysis. The MDASI-BT will be completed only by the patient, unless changes in vision or weakness make this difficult. If this occurs, then the caregiver or research assistant may read the questions to the patient or assist with marking the severity number or score as described by the patient. A patient caregiver may complete the questionnaires as

a patient-preference proxy if the patient's deficits preclude self-report. These reports will be used for descriptive purposes only.

16.3 Patient Related Outcome Statistical Section:

The sample size for this trial was based on the primary end point of the study.

Received MDASI-BT forms will be checked versus the timing schedule and considered as valid if they fall within ten days of the scheduled assessment. Compliance rates will be calculated as the number of received valid forms over the number of expected forms. Differences between groups in compliance will be tested by use of Fisher's exact test at every time point.

We will use descriptive statistics to describe how patients rate symptom severity and interference with function at each time point. Error bar graphs for each of the symptoms will be constructed at each time point. The proportion of patients rating their symptoms to be 7 or greater (on a 0-10 scale) will also be reported. We will construct individual patient profiles for each of the selected symptoms to describe the individual patients' patterns of change over time. We will calculate the mean core symptom severity, mean severity of the MDASI-BT and mean symptom interference at the time of clinical evaluation. Estimates of differences in the mean symptom severity and mean symptom interference between responders and non-responders will be estimated in the intent to treat population. All patients with at least one valid questionnaire will be included in the analyses. Questionnaires completed at study registration will be considered baseline. All questionnaire data received after randomization will be used in the primary analyses.

Differences of at least 2 points will be classified as the minimum clinically meaningful change in the symptom severity and symptom interference measures. For example, an increase of 2 points or more would mean a moderate improvement, whereas a decrease of 2 points or more would be interpreted as moderate worsening. For individual symptoms, a rise in a symptom score means deterioration, whereas a reduced score means improvement of the specific symptom.

17.0 REFERENCES

- Carmichael, J., et al (1996). Phase II study of gemcitabine in patients with advanced pancreatic cancer. *British Journal of Cancer*, 73(1), 101-105.
- Chinnaiyan et al. (2012). Phase I trial of vorinostat combined with bevacizumab and CPT-11 in recurrent glioblastoma. *Neurooncology*. 2012 Jan;14(1):93-100.
- Armstrong, T.S., Mendoza, T., Gning, et al (2006). Validation of the MD Anderson Symptom Inventory Brain Tumor Module (MDASI-BT). *Journal of Neuro-Oncology*, 80(1), 27-35.
- Batchelor, T. T., Sorensen, A. G., di Tomaso, E., Zhang, W. T., Duda, D. G., Cohen, K. S., Kozak, K. R., Cahill, D. P., Chen, P. J., Zhu, M., et al. (2007). AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. *Cancer Cell* 11, 83-95.
- Bergers, G., and Hanahan, D. (2008). Modes of resistance to anti-angiogenic therapy. *Nat Rev Cancer* 8, 592-603.
- Bergers, G., Song, S., Meyer-Morse, N., Bergsland, E., and Hanahan, D. (2003). Benefits of targeting both pericytes and endothelial cells in the tumor vasculature with kinase inhibitors. *J Clin Invest* 111, 1287-1295.
- Bolden, J. E., Peart, M. J., and Johnstone, R. W. (2006). Anticancer activities of histone deacetylase inhibitors. *Nat Rev Drug Discov* 5, 769-784.
- Calvani, M., Rapisarda, A., Uranchimeg, B., Shoemaker, R. H., and Melillo, G. (2006). Hypoxic induction of an HIF-1alpha-dependent bFGF autocrine loop drives angiogenesis in human endothelial cells. *Blood* 107, 2705-2712.
- Casanovas, O., Hicklin, D. J., Bergers, G., and Hanahan, D. (2005). Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors. *Cancer Cell* 8, 299-309.
- Ceradini, D. J., Kulkarni, A. R., Callaghan, M. J., Tepper, O. M., Bastidas, N., Kleinman, M. E., Capla, J. M., Galiano, R. D., Levine, J. P., and Gurtner, G. C. (2004). Progenitor cell trafficking is regulated by hypoxic gradients through HIF-1 induction of SDF-1. *Nat Med* 10, 858-864.
- Du, R., Lu, K. V., Petritsch, C., Liu, P., Ganss, R., Passegue, E., Song, H., Vandenberg, S., Johnson, R. S., Werb, Z., and Bergers, G. (2008). HIF1alpha induces the recruitment of bone marrow-derived vascular modulatory cells to regulate tumor angiogenesis and invasion. *Cancer Cell* 13, 206-220.
- Fernando, N. T., Koch, M., Rothrock, C., Gollogly, L. K., D'Amore, P. A., Ryeom, S., and Yoon, S. S. (2008). Tumor escape from endogenous, extracellular matrix-associated angiogenesis inhibitors by up-regulation of multiple proangiogenic factors. *Clin Cancer Res* 14, 1529-1539.
- Folkman, J. (1971). Tumor angiogenesis: therapeutic implications. *N Engl J Med* 285, 1182-1186.
- Folkman, J. (2006). Angiogenesis. *Annu Rev Med* 57, 1-18.
- Glusker, P., Recht, L., and Lane, B. (2006). Reversible posterior leukoencephalopathy syndrome and bevacizumab. *N Engl J Med* 354, 980-982; discussion 980-982.
- Gurney, J. G., and Kadan-Lottick, N. (2001). Brain and other central nervous system tumors: rates, trends, and epidemiology. *Curr Opin Oncol* 13, 160-166.
- Holash, J., Maisonpierre, P. C., Compton, D., Boland, P., Alexander, C. R., Zagzag, D., Yancopoulos, G. D., and Wiegand, S. J. (1999). Vessel cooption, regression, and growth in tumors mediated by angiopoietins and VEGF. *Science* 284, 1994-1998.
- Jain, R. K., di Tomaso, E., Duda, D. G., Loeffler, J. S., Sorensen, A. G., and Batchelor, T. T. (2007). Angiogenesis in brain tumours. *Nat Rev Neurosci* 8, 610-622.

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- Karp, J. E., Gojo, I., Pili, R., Gocke, C. D., Greer, J., Guo, C., Qian, D., Morris, L., Tidwell, M., Chen, H., and Zwiebel, J. (2004). Targeting vascular endothelial growth factor for relapsed and refractory adult acute myelogenous leukemias: therapy with sequential 1-beta-d-arabinofuranosylcytosine, mitoxantrone, and bevacizumab. *Clin Cancer Res* *10*, 3577-3585.
- Kim, M. S., Kwon, H. J., Lee, Y. M., Baek, J. H., Jang, J. E., Lee, S. W., Moon, E. J., Kim, H. S., Lee, S. K., Chung, H. Y., *et al.* (2001). Histone deacetylases induce angiogenesis by negative regulation of tumor suppressor genes. *Nat Med* *7*, 437-443.
- Kim, S. H., Jeong, J. W., Park, J. A., Lee, J. W., Seo, J. H., Jung, B. K., Bae, M. K., and Kim, K. W. (2007). Regulation of the HIF-1alpha stability by histone deacetylases. *Oncol Rep* *17*, 647-651.
- Kopp, H. G., Ramos, C. A., and Rafii, S. (2006). Contribution of endothelial progenitors and proangiogenic hematopoietic cells to vascularization of tumor and ischemic tissue. *Curr Opin Hematol* *13*, 175-181.
- Lamszus, K., Kunkel, P., and Westphal, M. (2003). Invasion as limitation to anti-angiogenic glioma therapy. *Acta Neurochir Suppl* *88*, 169-177.
- Mahon, P. C., Hirota, K., and Semenza, G. L. (2001). FIH-1: a novel protein that interacts with HIF-1alpha and VHL to mediate repression of HIF-1 transcriptional activity. *Genes Dev* *15*, 2675-2686.
- Mancuso, M. R., Davis, R., Norberg, S. M., O'Brien, S., Sennino, B., Nakahara, T., Yao, V. J., Inai, T., Brooks, P., Freimark, B., *et al.* (2006). Rapid vascular regrowth in tumors after reversal of VEGF inhibition. *J Clin Invest* *116*, 2610-2621.
- Marks, P. A., Richon, V. M., Miller, T., and Kelly, W. K. (2004). Histone deacetylase inhibitors. *Adv Cancer Res* *91*, 137-168.
- Mastronardi, L., Puzzilli, F., Couldwell, W. T., Farah, J. O., and Lunardi, P. (1998). Tamoxifen and carboplatin combinational treatment of high-grade gliomas. Results of a clinical trial on newly diagnosed patients. *J Neurooncol* *38*, 59-68.
- Miller, D. L., Dou, C., and Armstrong, W. F. (2005). The influence of agent delivery mode on cardiomyocyte injury induced by myocardial contrast echocardiography in rats. *Ultrasound Med Biol* *31*, 1257-1263.
- Munster, P. N., Rubin, E. H., Van Belle, S., Friedman, E., Patterson, J. K., Van Dyck, K., Li, X., Comisar, W., Chodakewitz, J. A., Wagner, J. A., and Iwamoto, M. (2009). A Single Supratherapeutic Dose of Vorinostat Does Not Prolong the QTc Interval in Patients with Advanced Cancer. *Clinical Cancer Research* *15*, 7077-7084.
- Norden, A. D., Young, G. S., Setayesh, K., Muzikansky, A., Klufas, R., Ross, G. L., Ciampa, A. S., Ebbeling, L. G., Levy, B., Drappatz, J., *et al.* (2008). Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence. *Neurology* *70*, 779-787.
- Oh, J., Cha, S., Aiken, A. H., Han, E. T., Crane, J. C., Stainsby, J. A., Wright, G. A., Dillon, W. P., and Nelson, S. J. (2005). Quantitative apparent diffusion coefficients and T2 relaxation times in characterizing contrast enhancing brain tumors and regions of peritumoral edema. *J Magn Reson Imaging* *21*, 701-708.
- Okuyama, H., Krishnamachary, B., Zhou, Y. F., Nagasawa, H., Bosch-Marce, M., and Semenza, G. L. (2006). Expression of vascular endothelial growth factor receptor 1 in bone marrow-derived mesenchymal cells is dependent on hypoxia-inducible factor 1. *J Biol Chem* *281*, 15554-15563.
- Ozcan, C., Wong, S. J., and Hari, P. (2006). Reversible posterior leukoencephalopathy syndrome and bevacizumab. *N Engl J Med* *354*, 980-982; discussion 980-982.
- Petit, I., Jin, D., and Rafii, S. (2007). The SDF-1-CXCR4 signaling pathway: a molecular hub modulating neo-angiogenesis. *Trends Immunol* *28*, 299-307.

- Phillips, H. S., Kharbanda, S., Chen, R., Forrest, W. F., Soriano, R. H., Wu, T. D., Misra, A., Nigro, J. M., Colman, H., Soroceanu, L., *et al.* (2006). Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis. *Cancer Cell* 9, 157-173.
- Qian, D. Z., Wang, X., Kachhap, S. K., Kato, Y., Wei, Y., Zhang, L., Atadja, P., and Pili, R. (2004). The histone deacetylase inhibitor NVP-LAQ824 inhibits angiogenesis and has a greater antitumor effect in combination with the vascular endothelial growth factor receptor tyrosine kinase inhibitor PTK787/ZK222584. *Cancer Res* 64, 6626-6634.
- Rossig, L., Urbich, C., Bruhl, T., Dernbach, E., Heeschen, C., Chavakis, E., Sasaki, K., Aicher, D., Diehl, F., Seeger, F., *et al.* (2005). Histone deacetylase activity is essential for the expression of HoxA9 and for endothelial commitment of progenitor cells. *J Exp Med* 201, 1825-1835.
- Scappaticci, F. A., Fehrenbacher, L., Cartwright, T., Hainsworth, J. D., Heim, W., Berlin, J., Kabbinavar, F., Novotny, W., Sarkar, S., and Hurwitz, H. (2005). Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. *J Surg Oncol* 91, 173-180.
- Sorensen, A. G., Patel, S., Harmath, C., Bridges, S., Synnott, J., Sievers, A., Yoon, Y. H., Lee, E. J., Yang, M. C., Lewis, R. F., *et al.* (2001). Comparison of diameter and perimeter methods for tumor volume calculation. *J Clin Oncol* 19, 551-557.
- Stupp, R., Mason, W. P., van den Bent, M. J., Weller, M., Fisher, B., Taphoorn, M. J., Belanger, K., Brandes, A. A., Marosi, C., Bogdahn, U., *et al.* (2005). Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 352, 987-996.
- Tofts, P. S., Brix, G., Buckley, D. L., Evelhoch, J. L., Henderson, E., Knopp, M. V., Larsson, H. B., Lee, T. Y., Mayr, N. A., Parker, G. J., *et al.* (1999). Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. *J Magn Reson Imaging* 10, 223-232.
- Tso, C. L., Shintaku, P., Chen, J., Liu, Q., Liu, J., Chen, Z., Yoshimoto, K., Mischel, P. S., Cloughesy, T. F., Liau, L. M., and Nelson, S. F. (2006). Primary glioblastomas express mesenchymal stem-like properties. *Mol Cancer Res* 4, 607-619.
- Vredenburgh, J. J., Desjardins, A., Herndon, J. E., 2nd, Marcello, J., Reardon, D. A., Quinn, J. A., Rich, J. N., Sathornsumetee, S., Gururangan, S., Sampson, J., *et al.* (2007). Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol* 25, 4722-4729.
- Wong, E. T., Hess, K. R., Gleason, M. J., Jaeckle, K. A., Kyritsis, A. P., Prados, M. D., Levin, V. A., and Yung, W. K. (1999). Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. *J Clin Oncol* 17, 2572-2578.
- Yu, J. L., Rak, J. W., Coomber, B. L., Hicklin, D. J., and Kerbel, R. S. (2002). Effect of p53 status on tumor response to antiangiogenic therapy. *Science* 295, 1526-1528.

18.0 **APPENDIX**

- 18.1 NCI Common Terminology Criteria for Adverse Events
- 18.2 Karnofsky Performance Status and Neurologic Function
- 18.3 EIAEDs and Non-EIAEDs
- 18.4 Peripheral Blood Mononuclear Cell (PBMC) Isolation for Circulating Endothelial Cells Assays
- 18.5 Blood and tissue biomarker collection and analysis
- 18.6 Bayesian Adaptive Algorithm: Technical Details
- 18.7 Study Flow Chart / Schema
- 18.8 Multicenter Serious Adverse Event Form
- 18.9 New York Heart Association (NYHA) Guidelines
- 18.10 Procedure for Obtaining a Urine Protein: Creatinine Ratio
- 18.11 Pregnancy Tests for Females of Childbearing Potential and Adequate Methods of Contraception
- 18.12 MD Anderson Symptom Inventory for Brain Tumors (MDASI – BT)
- 18.13 Drug Accountability
- 18.14 Patient Study Drug Diary

18.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE version 4.0 for Toxicity and Adverse Event reporting. A copy of the CTCAE version 4.0 can be downloaded from the www at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

18.2 **Karnofsky Performance Status Score and Neurological Function**

Patient's performance status and Neurologic Functions will be graded according to the following scales:

Karnofsky Performance Status

KPS 100	Normal; no complaints; no evidence of disease
KPS 90	Able to carry on normal activity; minor signs or symptoms of disease
KPS 80	Normal activity with effort; some sign or symptoms of disease
KPS 70	Cares for self; unable to carry on normal activity or do active work
KPS 60	Requires occasional assistance, but is able to care for most personal needs
KPS 50	Requires considerable assistance and frequent medical care
KPS 40	Disabled; requires special care and assistance
KPS 30	Severely disabled; hospitalization is indicated, although death no imminent
KPS 20	Very sick; hospitalization necessary; active support treatment is necessary
KPS 10	Moribund; fatal processes progressing rapidly
KPS 0	Dead

Neurologic Function

	+2	Definitely Better
	+1	Possibly Better
	0	Unchanged
	-1	Possibly Worse
	-2	Definitely Worse

18.3 LIST OF ENZYME INDUCING & NON_ENZYME INDUCING ANTICONVULSANTS

Enzyme inducing antiepileptic medications

Carbamazepine (Tegretol, Tegretol XR, Carbatrol)
Oxcarbazepine (Trileptal)
Phenytoin (Dilantin, Phenytek)
Fosphenytoin (Cerebyx)
Phenobarbital (Solfoton)
Primidone (Mysoline)

Non enzyme inducing antiepileptic medications

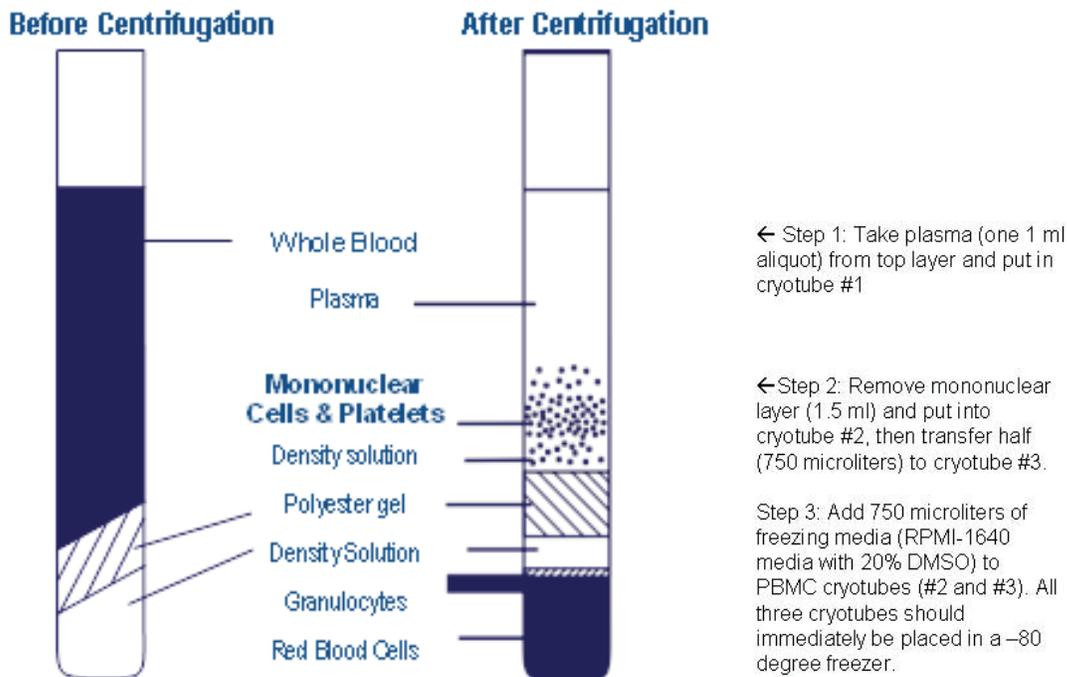
Benzodiazepines
Oxcarbazepine*(Trileptal)
Topiramate* (Topamax, Topiragen)
Ethosuximide (Zarontin)
Gabapentin (Neurontin, Fanatrex, Gabarone, Horizant)
Lacosamide (Vimpat)
Lamotrigine* (Lamictal)
Levetiracetam (Keppra)
Pregabalin (Lyrica)
Tiagabine (Gabatril)
Valproic acid** (Depakote, Depakene, Epilim, Stavzor)
Vigabatrin (Sabril)
Zonisamide (Zonegran)
Clonazepam (Klonopin, Klonopin Wafer, Ceberclon, Valpax)
Clobazam (Frisium, Urbanol)

* Weak inducers of Cyp3A4 and only at higher doses

18.4 Peripheral Blood Mononuclear Cell (PBMC) Isolation for Circulating Endothelial Cells Assays

A. Instructions for Sample Collection and Processing:

- Approximately 7 cc of venous blood will be collected into a BD Vacutainer CPT™ tube with Sodium Citrate (Becton Dickinson product #362761). (If your center will participate in this part of the study, please ensure availability of these tubes in advance of patient enrollment)
- The tube should be gently inverted 5-8 times to ensure mixing with the anticoagulant.
- Within two hours the CPT tube should be centrifuged **at room temperature** in a horizontal rotor for 30 minutes at 1500g 18°C to 25°C without the brake.
- Prepare and label cryotubes as specified below.
- After centrifugation, the mononuclear cells will be visible in a whitish layer just under the plasma. Remove 1 ml of plasma (top layer) **carefully** without disturbing the lower layer using a 3 ml pipette and put into cryotube #1.
- Then remove mononuclear layer (1.5 ml) and put into cryotube #2.
- Then transfer half of mononuclear cells (750 microliters) to cryotube #3.
- Add 750 microliters of freezing media (RPMI-1640 media with 20% dimethyl sulfoxide) to PBMC cryotubes (#2 and #3). All three cryotubes should immediately be placed in a –80 degree freezer.



B. Labeling and Storage of Samples: Cryotubes should be labeled with the following information (do not include any patient identifiers other than the ones indicated below):

Patient BTTC Number
 Protocol number BTTC 11-02
 Collection date
 Tube number
 Cells (PBMC) or plasma

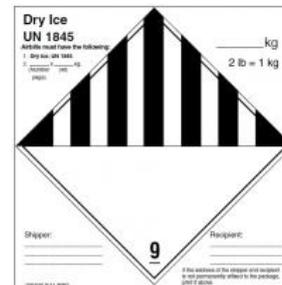
- Samples should be stored at -70° to -80°C and shipped as soon as possible – specimens have to be analyzed within 3 months of collection. Shipping should be on DRY ICE
 Analysis of CECs and other peripheral blood mononuclear populations will be performed by four-color flow cytometry. Briefly, analysis will be conducted with using a panel of antibodies to identify different cellular populations such as: CD146 as a marker of mature ECs; CD133 as a marker of EC precursors; CD45 to exclude hematopoietic cells; and anti-KDR as a marker of both precursor and mature endothelial cells. Apoptosis markers (i.e. annexin V) will also be incorporated. Standard analysis gates will be used to exclude dead cells and platelets. The number of mature CECs, expressed as a percentage of PBMCs, will be recorded and the absolute number of CECs and CEPs (number per microliter of blood) will be derived using the patients white count and differential.

C. Packaging of Blood Specimens: For clinical blood samples, the following four layers of packaging should be included:

- 1. Primary watertight inner receptacle.** Use watertight containers for liquid specimens with a positive closure such as a screw-on, snap-on or push-on lid, taped for an additional seal. If you place multiple fragile primary receptacles in a single secondary receptacle, they must be individually wrapped or separated to prevent contact between them.
- 2. Absorbent material.** Place absorbent material such as paper towels or cotton balls between the primary and secondary receptacles, using enough material to absorb the entire contents of all primary receptacles.
- 3. Secondary watertight inner receptacle.** Use a watertight sealed plastic bag or plastic canister
- 4. Sturdy outer packaging.** Use rigid outer packaging constructed of corrugated fiberboard appropriately sized for the contents.

D. Shipping Instructions: The samples should be shipped to the following address ON DRY ICE in appropriately labeled package (include dry ice label – ensure that sufficient amount of dry ice is included to maintain samples frozen) in accordance with local and federal regulations for biological material. (Note: The samples may be batched with the PBMC/CEC samples from section 18.5)

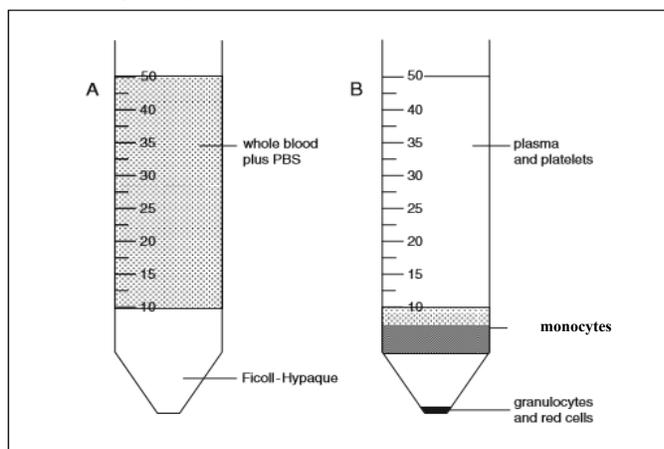
Jihong Xu/Puduvalli Lab
 Room 370 CCC, Wiseman Hall,
 400 W Twelfth Ave
 Columbus ,OH 43210
 Ph : 614-292-6618 or 614-688-7592
 Email : jihong.xu@osumc.edu



Prior to shipping the samples, please contact Dr. Xu by phone or email to ensure appropriate tracking and receipt of the sample. Samples can be batched and sent as a single shipment Mondays through Wednesdays by overnight shipment to ensure timely arrival of samples during working days and not on a weekend.

18.4. Alternative Method of PBMC Processing (If BD Vacutainer CPT Tubes are not procurable)

1. Collect 7 cc of whole blood in a Sodium citrate blood collection tube and gently invert to ensure good mixing. Pipet this collected sample into a 50-ml conical centrifuge tube and add 13 ml room temperature PBS
2. Using a 10-ml pipet, underlay with 5 ml room temperature Ficoll-Hypaque solution.
3. Separate cells by centrifuging for 20 min at $800 \times g$ (2000 rpm in H-1000 rotor), at 20°C , with the brake off.
4. Gently aspirate most of the plasma- and platelet-containing supernatant above the interface band (granulocytes and erythrocytes will be in red pellet; see Fig below – A. Before centrifugation; B: After centrifugation).



Aspirate the interface band (which includes the monocytes) along with no more than 2 ml of fluid above the pellet into a 10-ml pipet, then transfer to a new 50-ml conical centrifuge tube, Add PBS to 50-ml mark.

5. Centrifuge 10 min at $600 \times g$ (1500 rpm in H-1000 rotor), 20°C , with the brake on.
6. Aspirate supernatants and resuspend the pellet in the tube with 10 ml room temperature PBS.
7. Centrifuge 15 min $300 \times g$ (750 rpm in H-1000 rotor), 20°C , with brake on. This low-speed centrifugation permits as many platelets as possible to remain above the pellet of monocytes.
8. Prepare and label cryotubes as specified in protocol 18.4 B.
9. After centrifugation, the mononuclear cells will be visible in a whitish layer just under the plasma. Remove and discard nearly all the overlying plasma (about 7 ml) leaving about 1 ml of plasma behind in the tube (as the top layer); **carefully extract** this 1 ml of plasma without disturbing the lower layer using a 3 ml pipette and put into cryotube #1.
10. Then remove ALL of the mononuclear layer (1.5 ml) and put into cryotube #2.
11. Then transfer half of mononuclear cells from cryotube 2 (750 microliters) to cryotube #3.
12. Add 750 microliters of freezing media (RPMI-1640 media with 20% dimethyl sulfoxide) to PBMC cryotubes (#2 and #3). All three cryotubes should immediately be placed in a -80 degree freezer.

18.5 Blood and Tissue biomarker collection and analysis

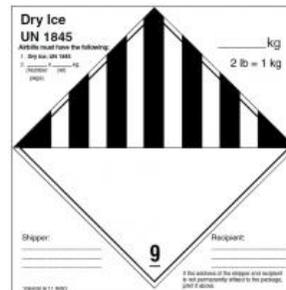
A. Guidelines for Collection, storage and shipment of Blood Samples for Biomarkers

- Collect 5 mL of whole blood into a CTAD (Becton-Dickinson Cat #367947 Hemogard, 4.5 mL tubes) vacutainer tube, being careful to minimize agitation of the sample and using the largest-bore needle that is feasible for the patient.
- Mix by gently inverting the tube 4 times.
- Centrifuge at 2000 x g for 15 minutes at room temperature within 1 hour of draw.
- Within 30 minutes after centrifugation, draw off plasma very slowly with transfer pipette to within 0.5 cm of the buffy coat, taking great care not to disturb the buffy coat. **(NOTE: Any contamination may invalidate the assay. If there is inadvertent mixing of these layers, please indicate this in the shipment paperwork)**
- Pipette the plasma specimen equally into TWO separate pre-chilled plastic cryovials. Do not transfer more than 1.5 mL into each tube.
- All specimens must be stored frozen at -20°C (or colder) in a freezer.
- One vial is labeled VEGF/bFGF and the other vial is labeled as reserve. These reserve tubes will be used to measure soluble VEGFR-1 and -2, placental growth factor (PlGF), SDF1α, angiopoietin-1 and 2.
- **Labeling of samples:** All samples should be labeled with the following information: (do not include any patient identifiers other than the ones indicated below):

Patient BTTC Number
Protocol number
Collection date
Tube number
Cells or plasma

- **Packaging and Shipping instructions:** The samples should be packaged as described in Section 18.4 C and shipped to the following address ON DRY ICE in appropriately labeled package (include dry ice label shown– ensure that sufficient amount of dry ice is added to cover the sample and keep it frozen for overnight shipment) in accordance with local and federal regulations for biological material. (Note: The samples may be batched with the PBMC/CEC samples from section 18.4)

Hong Xu/Puduvalli Lab
Room 370 CCC, Wiseman Hall
400 W Twelfth Ave
Columbus, OH 43210
Ph: 614-292-6618 or 614-688-7592
Email: jihong.xu@osumc.edu



Prior to shipping the samples, please contact Dr. Xu by phone or email to ensure appropriate tracking and receipt of the sample. Samples can be batched and sent as a single

shipment Mondays through Wednesdays by overnight shipment to ensure timely arrival of samples during working days and not on a weekend.

B. Guidelines for Collection, Processing and Shipment of Tissue and Intraoperative Blood Samples

1. **Presurgical Tissue Sample- Surgical Arm:** Patients who are candidates for surgery (in MDACC or other participating sites) and consent to taking part in the pre-surgical portion of the phase II study will be assessed under the following guidelines to ensure uniform tissue collection and processing
 - After a patient has consented for the pre-surgical portion of the study, the laboratory personnel (jihong.xu@osumc.edu) at **614-292-6618 or 614- 688-7592**, should be notified by the research nurse regarding the planned date of surgery.
 - Following surgery and verification of tumor recurrence, two specimens of tissue will be collected
 1. **Snap Frozen:** One part (1 cm³) will be collected as soon as possible after resection and **snap frozen** for genomic profiling (see instructions below). To ensure that the highest quality data can be obtained, it is essential that tissue should be processed in an expedited manner. If this tissue cannot be processed right after resection, it should be transported to the lab on ice as soon as possible and snap-frozen and stored as indicated below.

Standard Instructions for Collecting Snap Frozen Tissue

 - ▶ Pre-label one cryovial according to the specimen labeling requirements indicated in the Labeling Instructions below.
 - ▶ Pre-chill cryovial by placing on dry ice.
 - ▶ Tissue specimen should be a minimum of 1 cm³ in size. If needed, remove any blood from the specimen by touching the tissue with a sterile swab.
 - ▶ Snap freeze tissue *as soon as possible* after resection on dry ice or in the vapor phase liquid nitrogen (do not submerge the tissue in liquid nitrogen).
 - ▶ Transfer frozen specimen to pre-chilled tube to prevent thawing of the tissue
 - ▶ *Store snap frozen tissue in a -70°C to -80°C freezer until ready to ship.*
 2. **FFPE Specimen:** A second part will be obtained from the routinely processed formalin fixed and paraffin-embedded (FFPE) blocks generated for immunohistochemical studies. This part can either be provided as 20 unstained slides or an equivalent section from the paraffin block and should be verified to contain non-necrotic tumor tissue.
- ***Intraoperative blood samples*** should be processed as described in Section 18.5 A above
- Contact the following personnel for sample processing guidelines prior to shipment to MDACC

Jihong Xu/Puduvalli Lab
Room 370 CCC, Wiseman Hall
400 W Twelfth Ave,
Columbus, OH 43210
Ph: 614-292-6618 or 614-688-7592

3. Tissue samples from PRIOR surgeries

Samples from prior surgeries (sections of paraffin blocks) should be collected whenever available from patients who consented to optional procedures. If paraffin blocks are unavailable, 20 unstained slides can be provided. The samples should be shipped to OSU and will be stored in the Pudevalli Lab for correlative studies. These specimens will not be used to determine treatment or procedures; hence, they can be procured whenever feasible from the initial surgery source (e.g. outside hospitals) and any subsequent surgeries (from participating centers or outside center by a formal request based on this IRB approved protocol).

- **Labeling Instructions for tissue specimens**

Labels on all samples should include the following information (Do not include any other personal identification details):

Patient BTTC Number
Protocol number BTTC 11-02
Collection date and time
Vial # and type of specimen (e.g. snap frozen tissue)
Number of tubes, specimens or slides

- **Instructions for Packaging and Shipping Snap Frozen Tissue** (*The following are general guidelines— Each institution should ensure that all required regulation for clinical sample shipment are followed*)

Packaging: To eliminate the possibility of thawing of frozen samples during packaging and shipment, prepare packaging material in advance

- The cryovial must be wrapped in absorbable material such as paper towels and secured with a rubber band.
- Place the specimen in an secondary container such as a sealable plastic bag compatible with frozen specimens and seal the same.
- Place packaged specimen in an appropriate shipping container (composed of an inner styrofoam and outer cardboard layer) containing dry ice. Surround the package with dry ice.
- Mark the outside shipping container with an "Exempt Human Specimen" label and a dry ice label.

Shipping:

- a. Ship frozen tissue on DRY ICE using Federal Express Priority Overnight service in accordance with the required regulations. Use of other courier services may delay package receipt.
- b. Frozen specimens may only be shipped Monday through Wednesday using only overnight delivery to arrive on weekdays. Do NOT ship frozen specimens on Friday for Saturday delivery.
- c. The samples should be shipped to the following address in appropriately labeled package in accordance with local and federal regulations for biological material. **Prior to shipping the samples, please contact Dr. Xu by phone or email to ensure appropriate tracking and**

Bevacizumab + Vorinostat Protocol

receipt of the sample. Samples can be batched and sent as a single shipment by overnight shipment Mondays through Wednesdays to ensure timely arrival of samples during working days.

Jihong Xu/Puduvalli Lab
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Columbus, OH 43210
Ph: 614-292-6618 or 614-688-7592
Email jihong.Xu@osumc.edu

- **Standard Instructions for Packaging and Shipping FFPE Tissue Specimens** (*The following are general guidelines– Each institution should ensure that all required regulation for clinical sample shipment are followed*)

Packaging

- The specimen should be in a plastic container (for blocks) or in a slide container (for unstained slides). It must be wrapped in absorbable material such as paper towels and secured with a rubber band.
- Place the specimen in an AIRTIGHT container (must have a primary and secondary container, ex a Saf-T-Pak).
- Place packaged specimen in an appropriate shipping container (ex. FedEx box or clinical pack).
- Mark the outside shipping container with an "Exempt Human Specimen" label.

Shipping

- The samples should be shipped to the following address in appropriately labeled package in accordance with local and federal regulations for biological material.
- **Prior to shipping the samples, please contact Dr. Xu/Puduvalli Lab by phone or email to ensure appropriate tracking and receipt of the sample.**
- Samples can be batched and sent as a single shipment by overnight shipment Mondays through Thursdays to ensure timely arrival of samples during working days.

Jihong.Xu/Puduvalli Lab
Room 370 CCC, Wiseman Hall
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Columbus, OH 43210
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18.6 BAYESIAN ADAPTIVE ALGORITHM: TECHNICAL DETAILS

Approved by UTMDACC IRB#3 on December 17, 2003

Denote the time to progression for the patients as T_1, T_2, \dots and index the two treatment arms by $t = 1, 2$. Assume that the T_i are independent, $[T_i | t] \sim$ exponential with median μ^*t , for $t = 1, 2$ and that *a priori* $\{\mu^*1, \mu^*2\}$ are independent following an inverse gamma distribution with parameters $\alpha = 2.016$ and $\beta = 4.064$. This parameterization was chosen to set the mean of the prior equal to 4 (the historical median TTP in months) and a variance of 1000. This gives a 95% credible interval for the median TTP of (0.73, 16.44). For each patient, the randomization probability for treatment $t=1$ will be the posterior probability that it has the largest median TTP, that is $\pi_1(\text{data}) = \Pr(\mu_1 > \mu_2 | \text{data})$; the randomization probability for treatment $t=2$ is $\pi_2(\text{data}) = \Pr(\mu_2 > \mu_1 | \text{data})$. If at any point during the trial $\pi_i(\text{data}) > 0.995$ (< 0.005) the trial will be terminated and treatment i will be selected as superior (inferior). If the maximum accrual is reached and $\pi_i(\text{data}) > 0.975$ (< 0.025), treatment i will be selected as superior (inferior). A treatment arm will be dropped at any point during the trial if $\Pr(\mu_i > 4 | \text{data}) < 0.01$, for $i=1, 2$.

Prior Distribution (Time-To-Event Trial)

The time-to-event (TTE) variable, T_{ji} , for each arm j is assumed to be *Exponential* with mean μ_j ; $p(T_{ji} | \mu_j) = 1/(\mu_j D_j) \exp(-T_{ji} / \mu_j)$. However, since most of the time we are interested in the median tte, $\mu^*j = \ln(2) * \mu_j$, therefore, $p(T_{ji} | \mu^*j) = (\ln(2) D_j) / (\mu^*j D_j) \exp(-\ln(2) * T_{ji} / \mu^*j)$. Where $T_{j+} = \sum_i T_{ji}$ = event or censoring times for arm j and $D_j = \#$ of events for arm j .

a priori $\mu^*j \sim$ Inverse Gamma(α_j, β_j).

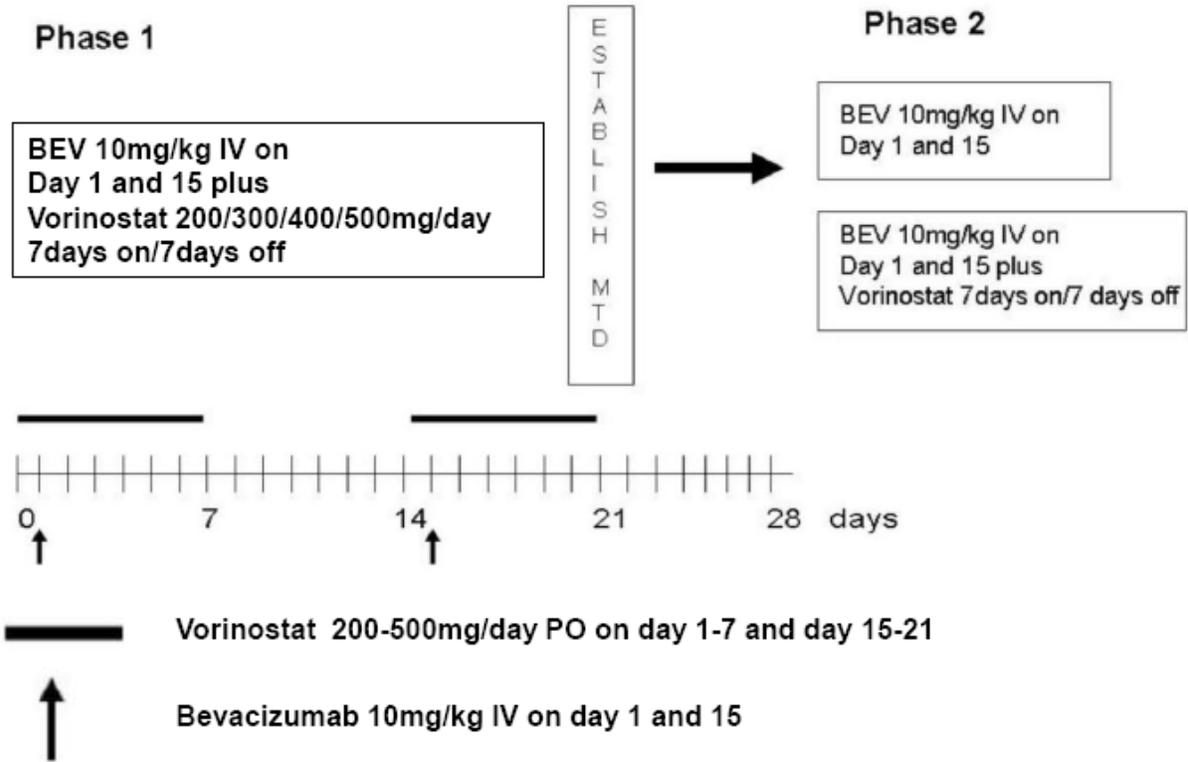
$$E(\mu^*j) = \beta_j / (\alpha_j - 1) ; \alpha_j > 1$$

$$\text{Var}(\mu^*j) = \beta_j^2 / [(\alpha_j - 1)^2 (\alpha_j - 2)] ; \alpha_j > 2$$

Therefore; $\mu^*j | T_{j+} \sim$ Inverse Gamma ($\alpha_j + D_j, \beta_j + \ln(2) * T_{j+}$).

18.7 STUDY FLOW CHART/SCHEMA

Recurrent Glioblastoma



Study Flow Chart

Phase I/II Adaptive Randomized Trial of Bevacizumab versus Bevacizumab plus Vorinostat Adults with Recurrent Glioblastoma

Procedure	BL	Cycle 1				Cycle 2				Subsequent every 2 Cycles				Off Treatment
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4	Wk 2	Wk 4	Wk 6	Wk 8	
Informed Consent	X													
Medical History	X													
Physical Exam ¹	X				X				X				X	X
BP Recorded ⁹	X		X		X		X		X	X	X	X	X	
MDASI-BT ⁸	X								X				X	X
MRI (with DCE/DSC ⁷)	X								X				X ⁷	X
Hematology ²	X		X		X		X		X	X	X	X	X	X
Chemistry ³	X				X				X		X		X	X
Urine protein: creatinine ratio	X		X		X				X		X		X	
Pregnancy Test ⁴	X				X				X		X		X	X
Tumor Pathology	X													
Paraffin Tissue block ⁵	X													
Biomarker measurement ⁶	X	D2		D1		D1								

1. Physical examination includes vital signs, neurological exam, neurological function score, Karnofsky performance score.,
2. Includes CBC with differential
3. Includes: Total protein, albumin, Ca, glucose, BUN, creatinine, Na, K, , total bilirubin, alkaline phosphatase, LDH, SGPT (ALT), SGOT (AST).
4. Only for women of childbearing potential as defined by Appendix 18.11. To be performed before each new cycle of therapy.

Bevacizumab + Vorinostat Protocol

5. Optional procedure.
6. Optional procedure. Including 5 cc blood sample for VEGF, PIGF, bFGF, SDF1 α , angiopoietin 1 and 2 and 7 cc of blood for isolation of peripheral blood monocytes will be collected for CEC and CEPC, at baseline before treatment, cycle 1 day 2, day 15 (pre-infusion and post-infusion) and cycle 2 (pre-infusion). The post-infusion blood drawn between 12-24 hr after infusion.
7. MRI scan with and without contrast to be obtained every 2 cycles during treatment and every other cycle until disease progression if treatment is discontinued for reasons other than progressive disease and no other new treatment is started. Optional DCE/DSC studies are preferred but not required.
8. MDASI-BT at Baseline, prior to results of each MRI Evaluation are shared with the patient, and at end of therapy (optional procedure).
9. Blood Pressure monitoring every 2 weeks prior to Bevacizumab infusion.

18.8 Multicenter SAE Form

MULTICENTER SERIOUS ADVERSE EVENT REPORT

SPONSOR: UT MD ANDERSON CANCER CENTER/BRAIN TUMOR TRIALS COLLABORATION IND#: NA	SITE'S PROTOCOL No.		PRINCIPAL INVESTIGATOR		PROTOCOL TITLE:		
	<input type="checkbox"/> INITIAL REPORT <input type="checkbox"/> F/U REPORT (CHECK ONLY ONE)		PROTOCOL STATUS (CHECK ONE): <input type="checkbox"/> ACTIVE <input type="checkbox"/> TERMINATED <input type="checkbox"/> CLOSED TO NEW PATIENT ENTRY AND PATIENTS ON TREATMENT <input type="checkbox"/> CLOSED TO NEW PATIENT ENTRY AND PATIENTS OFF TREATMENT				
	DATE RESEARCH TEAM NOTIFIED OF EVENT OR FOLLOW-UP	DATE SUBMITTED TO LOCAL IRB	SITE NAME	TOTAL NO. OF PT'S ON PROTOCOL AT THIS SITE			
PATIENT REACTION INFORMATION							
MEDICAL RECORD NUMBER	PATIENT STUDY NUMBER		PATIENT INITIALS		REACTION OUTCOME: DEATH (PROVIDE DATE OF DEATH)		
AGE	GENDER		REACTION ONSET (MO/DAY/YEAR)		HOSPITALIZATION		
				DISABILITY			
				CONGENITAL ANOMALY			
				LIFE THREATENING			
				IMPORTANT MEDICAL EVENT			
Event/Reaction (use appropriate Title from NCI CTC for all events reported) (More than one event may be listed if related and occurs around same time)		Event Grade (1-5)	Attribution(s): Definite Probable Possible Unlikely Unrelated			IS EVENT EXPECTED? (NOTED IN THE DRUG INFORMATION)	
_____		_____	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>			YES <input type="checkbox"/> NO <input type="checkbox"/>	
_____		_____	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>			YES <input type="checkbox"/> NO <input type="checkbox"/>	
_____		_____	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>			YES <input type="checkbox"/> NO <input type="checkbox"/>	
_____		_____	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>			YES <input type="checkbox"/> NO <input type="checkbox"/>	
_____		_____	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>			YES <input type="checkbox"/> NO <input type="checkbox"/>	
PLEASE WRITE A SHORT SUMMARY DESCRIBING THE EVENT(S) IF NEEDED							

--

CURRENT CONDITION BEING TREATED WITH INVESTIGATIONAL AGENT	
OTHER RELEVANT MEDICAL HISTORY	
LIST OR ATTACH RELEVANT TESTS, NOTES, AND LABORATORY DATA	
LIST OR ATTACH ALL CONCOMITANT MEDICATIONS PT TAKING AT TIME OF THE EVENT	

NAME OF AGENT OR DEVICE (LIST MANUFACTURER AND LOT ##)		DID REACTION ABATE AFTER STOPPING THE DRUG?	
		YES	DATE
		NO	
DOSE (LIST FREQUENCY OR SCHEDULE)		NOT KNOWN	
ROUTE OF ADMINISTRATION		DID REACTION REAPPEAR AFTER REINTRODUCTION?	
DATE(S) OF ADMINISTRATION			
HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?		YES	DATE:
		NO	
		NA	

PRINTED NAME OF PI		PHONE #
PERSON FILLING OUT THIS FORM		

COMPLETED SAE REPORT FORMS FOR MULTICENTER REPORTING ARE TO BE SUBMITTED TO THE OMCR VIA EDMS OR FAX AT:

EDMS: [HTTPS://VIEW.MDANDERSON.ORG/](https://view.mdanderson.org/)
Fax: 713-794-1902

THE SITE REPORTING THE SAE MUST IMMEDIATELY ALERT THE OMCR VIA EMAIL OR PHONE THAT AN SAE HAS BEEN SUBMITTED.

FOR PROBLEMS SENDING THE FORM OR OTHER QUESTIONS, PLEASE CONTACT THE PROJECT MANAGER.

18.9 New York Heart Association (NYHA) Guidelines

The New York Heart Association (NYHA) Functional Classification provides a simple way of classifying the extent of heart failure. It places patients in 1 of 4 categories based on how much they are limited during physical activity:

Functional Capacity	Objective Assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	A. No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	B. Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	C. Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	D. Objective evidence of severe cardiovascular disease.

18.10 PROCEDURE FOR OBTAINING A URINE PROTEIN: CREATININE RATIO

- 1) Obtain at least 4 ml of a random urine sample (does not have to be a 24 hour urine)
- 2) Determine protein concentration (mg/dL)
- 3) Determine creatinine concentration (mg/dL)
- 4) Divide #2 by #3 above: $\text{urine protein} / \text{creatinine ratio} = \text{protein concentration (mg /dL)} / \text{creatinine concentration (mg /dL)}$

The UPC directly correlates with the amount of protein excreted in the urine per 24 hrs (i.e. a UPC of 1 should be equivalent to 1g protein in a 24hr urine collection)

Protein and creatinine concentrations should be available on standard reports of urinalyses, not dipsticks. If protein and creatinine concentrations are not routinely reported at an Institution, their measurements and reports may need to be requested.

18.11 Pregnancy tests for females of childbearing potential and adequate methods of contraception

A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Pregnancy tests must occur within 14 days prior to initiation of study. FCBP must have a pregnancy test before each new cycle; at discontinuation of vorinostat and at Day 28 post the last dose of vorinostat.

Required Pregnancy test: Serum β -HCG

Adequate method of contraception: one highly effective method or more than one additional methods.

Highly effective methods:

- Intrauterine device (IUD)
- Hormonal (birth control pills, injections, implants)
- Tubal ligation
- Partner's vasectomy

Additional effective methods:

- Latex condom
- Diaphragm
- Cervical Cap

18.12 MD ANDERSON SYMPTOM INVENTORY FOR BRAIN TUMORS (MDASI-BT)

(The MDASI – BT is created by the OMCR programming staff upon request for each protocol. The standard MDASI – BT questionnaire is used as a template. This form will contain coding “landmarks” that enable the data to be scanned into the MD ANDERSON CANCER CENTER data repository for MDASI results. Please contact the OMCR to obtain the questionnaire that is to be attached to the protocol before submission to the IRB.)

(Rest of this page is left blank on purpose)



Date: / /
(month) (day) (Year)

MDASI BT
Protocol
Number: BTTC11-02
PI: Dr. Vinay Puduvalli

Participant's
Initials:

PLEASE USE A
BLACK INK PEN

BTTC11-02 Patient #:

Protocol
Acc #:

M.D. Anderson Symptom Inventory (MDASI - BT)

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present	As Bad As You can Imagine									
	0	1	2	3	4	5	6	7	8	9	10
1. Your pain at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. Your fatigue (tiredness) at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. Your nausea at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. Your disturbed sleep at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. Your feeling of being distressed (upset) at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. Your shortness of breath at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
7. Your problem with remembering things at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
8. Your problem with lack of appetite at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
9. Your feeling drowsy (sleepy) at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
10. Your having a dry mouth at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
11. Your feeling sad at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
12. Your vomiting at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
13. Your numbness or tingling at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
14. Your weakness on one side of the body at its WORST	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
15. Your difficulty understanding at its WORST	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
16. Your difficulty speaking (finding the words) at its WORST	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

 20542
 Date: / /
 (month) (Day) (Year)
 MDASI BT
 Protocol
 Number: BTTC11-02
 PI: Dr. Vinay Puduvalli

Participant's Initials:
 BTTC11-02 Patient #:
 Protocol
 Acc #:

PLEASE USE A BLACK INK PEN

	As Bad As You can Imagine										
	0	1	2	3	4	5	6	7	8	9	10
17. Your seizures at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
18. Your difficulty concentrating at its WORST	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
19. Your vision at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
20. Your change in appearance at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
21. Your change in bowel pattern (diarrhea or constipation) at its WORST	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
22. Your irritability at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Interfered Completely										
	0	1	2	3	4	5	6	7	8	9	10
23. General activity ?	<input type="radio"/>										
24. Mood ?	<input type="radio"/>										
25. Work (including work around the house) ?	<input type="radio"/>										
26. Relations with other people?	<input type="radio"/>										
27. Walking?	<input type="radio"/>										
28. Enjoyment of life ?	<input type="radio"/>										

18.14 BTTC11-02 Patient Study Drug Diary

PATIENT INITIALS: _____ **BTTC I.D. #** _____ **Cycle#** _____ **Start Date:** _____

This calendar is for you to indicate that you took the study drug as instructed. Please put a check mark or your initials after each dose. If not taken, write 0 mg. **Please sign this calendar at the end of the cycle and bring the calendar and all study drug bottle(s) back to your next clinic visit.**

DOSE prescribed: Vorinostat _____ mg (_____ capsules) by mouth on days 1 to 7 and 15 to 21.

Vorinostat capsules should not be opened or crushed and must be administered whole.

Day 1 _____ _____ mg	Day 2 _____ _____ mg	Day 3 _____ _____ mg	Day 4 _____ _____ mg	Day 5 _____ _____ mg	Day 6 _____ _____ mg	Day 7 _____ _____ mg
Day 8 _____	Day 9 _____	Day 10 _____	Day 11 _____	Day 12 _____	Day 13 _____	Day 14 _____
Day 15 _____ _____ mg	Day 16 _____ _____ mg	Day 17 _____ _____ mg	Day 18 _____ _____ mg	Day 19 _____ _____ mg	Day 20 _____ _____ mg	Day 21 _____ _____ mg
Day 22 _____	Day 23 _____	Day 24 _____	Day 25 _____	Day 26 _____	Day 27 _____	Day 28 _____
Day 29 _____	Day 30 _____	My signature confirms that the study drug was taken as documented Signature of Patient: _____ Date: _____				

