BRAIN TUMOR TRIALS COLLABORATIVE (BTTC)

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Note: These sites will be collecting and submitting data to the BTTC Coordinating Center at NCI (e.g. through data entry in C3D) and will not be re-opening to accrual.

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PRÉCIS

Background

- Although malignant gliomas display genetic heterogeneity, several key proliferation and survival signaling pathways have been identified.
- Recent work has focused on targeting these tumor specific pathways in hopes of improving treatment efficacy and minimizing treatment toxicity. Because molecularly targeted agents have been mostly ineffective when used alone, combination therapy that inhibits multiple pathways is an appealing strategy.
- Sorafenib is an oral multi-kinase inhibitor with effects on tumor proliferation and tumor angiogenesis. Although most GBMs lack RAF mutations, targeting the RAF/MEK/ERK pathway may be beneficial as this pathway may be activated by other genetic alterations upstream from RAF.
- The mammalian target of rapamycin (mTOR) protein is a downstream component of the PI3K/Akt pathway. Everolimus (everolimus; Novartis) is a novel oral derivative of rapamycin
- Combining everolimus and sorafenib allows targeting of both the PI3K pathway and the RAF-MAPK pathway and in addition targets VEGF and PDGF, other active targets in malignant glioma.

Objectives

Phase 1

- To determine the maximum tolerated dose and safety of everolimus in combination with sorafenib for patients with recurrent malignant gliomas.

Phase 2

- 6-month progression free survival rate for glioblastoma patients with no prior bevacizumab exposure treated with everolimus and sorafenib at the maximum tolerated dose as determined in the phase I study.
- 3-month progression free survival rate for glioblastoma patients with prior bevacizumab exposure treated with everolimus and sorafenib at the maximum tolerated dose as determined in the phase I study.
- 6-month progression free survival rate for AG patients with no prior bevacizumab exposure treated with everolimus and sorafenib at the maximum tolerated dose as determined in the phase I study.

Eligibility

- Patients with histologically proven recurrent intracranial malignant glioma will be eligible for the phase I/II component of this protocol.
- Patients must be $\geq$ 18 years old with a Karnofsky performance status of $\geq$ 60.
- No more than 2 prior chemotherapies and 1 relapse. Prior bevacizumab therapy is allowed.

Design

- This is a phase 1 /2 study of everolimus and sorafenib in patients with recurrent high-grade gliomas.
- Phase 1: Patients will be treated with daily everolimus (days 1-28) in combination with sorafenib.
- Phase 2: Patients will be treated with the combination of sorafenib and everolimus. Sorafenib will be taken daily for 7 days on, then 7 days off. Everolimus will be taken daily.
- There is not a defined set maximum number of cycles that a patient may have. Patients may continue with protocol therapy until criteria for "Off Treatment" is met. Patients will then be followed every 3 months for survival status.
- There will be an accrual of approximately 3-6 eligible patients per cohort to the Phase I component of the study. Patients removed at any time for toxicity are evaluable. Phase I patients removed from study treatment within 28 days for reasons other than toxicity may be replaced.
- There will be a total accrual of approximately 82 eligible patients to the Phase II study (34 recurrent GBM with no prior exposure to bevacizumab, 16 recurrent Anaplastic Glioma with no prior exposure to bevacizumab, and 32 glioblastoma with prior exposure to bevacizumab).

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1.0 INTRODUCTION

1.1 OBJECTIVES

1.1.1 Phase I

- To determine the maximum tolerated dose and safety of everolimus in combination with sorafenib for patients with recurrent malignant gliomas.

1.1.2 Phase II

1.1.2.1 Primary endpoints:

- 6 month progression free survival rate for glioblastoma patients with no prior bevacizumab exposure treated with everolimus and sorafenib at the maximum tolerated dose as determined in the phase I study.
- 3 month progression free survival rate for glioblastoma patients with prior bevacizumab exposure treated with everolimus and sorafenib at the maximum tolerated dose as determined in the phase I study.
- 6 month progression free survival rate for AG patients with no prior bevacizumab exposure treated with everolimus and sorafenib at the maximum tolerated dose as determined in the phase I study.

1.1.2.2 Secondary endpoints:

- Time to progression and overall survival for recurrent malignant glioma patients (Group A, Group B, and Group C) treated with everolimus and sorafenib measured from time of study enrollment.
- Objective response rate for recurrent malignant gliomas (Group A, Group B, and Group C treated with everolimus and sorafenib
- Patient related outcome measures

  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. This will include:

  - To evaluate longitudinal changes in symptom measures and determine the impact of the therapy on these parameters.
  - 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.
  - To describe the variability of symptom severity longitudinally over the treatment course and follow-up period.

1.2 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. (1) Cure is exceptional and most patients have

evidence of tumor progression within one year of diagnosis despite treatment. At progression, treatment options are limited and mostly ineffective; most clinical trials demonstrate six month progression free survival rate of only 9-15% and median overall survival is less than 25 weeks from time of tumor progression. (2) Recently, bevacizumab was approved for recurrent GBM based on data from Vredenburgh et al. and Kreisl et al.(3, 4) Data on patients who fail bevacizumab indicate a short survival, on the order of 10 weeks, an approximate PFS 3 and 6 months of 0%.

Anaplastic Astrocytoma (WHO grade III astrocytoma), although less aggressive than GBM, is a malignant tumor with a median survival of less than 3 years from diagnosis and estimated 5-year survival of 28% despite best treatment (2, 5)

Although malignant gliomas display genetic heterogeneity, several key proliferation and survival signaling pathways have been identified (6). Recent work has focused on targeting these tumor specific pathways in hopes of improving treatment efficacy and minimizing treatment toxicity. Because molecularly targeted agents have been mostly ineffective when used alone, combination therapy that inhibits multiple pathways is an appealing strategy.

1.2.1 Kinase Inhibitors:

Most growth factors initiate intracellular second messenger signaling systems through activation of tyrosine and/or serine/threonine kinase receptors. The kinase regions catalyze transfer of phosphate groups from adenosine triphosphate (ATP) to transmembrane receptors or signal transducers to initiate signaling pathway activation. The development of kinase inhibitors in cancer treatment has been stimulated by the success of imatinib mesylate in treating chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GIT). Imatinib mesylate specifically inhibits kinase activities associated with bcr-abl, c-kit, and PDGF receptor which are improperly regulated in CML and GIT.

Research has identified specific aberrant pathways that are thought to be important in malignant gliomas. (6) Specifically inhibiting these aberrant pathways may improve outcome without significant toxicity.

1.2.2 Vascular endothelial growth factor (VEGF) pathway inhibitors:

Malignant gliomas are highly vascular tumors that depend on angiogenesis for growth and proliferation. VEGF pathway inhibitors were developed to inhibit tumor angiogenesis. Despite promising preclinical results, most VEGF inhibitors failed to yield long term survival benefits as single agents. Success has been achieved by combining inhibitors of VEGF signaling with standard cytotoxic chemotherapy (7). Bevacizumab, an anti-VEGF antibody, has shown encouraging results when combined with irinotecan in a phase II trial for GBM.(4) (8)

1.2.3 Multi-targeted kinase inhibitors:

When used alone, targeted agents have been mostly ineffective in the treatment of malignant gliomas. This is thought to be secondary to the existence of multiple parallel or compensatory oncogenic pathways that allow tumor cells to escape and survive. To combat this problem, newer-generation small-molecule kinase inhibitors are designed to target multiple aberrant signaling pathways in the tumors and tumor-associated vasculature.

1.2.3.1 Sorafenib (BAY 43-9006):

Sorafenib is an oral multi-kinase inhibitor with effects on tumor proliferation and tumor angiogenesis. (9) It was initially selected based on inhibitory activity against the serine/threonine kinases Raf-1 and wild-type B-Raf, which are pivotal components of the Ras/Raf/MEK/ERK signaling pathway. Inhibitory activity was subsequently demonstrated against tyrosine kinases for vascular endothelial growth factor (VEGF) receptor and platelet-derived growth factor (PDGF) receptor as well as Flt-3 and c-Kit. (9) Although most GBMs lack RAF mutations, targeting the RAF/MEK/ERK pathway may be beneficial as this pathway may be activated by other genetic alterations upstream from Raf.

The Raf/MEK/ERK pathway is an important mediator of responses to growth factors, and a strong inducer of genes involved in tumorigenesis, angiogenesis, apoptosis, and tumorigenesis. (10)

In preclinical studies, sorafenib demonstrated broad-spectrum anti-tumor activity by inducing complete tumor stasis and inhibition of tumor angiogenesis in a variety of tumor types. In the murine renal adenocarcinoma (Renca) (11) and VHL $^{-/-}$ xenograft models, sorafenib prevented tumor growth, primarily through the inhibition of tumor-cell-induced angiogenesis and also induced tumor apoptosis and necrosis.

The safety and clinical activity of sorafenib, alone (12-15) or in combination (16,17) with chemotherapy, has been examined in a series of phase I studies conducted in patients with solid tumors. Results of a multi-center, randomized, placebo-controlled, double-blind phase III trial of sorafenib in advanced renal cell carcinoma (RCC) were first reported in 2005. (18) There was a progression free survival advantage for the sorafenib group (5.5 months vs 2.8 months). Subsequent overall survival was not different between the groups overall, but when patients who crossed over to receive sorafenib were excluded, there was a survival benefit.

1.2.3.2 Rationale and Experience for Use of Sorafenib in GBM

Both increased activation of angiogenesis and the MAP Kinase pathway are associated with the mesenchymal/angiogenic phenotype and resistance to standard therapy in newly diagnosed glioblastoma (GBM). Sorafenib is a multi-functional small molecule inhibitor that targets both the Raf/MAP Kinase pathway and VEGF receptors, and is thus a potentially ideal agent for targeting GBM with the mesenchymal/angiogenic phenotype.

A Phase I study of single agent sorafenib in recurrent malignant glioma (B. Nabors, PI, NABTT study) has accrued 43 patients, including 27 glioblastoma patients. Dosages up to 800mg BID were tolerated well, with only grade 3 hand-foot syndrome observed in up to 33% of patients at 400mg BID and 800mg BID. Observed toxicities were similar in patients on enzyme-inducing anti-epileptics and those not on enzyme-inducing anti-epileptics. Pharmacokinetic parameters also demonstrated no significant differences between enzyme-inducing and non-enzyme inducing anti-epileptic medication groups. There were 3 complete responses and 5 partial responses amongst 41 evaluable patients, suggesting significant single agent activity.

1.2.4 PI3K/AKT/mTOR pathways:

Apoptosis, commonly called programmed cell death in developmental biology, is a major mechanism of cell death in response to many toxic stimuli, including withdrawal of external survival signals and DNA damage. Resistance to apoptosis is one of the hallmarks of cancer. The mammalian target of rapamycin (mTOR) protein is a downstream component of the PI3K/Akt pathway.(6) It regulates proliferation by activating downstream protein kinases required for ribosomal biosynthesis and mRNA translation, thus driving cell cycle progression. Tumors that

depend on the activation of the PI3K pathway or that harbor mutations causing constitutive activation of the PI3K pathway may be more susceptible to rapamycin and its derivatives that inhibit mTOR. Activation of the PI3K pathway by overexpression of upstream growth factor receptors (eg. EGFR and/or deletion of PTEN) is significantly associated with increasing tumor grade, decreased levels of apoptosis, and adverse clinical outcome in human gliomas. mTOR is represented by two structurally and functionally distinct multiprotein signaling complexes, mTORC1 (mTOR complex 1, rapamycin sensitive) and mTORC2 (mTOR complex 2, rapamycin insensitive).(19) mTORC1 is mainly activated via the PI3 kinase pathway through AKT (also known as PKB, protein kinase B) and the tuberous sclerosis complex (TSC1/TSC2).(20) Activated AKT phosphorylates TSC2, which lead to the dissociation of TSC1/TSC2 complex, thus inhibiting the ability of TSC2 to act as a GTPase activating protein. This allows Rheb, a small G-protein, to remain in a GTP bound state and to activate mTORC1. AKT can also activate mTORC1 by PRAS40 phosphorylation, thereby relieving the PRAS40-mediated inhibition of mTORC1.(21) mTORC2 (mTOR complex 2) is activated through a currently unknown mechanism, possibly by receptor tyrosine kinase (RTK) signaling.(21) It has been suggested that mTORC2 phosphorylates and activates a different pool of AKT, that is not upstream of mTORC1. Therefore, targeting mTOR is a promising target in the clinical management of glioma patients. A phase II study of temsirolimus, a mTOR inhibitor, in recurrent GBM demonstrated modest efficacy with some evidence of activity based on molecular phenotype. (10) Everolimus (everolimus; Novartis) is a novel oral derivative of rapamycin.

It is not clear which molecular determinants predict responsiveness of tumor cells to everolimus. Molecular analysis has revealed that relative sensitivity to everolimus in vitro correlates with the degree of phosphorylation (activation) of the AKT/PKB protein kinase and the S6 ribosomal protein. PTEN status alone may not be predictive of everolimus relative in vitro sensitivity, however in some cases (i.e., GBM) there is also a correlation with PTEN status (active vs inactive). In preclinical models, the administration of everolimus is associated with reduction of protein phosphorylation in target proteins downstream of mTOR, notably phosphorylated S6 (pS6) and p4E-BP1, and occasionally with an increase in phosphorylation AKT (pAKT).

1.2.5 Rationale for combination therapy:

Preclinical data suggest that blocking more than one target more effectively inhibits tumor growth. (22) Combining everolimus and sorafenib allows targeting of both the PI3K pathway and the RAF-MAPK pathway and in addition targets VEGF and PDGF, other active targets in malignant glioma. Trials of mTOR inhibition (not everolimus) with sorafenib are underway but the dose of the mTOR inhibitor, in particular CCI-779, being used in one of these trials is sufficiently low that it is likely not therapeutic. We believe that the combination of everolimus and sorafenib will be more tolerable, thus allowing therapeutic doses of both. In addition, continuous oral dosing of both may provide a more sustained pathway inhibition.

1.2.6 Rationale for patient outcomes measures:

1.2.6.1 Rationale for the patient-reported outcomes:

This study seeks to establish effective therapies at recurrence and improve on current clinical results in patients with glioblastoma. We hypothesize that using a combination of everolimus and sorafenib will result in improved survival. However, given the intensive nature of this regimen, it will be important to determine whether any determined survival benefit is associated with improvements in symptoms or does a worsening of symptoms 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 best (23). There have been efforts in neuro-oncology to evaluate secondary endpoints using validated instruments as an additional indicator of benefit.

The M.D. 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 population (24). 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.

1.2.7 Summary of Phase I Toxicities

Dose Level 1 had 3/6 patients who had a DLT, necessitating a dose reduction to dose level -1. At that level only 1/6 DLTs was seen hence this is the MTD for phase II.

(DOSE LEVEL 1)			
Patient 1	Grade 3	HTN	DLT
		Elevated ALT	DLT
		Hypercholesterolemia	DLT
		Hyperglycemia	DLT
	Grade 4	Hypertriglyceridemia	DLT
Patient 2	Grade 3	Lymphopenia	
Patient 3	Grade 3	Lymphopenia	
Patient 4	None	N/A	n/a
Patient 5	Grade 3	Thrombocytopenia	
		Chest Pain	DLT
		Fatigue	DLT
Patient 6	Grade 3	Fatigue	DLT
		Lymphopenia	
(DOSE LEVEL -1)			
Patient 1	Grade 3	Myositis	DLT
		Nausea	DLT
		Fatigue	DLT
		Hypertension	DLT
		Lymphopenia	
		Thrombocytopenia	

		Hypercholesterolemia	DLT
Patient 2,3,4,5,6	None	N/A	n/a

2.0 ELIGIBILITY ASSESSMENT AND ENROLLMENT

Unless otherwise specified, in the Inclusion Criteria for Phase I or Phase II, all patients must meet the General Eligibility Criteria described below. Eligibility waivers are not permitted.

Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. See section **2.3** for registration procedures.

2.1 ELIGIBILITY CRITERIA

2.1.1 General Inclusion Criteria

2.1.1.1 Patients with histologically proven recurrent intracranial malignant glioma will be eligible for the phase I/II component of this protocol. Malignant glioma includes glioblastoma (GBM), Gliosarcoma (GS), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), anaplastic mixed oligoastrocytoma (AMO), or malignant astrocytoma 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.

2.1.1.2 All patients must sign an informed consent indicating that they are aware of the investigational nature of this study. Patients must have signed an authorization for the release of their protected health information at all sites except the NIH.

2.1.1.3 Patients must be $\geq$ 18 years old.

2.1.1.4 Patients must have a Karnofsky performance status of $\geq$ 60.

2.1.1.5 No more than 2 prior chemotherapies and 1 relapse. Prior bevacizumab therapy is allowed.

- Patients must have recovered from the toxic effects of prior therapy: >3 weeks for biologic therapies or non-cytotoxic therapies, >4 weeks for cytotoxic therapies, and >6 weeks for nitrosoureas. Any questions related to the definition of non-cytotoxic agents should be directed to the Study Chair.

NOTE: 13 cis-retinoic acid (Accutane) as biologic therapy has a washout period of 14 days.

2.1.1.6 Patients must have adequate bone marrow function (WBC $\geq$ 3.0 x 10^9/L, ANC $\geq$ 1.5 X 10^9/L, platelet count of $\geq$100 x 10^9/L, and hemoglobin $\geq$ 10 gm/dL), adequate liver function (SGOT and bilirubin < 2 times ULN), and adequate renal function (creatinine < 1.7mg/dL or creatinine clearance $\geq$ 60 cc/min) before starting therapy. These tests must be performed within 14 days prior to registration. Eligibility level for hemoglobin may be reached by transfusion.

2.1.1.7 Patients must have shown unequivocal radiographic evidence for tumor progression by MRI or CT scan as defined by Section **5.2.1.3.5**. A scan should be performed within 14 days prior to registration 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 a new baseline MRI/CT is required. The same type of scan, i.e., MRI or CT must be used throughout the period of protocol treatment for tumor measurement. Measurable disease is NOT required.

Note: *MRI is the preferable imaging method; CT scan may be used in cases where an MRI cannot be obtained.

2.1.1.8 Patients having undergone recent resection of recurrent or progressive tumor will be eligible as long as all of the following conditions apply:

- They have recovered from the effects of surgery and be > 3 weeks from surgery.
- Residual disease following resection of recurrent malignant glioma is not mandated for eligibility into the study. To best assess the extent of residual disease post-operatively, a CT/ 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/CT is required on a stable steroid dosage for at least 5 days.

2.1.1.9 Patients must have failed prior radiation therapy and must have an interval of greater than or equal to 12 weeks from the completion of radiation therapy to registration; except if patients underwent surgery within 12 weeks and pathology is consistent with recurrent tumor.

2.1.1.10 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.

2.1.1.11 Women of childbearing potential must have a negative B-HCG pregnancy test documented within 7 days prior to taking the first dose of study medications.

2.1.1.12 Patients receiving anti-coagulation treatment with an agent such as warfarin or heparin may be allowed to participate. For patients on warfarin, the INR should be measured prior to initiation of sorafenib and monitored at least weekly, or as defined by the local standard of care, until INR is stable.

2.1.2 Phase I Inclusion Criteria

The following modifications to the general eligibility criteria apply to Phase I patients only.

- Patients may have had treatment for any number of prior relapses. Relapse is defined as progression following initial therapy (i.e. surgery and radiation+/- chemo if that was used as initial therapy).

2.1.3 Phase II Inclusion Criteria

- Phase II patients must meet the following Eligibility Criteria in addition to the General Criteria described above. Patients may have had treatment for no more than 1 prior relapse (i.e. failed 2 lines of treatment-initial therapy and therapy for first relapse) at 2nd relapse, treatment per BTTC09-01 is an option; see relapse and treatment count

table below). 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 2 prior therapies (initial and treatment for 1 relapse). 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.

Relapse and Treatment Count		
Initial diagnosis →	Surgical resection	Radiation + Chemotherapy #1
Relapse #1 →	+/- Surgical resection	Chemotherapy #2
Relapse (#2) →	Patient to be evaluated for enrollment to BTTC09-01	

- Patients must not have received prior therapy with sorafenib, everolimus, or related drugs such as tyrosine kinase inhibitors, VEGF inhibitors (except bevacizumab), or mTOR inhibitors.

2.1.4 General Exclusion Criteria

2.1.4.1 Patients has any significant medical illnesses that in the investigator's opinion cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate this therapy

2.1.4.2 Patients with a history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission and off of all therapy for that disease for a minimum of 3 years are ineligible.

2.1.4.3 Patient has an active infection or serious intercurrent medical illness.

2.1.4.4 Patient has any disease that will obscure toxicity or dangerously alter drug metabolism.

2.1.4.5 Patients is on an enzyme inducing anti-convulsants. If patients were previously on EIAEDs and these have been discontinued, patients must have been off the agent for at least 2 weeks prior to first study drug administration. For patients who need to start an AED or the AED needs to be changed, it is strongly recommended that all efforts should be made to use a non-EIAED.

2.1.4.6 Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as: Symptomatic congestive heart failure of New York heart Association Class III or IV unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction within 6 months of start of study drug or any other clinically significant cardiac disease severely impaired lung function as defined as spirometry and DLCO that is 50% of the normal predicted value and/or 02 saturation that is 88% or less at rest on room air, uncontrolled diabetes as defined by fasting serum glucose >1.5 x ULN, active (acute or chronic) or

uncontrolled severe infections, liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis.

2.1.4.7 Cardiac ventricular arrhythmias requiring anti-arrhythmic therapy.

2.1.4.8 Uncontrolled hypertension defined as systolic blood pressure > 140 mmHg or diastolic pressure > 90 mmHg, despite optimal medical management.

2.1.4.9 Known human immunodeficiency virus (HIV) infection or chronic or acute Hepatitis B or C. Note: Patients who have a history of HBV and HCB infection are eligible, however, they must receive prophylactic antiviral therapy for 1-2 weeks prior to receiving study drug (see Section **3.3.2**)

2.1.4.10 Thrombolic or embolic events (except DVT or pulmonary embolus) such as a Cerebrovascular accident including transient ischemic attacks within the past 6 months.

2.1.4.11 Pulmonary hemorrhage/bleeding event ≥ CTCAE Grade 2 within 4 weeks of first dose of study drug.

2.1.4.12 Any other hemorrhage/bleeding event ≥ CTCAE Grade 3 within 4 weeks of first dose of study drug.

2.1.4.13 Serious non-healing wound, non-healing ulcer, or bone fracture.

2.1.4.14 Evidence or history of bleeding diathesis or coagulopathy

2.1.4.15 Major surgery, open biopsy or significant traumatic injury within 4 weeks of first study drug.

2.1.4.16 Use of St. John's Wort, orrifampin (rifampicin), or other strong CYP34A inducers. Dexamethasone is okay as long as the dose is 16 mg /day or less. Note: Patients who are on the above referenced medications may be considered eligible with a washout period of 14 days. Contact the coordinating center to discuss patients with the above aforementioned agents before patient registration.

2.1.4.17 Known or suspected allergy to sorafenib, everolimus, or any agent given in the course of this trial.

2.1.4.18 Any condition that impairs patient's ability to swallow whole pills.

2.1.4.19 Any malabsorption problem.

2.1.4.20 Other malignancies within the past 3 years except for adequately treated carcinoma of the cervix or basal or squamous cell carcinomas of the skin.

2.1.4.21 Female patients who are pregnant or breast feeding, or adults of reproductive potential who are not using effective birth control methods. Barrier contraceptives must be used throughout the trial by both sexes. Hormonal contraceptives are not acceptable as a sole method of contraception. (Women of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to administration of everolimus and sorafenib).

2.1.4.22 Patients who have received prior treatment with an mTOR inhibitor (sirolimus, temsirolimus, everolimus).

2.1.4.23 Patients with a known hypersensitivity to everolimus or other rapamycins (sirolimus, temsirolimus) or to its excipients.

2.1.4.24 History of noncompliance to medical regimens.

2.1.4.25 Patients unwilling to or unable to comply with the protocol.

2.1.4.26 Patients on total daily dose of dexamethasone greater than 16 mg.

2.2 SCREENING EVALUATION

Prior to registration on the study, all patients will undergo the following screening tests within 14 days of registration:

- A complete medical history, concomitant medication review, physical exam with vital signs (heart rate, blood pressure, respiration rate, height and weight) and neurological examination (to include documentation of the patients Karnofsky Performance Status per Appendix **13.1**)
- Neuro-imaging confirming tumor progression shall be performed on all patients. The scan done prior to study entry documenting progression will be reviewed by the patient's treating physician to confirm progression of disease.
- Pre-study tests shall include ECG chest X-ray (or CT scan with lung windows) within 30 days of treatment, and laboratory studies including CBC, differential, platelets, serum creatinine, phosphate, lipase, amylase, bilirubin, SGOT, PT, PTT, fasting serum glucose and lipid panel, urinalysis with microanalysis, HBV-DNA, HbsAg, HBsAb (Qualitative), HBcAb, HCV-RNA-PCR and serum pregnancy test for women of childbearing potential. All patients should be screened for hepatitis risk factors and any past illnesses of hepatitis B and hepatitis C infection. All patients with positive HBV-DNA or HBsAg should be treated prophylactically with an antiviral (i.e. Lamivudine) for 1-2 weeks prior to receiving study drug (see Section **3.3.2**). The antiviral treatment should continue throughout the entire study period and for at least 4 weeks after the last dose of everolimus. Patients with viral hepatitis C risk factors should be screened for HCV RNA-PCR. UPC ratio must be obtained if urinalysis has >2+ protein. Pre-study tests (except pregnancy test) must be obtained within 14 days of registration. Pregnancy test must be obtained within 7 days prior to starting the study drugs.
- Documentation of tumor diagnosis. Following registration, slides from the most recent pre-registration biopsy or resection must be submitted for review to local institution if surgery was not done there.
- Neuro-imaging confirming tumor. (See section **2.5**)

2.3 REGISTRATION PROCEDURES

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.

BTTC patients will be registered with the BTTC Coordinating 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.

2.3.1 Informed Consent

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

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 BTTC Coordinating Center:

- A copy of a completed and signed, protocol specific, Eligibility Checklist form
- One copy of the signed and dated Informed Consent.
- Copies of all source documents to support protocol specific eligibility. Please refer to the Operations Manual for specific source documents required.

2.3.2 Registration at the NCI

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent for patients enrolling at the lead institution. A registration Eligibility Checklist from the web site **(**http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and hand delivered to the BTTC Coordinating Center or sent via encrypted email to the BTTC Coordinating Center Research Nurse.. After confirmation of consent, available slot, and eligibility, the BTTC CC research nurse will send the registration Eligibility Checklist to CRO ncicentralregistration-l@mail.nih.gov via encrypted email. CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team with a copy to the BTTC Coordinating Center. A recorder is available during non-working hours.

2.3.3 Participating Site Registration (Not Applicable as of Amendment C)

All patients must be registered through the NCI Central Registration Office (CRO). A protocol registration form and cover memo will be supplied by the Coordinating Center, NCI CCR and updates will be provided as needed. Subject eligibility and demographic information is required for registration. To initially register a subject, after the participant has signed consent, complete the top portion of the form and send to NCI BTTC Coordinating Center's Research Nurse, Melanie Herrin, RN, Fax 301-451-5429, email Melanie.Herrin nci_bttc@mail.nih.gov. Once eligibility is confirmed, send the completed eligibility checklist with the attached supporting source documents to NCI BTTC Coordinating Center's Research Nurse, Melanie Herrin, RN. If patient is not eligible, please notify NCI BTTC Coordinating Center's Research Nurse, Melanie Herrin, RN. The CRO will notify you either by e-mail or fax that the protocol registration form has been received. Questions about eligibility should be directed to the NCI BTTC Coordinating Center's Research Nurse, Melanie Herrin, RN.

2.3.3.1 Patient Number for Participating Institutions (Not Applicable as of Amendment C)

Once eligibility has been confirmed by the Coordinating Center, the patient from the participating institution will be registered through the Central Registration Office. A Verification of Registration will be received from the Central Registration Office with the assigned patient ID number. The

patient ID number is unique to the patient and must be written on all data and correspondence for the patient and used to enter data into the C3D database. The participating site will receive the Verification of Registration via fax or email within one working day of registration.

2.3.4 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 Central Registration Office.

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

The BTTC Coordinating Center must be notified in writing of any exceptions to this policy.

2.3.5 Eligibility Exceptions

Eligibility Exceptions will not be granted.

2.4 TREATMENT ASSIGNMENT AND DESCRIPTIVE FACTORS

Patients with recurrent malignant glioma will be enrolled into one of the following groups. Accrual goals and endpoints for each group are determined separately as described in the statistical section.

There will be an accrual of approximately 3-6 eligible patients per dose level to the Phase I component of the study. Patients removed at any time for toxicity are evaluable. Phase I patients removed from study treatment within 28 days for reasons other than toxicity may be replaced.

Cohorts

Number	Name	Description
1	Phase 1 (closed)	Patients with Glioblastoma or Anaplastic Glioma
2A	Phase 2 Group A (closed)	Patients with Glioblastoma with NO prior bevacizumab exposure
2B	Phase 2 Group B	Patients with Glioblastoma with PRIOR bevacizumab exposure
2C	Phase 2 Group C (closed)	Patients with Anaplastic Glioma with NO prior exposure to bevacizumab (Grade III Glioma Group)

Arms

Number	Name	De`scription
1	Phase 1 (closed)	Combination of sorafenib (7 days on, 7 days off) and everolimus daily over a 28-day cycle at escalating doses

2	Phase 2	Combination of sorafenib (7 days on, 7 days off) and everolimus daily over a 28-day cycle: **Sorafenib** 400 mg BID PO (days 1-7 and days 15-21) **Everolimus** 5 mg PO daily (days 1-28)

There will be a total accrual of approximately 82 eligible patients to the Phase II study (34 recurrent GBM with no prior exposure to bevacizumab, 16 recurrent Anaplastic Glioma with no prior exposure to bevacizumab, and 32 glioblastoma with prior exposure to bevacizumab).

Subjects in Cohort 1 were directly assigned to Arm 1.

Subjects in Cohorts 2A, 2B and 2C will be directly assigned into Arm 2.

2.5 BASELINE EVALUATION

After eligibility is confirmed, complete the following baseline study tasks:

- Patients will complete a baseline MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT) (Appendix **13.4**) within 14 days (+ 3 working days) after enrollment 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.
- The screening scan can be used as the baseline scan if performed within 14 days of registration on a stable dose of steroids. Patients should not be on a steroid dose higher than 16 mg/day. (Refer to **2.1.1.7** and **2.1.1.8**)
- Document baseline adverse events
- For all women of childbearing potential, negative serum pregnancy test within 7 days of starting treatment.
- If treatment will start > 14 days after screening evaluations were completed, then repeat the following labs:
    - CBC, differential, platelets
    - Serum creatinine, phosphate
    - lipase, amylase
    - bilirubin, SGOT
    - PT, PTT
    - Fasting serum glucose and fasting lipid panel
    - Urinalysis with microanalysis; UPC ratio must be obtained if urinalysis has >2+ protein.

3.0 STUDY IMPLEMENTATION

This is a phase 1 /2 study of everolimus and sorafenib in patients with recurrent high-grade gliomas. Patients must initiate study treatment within 96 hours after registration.

All 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 **3.5**.

3.1 PHASE 1 STUDY DESIGN

3.1.1 Drug Administration

Patients will be treated with daily everolimus (days 1-28) in combination with sorafenib (as per the table below).

The schedule providing highest dose without DLT (as defined above) will be used as the phase II dose. The dose levels are listed in **Table 3-11**.

There is not a defined set maximum number of cycles that a patient may have. Patients may continue with protocol therapy until criteria for "Off Treatment" is met. Off treatment criteria could be any of the following events/reasons; disease progression, intolerable side effects (toxicities) and/or withdrawal from study.

3.1.2 Dose Escalation

Patients will be treated at the dose levels in **Table 3-11** starting at dose level 1. Initially everolimus and sorafenib will be administered continuously. If two DLTs are encountered at the first dose level (sorafenib 400 mg twice daily and everolimus 5 mg daily) the dose for the next cohort of patients will be decreased to sorafenib 400 mg twice daily 7 days on, 7 days off and everolimus 5 mg daily (dose level -1). If dose level -1 is tolerated, dose escalations will occur along the "b" pathway (-1, 1b, 2b, 3b, 4b).

If two DLTs are encountered at dose level 2, the dose for the next cohort of patients will be reduced to sorafenib 400 twice daily, 7 days on 7 days off and everolimus 7.5 mg daily (dose level 1b). Subsequent dose escalations will occur along the "b" pathway (2, 1b, 2b, 3b, 4b).

The study drugs will be self-administered (by the patients themselves). The investigator will instruct the patient to take the study drug exactly as specified in the protocol. Patients will be instructed to take the study drugs in the morning, at the same time each day.

The study drugs must be taken 1 hour before or two hours after food. Consumption of grapefruit juice should be avoided while taking the study drugs. If vomiting occurs, no attempt should be made to replace a dose.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded.

Table 3-1: Phase I dosing table.

DOSE LEVEL	SORAFENIB	EVEROLIMUS
-1	400 mg BID,	5 mg daily

DOSE LEVEL	**SORAFENIB**	**EVEROLIMUS**
	7 days on 7 days off	
1	400 mg BID	5 mg daily
2	400 mg BID	7.5 mg daily
3	400 mg BID	10 mg daily
4	600 mg BID	10 mg daily
1b	400 mg BID, 7 days on 7 days off	7.5 mg daily
2b	400 mg BID, 7 days on 7 days off	10 mg daily
3b	600 mg BID, 7 days on 7 days off	10 mg daily
4b	800 mg BID, 7 days on 7 days off	10 mg daily

Note: On the sorafenib 7 days on 7 days off schedule, sorafenib will be given on days 1-7 and 15-21.

The MTD will be based on the assessment of DLT during the first 28 days of treatment only (cycle-1), and will be defined as the dose at which fewer than one-third of patients experience a DLT to one of the study drugs. The MTD is the dose level at which 0/6 or 1/6 patients experience DLT with the next higher dose having at least 2/3 or 2/6 patients encountering DLT. Three patients will be treated at each dose level. If one dose limiting toxicity (DLTs) is encountered an additional 3 patients will be added to that dose level. If at any point two DLTs are encountered within a given dose level, then the MTD has been exceeded and three more patients are treated at the next lower dose (if only three patients were previously treated at that prior dose).

3.1.3 Dose-Limiting Toxicity

Toxicities will be graded according to the NCI 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 during treatment with sorafenib and/or everolimus and attributable to one of the study drugs:

3.1.3.1 Any grade 3 thrombocytopenia, grade 4 anemia, grade 4 neutropenia, or febrile neutropenia of any grade.

3.1.3.2 Any non-hematologic grade 3 or grade 4 toxicity, excluding alopecia and/or hand/foot reaction.

3.1.3.3 Failure to recover from toxicities (to grade 1 or less) to be eligible for re-treatment with sorafenib and everolimus within 14 of the last dose of sorafenib and everolimus.

3.2 PHASE II STUDY DESIGN

3.2.1 Drug Administration

All patients treated on the phase II cohorts will receive a combination of sorafenib (7 days on, 7 days off) and everolimus daily over a 28-day cycle, as follows:

Sorafenib 400 mg BID PO (days 1-7 and days 15-21)

Everolimus 5 mg PO daily (days 1-28)

There is not a defined set of maximum number of cycles that a patient may have. Patients may continue with protocol therapy until criteria for "Off Treatment" is met. See Section **3.7.1.**

3.3 DOSE MODIFICATIONS IN PHASE I (POST CYCLE 1) AND PHASE II

Patients with stable or responding disease may be retreated at the same dose or at a reduced dose level, depending upon the adverse events observed in the current cycle and any adverse events (based on the CTCAE v.4) present on the first day of the next cycle. If multiple toxicities are seen, the dose administered in a subsequent cycle should be based on the most severe toxicity experienced in the current cycle.

Patients who experience toxicity should have laboratory testing at least weekly until the toxicity has resolved.

Toxicities will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. If multiple toxicities are seen, the toxicity should be based on the most severe toxicity experienced. Toxicities will be defined as any of the following events occurring during treatment with sorafenib and/or everolimus and attributable to one of the study drugs:

A. Any grade 3 thrombocytopenia, grade 4 anemia, grade 4 neutropenia, or febrile neutropenia of any grade.

B. Any non-hematologic grade 3 or grade 4 toxicity, excluding alopecia and/or hand/foot reaction.

C. Failure to recover from grade 3 or 4 toxicities (to grade 1 or less) to be eligible for re-treatment with sorafenib and everolimus within 14 of the last dose of sorafenib and everolimus.

3.3.1 Within Treatment Cycles

If a patient experiences toxicities during a treatment cycle, the treatment will be immediately suspended until a grade 1 or less toxicity. If the toxicity resolves to less than or equal to grade 1 within 2 weeks, the patient will be retreated at the dose level described in Table **3-2** below. (Refer to Table **3-6** and Table **3-7** for management of everolimus-induced toxicities and Table **3-8**, Table **3-9** and Table **3-10** for management of sorafenib-induced toxicities.) If toxicity persists, the patient should be taken off study.

Two dose reductions are permitted. Doses that are reduced for sorafenib or everolimus related toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose. Patients whose dose has been reduced for adverse events that are subsequently not felt to be related to sorafenib or everolimus may have the dose re-escalated after completion of one cycle with toxicities less than or equal to grade 1. If any patient has further toxicities that would require additional reductions, or if treatment is held for more than 2 consecutive weeks because of ongoing

toxicity, the Study PI will assess if the patient should remain in the study (if the patient has benefited from treatment).

Table 3-2: Dose Modification Table

DOSE LEVEL	SORAFENIB	EVEROLIMUS
1 (starting dose)	400 mg BID 7 days on 7 days off	5 mg daily
-1	400 mg AM dose 200 mg PM dose 7 days on 7 days off	5 mg daily
-2	200 mg AM dose 200 mg PM dose 7 days on 7 days off	5 mg daily

3.3.1.1 Hematologic Toxicity

Dose Modifications Based on ANC and Platelet Counts obtained weekly for Phase I and every 2 weeks for Phase II (**sorafenib or everolimus)**: Please note per CTCAE v 4, ANC 750-999 falls within grade 3 adverse event and Platelets 50,000 to <75,000 is grade 2.

ANC (/mL)		**Platelets (/mL)**	**% of Dose Planned**
> 1000	and	> 75,000	100%
750-999(G3)	or	50,000 to < 75,000(G2)	hold*
< 750	or	< 50,000 (G3-G4)	hold**

* Suspect drug should be held. Upon recovery to ANC ≥ 1,500/mL and platelets to ≥ 100,000/mL, the same dose level will be administered.

** Suspect drug should be held. Upon recovery to ANC ≥ 1,500/mL and platelets to ≥ 100,000/mL, one lower dose levels will be administered.

3.3.1.2 Non-hematologic Toxicity

Dose Modifications

Based on **sorafenib or everolimus** -Related Non-Hematologic Toxicities:

CTCAEv.4 Grade	**% of Dose Planned**
0-2+	100%+
3*	hold**
4	hold***

+For symptomatic Grade 2 toxicity, the suspect drug dose may be held at the discretion of the local investigator until recovery to CTCAE Grade 0-1, then resume at one dose lower.

*Except nausea/vomiting (unless patients are on optimal antiemetic therapy)

**Hold suspect drug until recovery to CTCAE Grade 0-1 (or to within 1 grade of starting values for pre-existing laboratory abnormalities), and then resume at one dose level lower.

***Hold suspect drug until recovery to CTCAE Grade 0-1 (or to within 1 grade of starting values for pre-existing laboratory abnormalities), and then resume at two dose levels lower.

3.3.2 Management of Hepatitis

3.3.2.1 Management of Hepatitis reactivation

In cancer patients with hepatitis B, whether carriers or in chronic state, use of antivirals during anticancer therapy has been shown to reduce the risk of hepatitis B virus (HBV) reactivation and associated HBV morbidity and mortality (Loomba et al. 2008).

3.3.2.1.1 Monitoring and prophylactic treatment for hepatitis B reactivation

Table 3-3 provides details of monitoring and prophylactic therapy according to the baseline results of viral load and serologic markers testing.

Table 3-3: Action to be taken for positive baseline hepatitis B results

Test	**Result**	**Result**	**Result**	**Result**	**Result**
HBV-DNA	+	+ or -	-	-	-
HBsAg	+ or -	+	-	-	-
HBs Ab	+ or -	+ or -	+ and no prior HBV vaccination	+ or -	- or + with prior HBV vaccination
HBc Ab	+ or -	+ or -	+ or -	+	-
Recommendation	Prophylaxis treatment should be started 1-2 weeks prior to first dose of study drug Monitor HBV-DNA approximately every 4 weeks		No prophylaxis Monitor HBV-DNA approximately every 4 weeks		No specific action

Antiviral prophylaxis therapy should continue for at least 4 weeks after last dose of study drug. For hepatitis B reactivation, definition and management guidelines, see Table **3-4** Guidelines for management of hepatitis B.

Table 3-4: Guidelines for management of hepatitis B

HBV reactivation (with or without clinical signs and symptoms)*	
For patients with baseline results: Positive HBV-DNA OR positive HBsAg --- reactivation is defined as: [Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value OR new appearance of measurable HBV-DNA] AND ALT elevation x 5 ULN	Treat: Start a second antiviral AND Interrupt study drug administration until resolution: ≤ grade 1 ALT (or baseline ALT, if > grade 1) and ≤ baseline HBV-DNA levels If resolution occurs within ≤ 28 days study drug should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Both antiviral therapies should continue at least 4 weeks after last dose of study drug. If resolution occurs > 28 days Patients should discontinue study drug but continue both antiviral therapies at least 4 weeks after last dose of study drug.
For patients with baseline results: Negative HBV-DNA and HBsAg AND [Positive HBs Ab (with no prior history of vaccination against HBV), OR positive HBc Ab] --- reactivation is defined as: New appearance of measurable HBV-DNA	Treat: Start first antiviral medication AND Interrupt study drug administration until resolution: ≤ baseline HBV-DNA levels If resolution occurs within ≤ 28 days study drug should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Antiviral therapy should continue at least 4 weeks after last dose of study drug. If resolution occurs > 28 days Patients should discontinue study drug but continue antiviral therapy at least 4 weeks after last dose of study drug.

* All reactivations of hepatitis B are to be recorded as grade 3 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Re-activation), unless considered life threatening by the investigator; in which case, they should be recorded as grade 4 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Re-activation). Date of viral reactivation is the date on which **both** DNA and ALT criteria were met (e.g. for a patient who was HBV-DNA positive on 01-JAN-10 and whose ALT reached ≥ 5 × ULN on 01-APR-10, the date of viral reactivation is 01-APR-10).

3.3.2.2 Monitoring for hepatitis C

The following two categories of patients should be monitored every 4 weeks for HCV reactivation:

- Patients with detectable HCV RNA-PCR test at baseline.
- Patients known to have a history of HCV infection, despite a negative viral load test at baseline (including those that were treated and are considered 'cured')

  For definition of hepatitis C reactivation and the management guidelines, see Table **3-5** Guidelines for management of hepatitis C.

Table 3-5: Guidelines for management of hepatitis C

HCV reactivation*	
For patients with baseline results: Detectable HCV-RNA, reactivation is defined as: ALT elevation x 5 ULN	Discontinue study drug
For patients with baseline results: Knowledge of past hepatitis C infection with no detectable HCV-RNA, reactivation is defined as: New appearance of detectable HCV-RNA	Discontinue study drug

* All reactivations of hepatitis C are to be recorded as grade 3 (CTCAE v4.0 Metabolic Laboratory/Other: Viral Re-activation), unless considered life threatening by the investigator; in which case, they should be recorded as grade 4 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Re-activation).

3.3.3 Management of stomatitis/oral mucositis/mouth ulcers

CTCAE v 4.0 grade 1-2 stomatitis/oral mucositis/mouth ulcers due to everolimus should lead to using local supportive care such as use of mouthwash (avoid those containing alcohol). The use of topical high potency steroids such as triamcinolone oral paste 0.1% (Kenalog in Orabase®) is allowed. Please refer to section **3.3.1.2** for dose modifications. Suggested guidelines for treatment of stomatitis/oral mucositis/mouth ulcers:

1. For mild toxicity (grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.
2. For more severe toxicity (grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (e.g., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).

3. Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.
4. Antifungal agents must be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of everolimus and sorafenib metabolism, therefore leading to higher everolimus exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

   Note: Stomatitis/oral mucositis should be appropriately graded using the functional grading given on the NCI-CTCAE, version 4.0.

3.3.4 Management of hyperlipidemia

Everolimus causes hyperlipidemia. Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits. Blood tests to monitor hyperlipidemia must be taken in the fasting state. Grade 2 or higher hypercholesterolemia (>300 mg/dL or 7.75 mmol/L) or grade 2 or higher hypertriglyceridemia (>2.5 x upper normal limit) should be treated with a statin or appropriate lipid-lowering medication, in addition to diet. Patients should be monitored clinically and through serum biochemistry for the development of rhabdomyolysis and other adverse events as required in the product label/data sheets for HMG-CoA reductase inhibitors. Please refer to section **3.3.1.2** for dose modifications of everolimus.

Note: Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatine kinase (CPK) levels and myoglobinuria, acute renal failure and sometimes death. The risk versus benefit of using this therapy should be determined for individual patients based on their risk of cardiovascular complications of hyperlipidemia.

3.3.5 Management of hyperglycemia

Grade 3 hyperglycemia has been observed in patients receiving everolimus therapy. In many cases the affected patients had an abnormal should have their glucose levels monitored during everolimus therapy. Please refer to section **3.3.1.2** for dose modifications.

3.3.6 Management of non-infectious pneumonitis

Table 3-6: Management of Everolimus-induced Pneumonitis

Worst grade pneumonitis	**Required investigations**	**Management of pneumonitis**	**everolimus dose adjustment**
Grade 1	CT scan with lung windows	No specific therapy is required	Administer 100% of everolimus dose
Grade 2	CT scan with lung windows. Consider pulmonary function	Symptomatic only. Prescribe corticosteroids if	Reduce everolimus dose

Worst grade pneumonitis	**Required investigations**	**Management of pneumonitis**	**everolimus dose adjustment**
	testing including: spirometry, DLCO, and room air O2 saturation at rest. Repeat each subsequent Cycle until return to within normal limits. Consider a bronchoscopy.	cough is troublesome.	until recovery to ≤ grade 1. Everolimus may also be interrupted if symptoms are troublesome. Patients will be withdrawn from the study if they fail to recover to ≤ grade 1 within 3 weeks.
Grade 3	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O2 saturation at rest; Repeat each subsequent Cycle until return to normal limits. Bronchoscopy is recommended.	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment until recovery to ≤ grade 1. May restart protocol treatment within 2 weeks at a reduced dose (by one level) if evidence of clinical benefit.
Grade 4	CT scan with lung windows and required pulmonary function testing includes: spirometry, DLCO, and room air O2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Bronchoscopy is strongly recommended.	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment.

3.3.7 Management of suspected everolimus toxicity

Table 3-7: Criteria for dose-modification in case of suspected everolimus toxicity and re-initiation of everolimus treatment

Toxicity	Actions
Non-hematological toxicity	
Grade 2 (except pneumonitis – refer to Table 3-6**)**	If the toxicity is tolerable to the patient, maintain the same dose. If the toxicity is intolerable to patient, interrupt everolimus until recovery to grade ≤1. Then reintroduce everolimus at same dose. If event returns to grade 2, then interrupt everolimus until recovery to grade ≤1. Then reintroduce everolimus at same dose level.
Grade 3 (except hyperlipidemia*) (except pneumonitis – refer to Table 3-6**)**	Interrupt everolimus until recovery to grade ≤1. Then reintroduce everolimus at same dose level. For pneumonitis consider the use of a short course of corticosteroids.
Grade 4	Discontinue everolimus.
Hematological toxicity	
Grade 2 Thrombocytopenia (platelets <75, ≥ 50x10^9/L)	Interrupt everolimus until recovery to grade ≤1 (>75 x10^9/L). Then reintroduce everolimus at initial dose. If thrombocytopenia again returns to grade 2, interrupt everolimus until recovery to grade ≤1. Then reintroduce everolimus at same dose level.
Grade 3 Thrombocytopenia (platelets <50, ≥ 25 x10^9/L)	Interrupt everolimus until recovery to grade ≤1 (platelets ≥ 75 x10^9/L). Then resume everolimus at same dose level. If grade 3 thrombocytopenia recurs, discontinue everolimus.
Grade 4 Thrombocytopenia (platelets < 25 x10^9/L)	Discontinue everolimus.

Toxicity	Actions
Grade 3 Neutropenia (neutrophils <1, ≥0.5 x10^9/L)	Interrupt everolimus until recovery to grade ≤1 (neutrophils ≥ 1.5 x 10^9/L). Then resume everolimus at the initial dose. If ANC again returns to Grade 3, hold everolimus until the ANC ≥ 1.5 x 10^9/L. Then resume everolimus dosing at same dose level. Discontinue patient from study therapy for a third episode of grade 3 neutropenia.
Grade 4 Neutropenia (neutrophils < 0.5 x10^9/L)	Interrupt everolimus until recovery to grade ≤ 1 (neutrophils ≥ 1.5 x 10^9/L). Then resume everolimus at the lower dose level. If grade 3 or grade 4 neutropenia occurs despite this dose reduction, discontinue everolimus.
Grade 3 febrile neutropenia (not life-threatening)	Interrupt everolimus until resolution of fever and neutropenia to grade ≤ 1. Hold further everolimus until the ANC ≥ 1,500/mm^3 and fever has resolved. Then resume everolimus at same dose level. If febrile neutropenia recurs, discontinue everolimus.
Grade 4 febrile neutropenia (life-threatening)	Discontinue everolimus.
Any hematological or non-hematological toxicity requiring interruption for ≥ 3 weeks	Discontinue everolimus

*Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) should be managed using medical therapies (see Sec. **3.3.4**).

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value suspected to be related to everolimus must be followed at least weekly until the adverse event or abnormal laboratory resolves or returns to grade 1. If a patient requires a dose delay of > 21 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study.

3.3.8 Management of sorafenib induced skin toxicity

It is common for patients treated with sorafenib to experience skin toxicity (rash/desquamation, hand/foot reaction, etc.). Guidelines for management are specified in the table below.

Table 3-8: Guidelines for management of sorafenib induced skin toxicity

Skin Toxicity Grade	Occurrence	Suggested Dose Modification
Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, and erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities.	Any occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief.
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities.	First occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief. If no improvement within 7 days, see below.
	No improvement within 7 days or 2nd occurrence	Interrupt sorafenib treatment until toxicity resolves to Grade 0-1. When resuming treatment, decrease sorafenib dose by one dose level.
	Third occurrence	Interrupt until resolved to grade 0-1. When resuming treatment, decrease dose by two dose levels (from the starting dose).
	Fourth occurrence	Discontinue sorafenib treatment.
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities.	First occurrence	Interrupt sorafenib treatment until toxicity resolves to Grade 0-1. When resuming treatment, decrease sorafenib by one dose level.
	Second occurrence	Interrupt until resolved to grade 0-1. When resuming treatment, decrease dose by two dose levels (from the starting dose).
	Third occurrence	Discontinue sorafenib treatment.

Table 3-9: Dose Modifications for Sorafenib-Associated Toxicity[1]

Toxicity	Grade 1	Grade 2	Grade 3*	Grade 4*
Non-hematologic	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is < 1. When resuming treatment reduce dose by one dose level.	Discontinue treatment.
Hematologic	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade <2. When resuming treatment reduce dose by one dose level.	Withhold dose until toxicity is grade <2. When resuming treatment reduce dose by two dose levels.

[1] See separate suggestions for dose modification due to hand-foot skin reactions.

*Patients who develop grade 3 fever/chills, grade 3 elevation of hepatic transaminases with ALT and AST <10X ULN, grade 3 hyperlipidemia or hyperamylasemia without clinical or other evidence of pancreatitis, grade 3 leukopenia, or grade 3/grade 4 lymphopenia may continue study treatment without interruption at the discretion of the investigator.

3.3.9 Hypertension: Dose Modifications of Sorafenib for Hypertension

Hypertension is a known and potentially serious adverse event associated with sorafenib treatment. Patients will have their blood pressure monitored and recorded weekly during the Cycle 1 and then every cycle of the entire treatment period, either at the doctor's office or by using any calibrated electronic device (such as those found at a local drug store or pharmacy). Patients will have a Blood Pressure Diary on which to record the measurements, which will be kept with research chart. If the patient's blood pressure is elevated at any time (>140/100), even outside clinic visits, they should contact their treating physician.

Table 3-10: Dose modifications for Sorafenib-associated hypertension

Grade (CTCAE v 4.0)	Antihypertensive Therapy	Blood Pressure Monitoring	Sorafenib Dose
Grade 1	None	Routine	No change
Grade 2 (asymptomatic)	Initiate monotherapy (suggest dihydropyridine calcium-channel blocker)	Increase frequency and monitor (by health professional) every 2 days until stabilized	No change
Grade 2 (symptomatic/ persistent) **OR** Diastolic BP > 110 mm Hg **OR** Grade 3	Add agent(s): Ca^{++} channel blocker (if not already used), K+ channel opener (angiotensin blockers), beta-blocker, thiazide diuretic	Increase frequency and monitor (by health professional) every 2 days until stabilized; continue qod monitoring to stabilization after dosing restarted.	Hold* Sorafenib until symptoms resolve and diastolic BP < 100 mm/Hg. Resume treatment at 1 dose level lower**
Grade 4			Off protocol therapy
* Patients requiring a delay of > 28 days should go off protocol therapy unless, in the treating physician's opinion, the patient may benefit from continued treatment. ** Patients requiring >2 dose reductions should go off protocol therapy.			
CTCAE v 4.0 definitions Grade 1: asymptomatic, transient (<24 hrs) increase by > 20 mmHg (diastolic) or > 150/100 if previously WNL; intervention not indicated Grade 2: recurrent or persistent (>24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated. Grade 3: requiring more than one drug or more intensive therapy than previously Grade 4: life threatening (*e.g.*, hypertensive crisis)			

For treatment or dose modification related questions, please contact the Study Chair or the BTTC Coordinating Center's Research Nurse.

3.4 QUESTIONNAIRES

The MDASI-BT will be utilized for this portion of the study. Full instruments are provided in the Appendix **13.4**. 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 (24, 25).

3.5 STUDY CALENDAR

STUDIES TO BE OBTAINED	PRE TREATMENT	DURING TREATMENT	OFF TREATMENT
Consent & HIPAA Authorization	X		
History	X[1]		
Physical exam (including vital signs) and Neurologic Examination	X[1]	X[5]	
Karnofsky Performance Status	X[1]	X[5]	
Blood Pressure	X[1]	X[14], X[5]	
CBC, with differential, platelets	X[1]	X[4] , X[15]	
PT, PTT	X[1]		
Serum creatinine, phosphate, lipase, amylase, bilirubin, SGOT, fasting serum glucose, fasting lipid panel	X[1]	X[5] , X[15]	
HBV-DNA, HbsAg, HBsAb, HBcAb, HCV-RNA-PCR	X[1]		
MRI or CT (brain) (X[5] (times 2) or X[5] (times 4) whichever is applicable per section **3.6.1.2**	X[1]	X[5] (times 2) or X[5] (times 4) then X[6], X[16]	
MDASI Symptom Assessment X[5] (times 2) or X[5] (times 4) whichever is applicable per sections **3.6.1.2** and **3.6.1.5**	X[10]	X[5] (times 2) or X[5] (times 4) then X[6]	
ECG	X[3]		
Chest X-ray or chest CT	X[3]		

STUDIES TO BE OBTAINED	PRE TREATMENT	DURING TREATMENT	OFF TREATMENT
Urinalysis with microanalysis	X[1]		
Serum pregnancy test (β-HCG)	X[2]		
UPC ratio	X[12]	X[12]	
Urine Dipstick/urinalysis	X[1]	X[5], X[15]	
HBV-DNA, HCV-RNA-PCR		X[9]	
Prophylactic antiviral agent (i.e. Lamivudine)	X[11]	X[11]	X[11]
Documentation of tumor diagnosis	X		
Information on drug doses, concomitant medications and doses, (baseline and treatment related) toxicity monitoring	X	X[5]	
Measurable lesions with measurements-tumor response (X[5] or X[6], whichever is applicable per section **3.6.1.2**)	X	X[5], X[6]	
Follow up for survival by phone or clinic visit on patients who discontinue treatment due to progression			X[7]
Follow up for survival by phone or clinic visit, for those who come off treatment other than progression should be followed until progression or institution of new anti- tumor therapy			X[7]
Adverse Events Notation	X	X[13]	

X[1] To be performed within 14 days of registration
X[2] To be performed within 14 days prior to starting study treatment
X[3] To be performed within 30 days prior to starting study treatment
X[4] To be performed every 2 weeks during treatment
X[5] To be performed every 4 weeks during treatment (prior to each cycle);
X[6] To be performed every 2 months during treatment (every other month)
X[7] To be performed every 3 months
X[8] To be performed weekly for Phase I Cycle 1
X[9] To be performed on Cycle 1 Day 1 and Day 1 of all subsequent cycles. Applicable to patients that are on antiviral prophylaxis treatment or positive HBV antibodies, and patients with positive

HCV RNA- PCR results at screening and/or a history of past infection (even if treated or considered cured).
X[10] To be performed within 14 days (+3 working days) after enrollment on the clinical trial.
X[11] All patients with positive HBV-DNA or HBsAg should be treated prophylactically with antiviral agent to be given 1 -2 weeks prior to study drugs, and should continue throughout the entire study period, to
last until at least 4 weeks after the last dose of everolimus.
X[12] If urinalysis has > 2+ protein present, then UPC will be obtained
X[13] To be performed at the end of each cycle
X[14] To be performed weekly during Cycle 1
X[15] Lab work (blood draws/urine) has a window of +/- 3 days of the cycle
X[16] MRI/CT imaging has a window of within 7 days of new cycle

3.6 ON STUDY EVALUATION

3.6.1 General Requirements

3.6.1.1 CBC with differential and platelets will be performed every two weeks during treatment. Creatinine, bilirubin, SGOT, phosphate, lipase, amylase, fasting glucose, serum lipid panel and urinalysis/urine dipstick will be performed every four weeks (+/- 3 days) prior to each cycle. If > 2+ protein is present on urine dipstick/urinalysis, then UPC should be obtained.

3.6.1.2 Brain MRI/CT

3.6.1.2.1 A brain MRI/CT will be done monthly x 2 then every other month, within 7 days of new cycle.

OR

3.6.1.2.2 For Phase II patients enrolled to the bevacizumab failure cohort, MRI/CT will be done every 4 weeks x 4, then every 8 weeks thereafter, within 7 days of new cycle.

Note: *MRI is the preferable imaging method, CT scan may be used in cases where an MRI cannot be obtained.

3.6.1.3 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.

3.6.1.4 A complete physical exam (with vital signs) and neurologic exam (to include documentation of the patients Karnofsky Performance Status) will be performed monthly. The MDASI-BT will be completed at baseline and at the time of each evaluation that includes an imaging study.

3.6.1.5 The patient will complete the MDASI-BT (Appendix **13.4**) 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.

3.6.1.6 Patients on antiviral prophylaxis treatment or positive HBV antibodies should be tested for HBV-DNA on Cycle 1 Day 1 and Day 1 of all subsequent cycles (every 28 days) to monitor for re-activation. If re-activation is confirmed, everolimus must be interrupted or discontinued according to the guidance in Table 6-3. Patients with positive HCV RNA-PCR results at screening and/or a history of past infection (even if treated and considered 'cured') should have HCV RNA-PCR testing performed on Cycle 1 Day 1 and Day 1 of all subsequent cycles (every 28 days) to monitor for reactivation. Everolimus must be discontinued if HCV reactivation is confirmed according to the guidance in Table **3-5**.

3.6.1.7 All 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 by phone call or clinic visit.

b) Patients who come off therapy for reasons other than progression should be followed until progression or institution of new anti-tumor therapy. They should then be followed for survival.

3.6.2 Phase I Requirements

3.6.2.1 Phase I patients will be evaluated for adverse events at least weekly during their first cycle of therapy (by either phone contact or personal visit). These adverse events will be reported to the Lead PI and the BTTC Coordinating Center weekly.

3.6.2.2 Adverse events for subsequent cycles will be reported to BTTC Coordinating Center at the end of each cycle. In addition all serious adverse events will be reported to the BTTC Coordinating Center and the Lead PI, as directed in section **6.4**

3.6.3 Phase II Requirements

3.6.3.1 Phase II patients will be evaluated for adverse events at the end of each cycle. In addition, all serious adverse events will be reported to the BTTC Coordinating Center and the Lead PI as directed in section **6.4**

3.6.4 Follow-up

When a subject is removed from treatment as per section **3.7.1**, they should continue to be followed until removed from protocol.

Follow up for survival should be done every 3 months by phone or clinic visit on patients who discontinue treatment due to progression. Those who come off treatment other than progression should be followed every 3 months by phone call or clinic visit until progression or institution of new anti- tumor therapy. Survival status will only be collected by phone or clinic visit. This data must be recorded on the appropriate follow up case report form.

3.7 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

3.7.1 Criteria for Removal from Protocol Therapy:

3.7.1.1 Progression of disease (as defined in Section **5.2.1**).

Patients must be followed by the same type of brain scan, as was used for baseline tumor measurements, and will be removed from study if progression is documented after any cycle of treatment. Patients with stable disease, partial or complete response will continue on therapy as defined in Section **3.0**.

3.7.1.2 Unacceptable toxicity (as defined by the investigator).

3.7.1.3 The patient may withdraw from the study at any time for any reason.

3.7.1.4 Medical or psychiatric illness which in the investigator's judgment renders the patient incapable of further therapy.

3.7.1.5 Treatment delay due to toxicity greater than 21 days measured from the start of the preceding cycle.

3.7.2 Off Study Criteria

3.7.2.1 Participant requests to be withdrawn from study

3.7.2.2 Institution of new anti-tumor therapy

3.7.2.3 Investigator discretion

3.7.2.4 Death

All reasons for discontinuation of treatment must be documented in the flow sheets.

3.7.3 Off Protocol Therapy and Off Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off study.

- NCI site: Complete the Participant Status Updates Form available from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page. Hand deliver the completed form to the BTTC Coordinating Center Research Nurse or send via encrypted email.
- Participating sites: The Participant Status Update Form will be supplied by the BTTC Coordinating Center's Research Nurse. Sites will send the completed form by secure fax to 240-541-4432 or by secure email (NIH Secure Email and File Transfer Service [SEFT]).
- BTTC Coordinating Center: The BTTC Research Nurse will review the Participant Status Updates Form and forward to the Central Registration Office (CRO).

4.0 CONCOMITANT MEDICATIONS/MEASURES

4.1.1 G-CSF Administration: Routine prophylactic use of G-CSF is not permitted. However, therapeutic use in patients with serious neutropenic complications, such as sepsis, may be considered at the investigator's discretion.

4.1.2 Corticosteroids should be used in the smallest dose to control symptoms of cerebral edema and mass effect, and discontinued if possible. Patients must not be on a dexamethasone dose of greater than 16 mg/ day.

4.1.3 Anti-seizure medications should be used as indicated. If for unavoidable clinical reasons (severe allergies, toxicities etc.) a patients AED is switched to the alternate AED group the following guidelines must be followed:

EVERY EFFORT SHOULD BE MADE TO MAINTAIN THE PATIENT ON NON-EIAED

Patients, who were previously on a non-EIAED and need to change anticonvulsants, should be started on another non-EIAED if at all possible. No delays in treatment would be required.

Patients who were previously on a non- EIAED and were inadvertently and temporarily changed to an EIAED, should immediately be started on another non-EIAED. The patient may continue the current treatment dose while a non- EIAED is re-started.

Patients who were previously on a non-EIAED and need to permanently change anticonvulsant, but who cannot change to another non-EIAED may continue the current treatment dose for the next 2 weeks while an EIAED is started. FOLLOWING

THIS 2 WEEK PERIOD, THE SUBSEQUENT TREATMENT DOSE MUST BE DISCUSSED WITH THE STUDY CHAIR. In some cases this dose may be higher than the previously used dose.

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

4.1.5 Antiemetics: The use of antiemetics will be left to the investigators' discretion.

4.1.6 Other Concomitant Medications: Therapies considered necessary for the well-being of the patient may be given at the discretion of the investigator. Other concomitant medications should be avoided except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems. All concomitant medications must be recorded.

4.1.7 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 drug under investigation may be used concomitantly with the study drug.

4.1.8 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. If possible, defer surgery for 4 weeks from last dose of therapy. Patients who undergo resection for presumed tumor

progression but are shown to only have treatment associated changes can resume treatment once they have recovered from the surgical procedure. Everolimus treatment can only resume > 1 week after surgery.

5.0 DATA COLLECTION AND EVALUATION

5.1 DATA COLLECTION

Certain BTTC participating institutions have collected baseline data of relevance to this clinical trial including certain identifiable private information, such as patient treatment dates. For purposes of this clinical trial, these BTTC participating institutions will transfer these data to NCI through direct data entry in the NCI-designated study database (C3D) and via secure transfer through the NIH's Secure Email and File Transfer Service (SEFT) system, in accordance with their applicable laws, regulations, and policies. The BTTC Research Nurse will provide instructions to these BTTC participating institutions for use of C3D and SEFT.

The PI at the site will be responsible for overseeing entry of data into an in-house password protected electronic system 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.

Data on this study will be entered into C3D and Scribe/Labmatrix. Designated research staff from the registering institution will enter the data via remote electronic data entry. The protocol specific electronic forms are to be used by the participating site. All investigators will utilize these forms for Baseline, Treatment, Adverse Events, Tumor Evaluation, Off Treatment, Survival, and Off-study data.

All 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. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

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 **6.3** and **6.5.**

An abnormal laboratory value will be recorded in the database as an AE **only** 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.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule 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.

5.1.1 Source Documentation Timeframes

The following information will be entered into C3D and Scribe/Labmatrix within the indicated timeframes. In addition, the source documents should be provided to the BTTC Coordinating Center's Research Nurse, fax 301-451-5429, or email within the indicated timeframe.

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 MDASI – BT Questionnaire	Within 14 days after the registration date
Baseline Source Documents	Within 14 days after the registration date

5.1.2 Database Entry Timeframes

The following data should be entered into C3D/Labmatrix within the specified timeframes. Source documentation will be kept at the participating site.

Treatment (Cycle) Data (To include treatment, response, AE, and clinical evaluation information)	Within 40 days after the first day of each treatment cycle.
Off Treatment Data	Within 10 days after the last date of any modality of protocol treatment
Follow-up (Survival) Data	Within 52 days after the last treatment date and then every 90 days until Off Study (unless otherwise specified by the protocol)
Non-Treatment Data (May include Quality of Life questionnaires (MDASI-BT), Specimen Tracking information, Pathology Specimen Submission, etc.)	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.

5.1.3 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 BTTC Coordinating Center must have the patient's full name & social security number "blacked out" and the assigned patient ID number and protocol number written in. Patient initials may be included or retained for cross verification of identification.

5.1.4 Safety Data

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. Life-threatening toxicities that are unexpected and assessed to be possibly related to the study agent/s should be reported immediately as per Section **6.5.**

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 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.

5.1.5 Data Sharing with Pharmaceutical Collaborators, Bayer and Novartis

NCI may share data from this study with pharmaceutical collaborators, Bayer and Novartis, pursuant to the NCI M-CRADAs with each company. Specifically, the collaborators may access and review analytical results and primary quantitative and empirical data including identifiable private information in accordance with the terms of the M-CRADAs.

5.2 RESPONSE CRITERIA

The primary efficacy endpoint for BTTC studies will be progression free survival (PFS) at six months from patient registration for bevacizumab naïve patients and at 3 months for patients with prior bevacizumab treatment. However, objective response status should be measured and recorded.

All measurements will be performed on the axial MRI T1 post contrast images when possible, although coronal images may be used if axial is not optimal for measurements (or CT post contrast if MRI is contraindicated). The same plane should be used for all measurements. Tumor size is defined as the largest (contrast enhancing) cross sectional area (largest cross-sectional diameter x largest diameter perpendicular to it).

- Evaluable for toxicity: All patients will be evaluated for toxicity from the time of their first treatment with Sorafenib or Everolimus.

- Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

5.2.1 Definitions of Response

5.2.1.1 Measurable Disease: Bi-dimensionally measurable CE lesions with clearly defined margins by CT or MRI scan, with a minimal diameter of 1 cm, and visible on 2 axial slices which are at least 5 mm apart with 0 mm skip. Measurement of tumor around a cyst or surgical cavity, if necessary, requires a minimum thickness of 3 mm.

5.2.1.2 Non-measurable Disease (contrast enhancing): Uni-dimensionally measurable lesions, masses with margins not clearly defined, lesions with maximal diameter < 1 cm.

5.2.1.3 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.

5.2.1.3.1 Complete Response (CR)

Complete disappearance of all CE 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 no steroids. There must be stable or improved non-enhancing (T2/FLAIR) lesions. Stable or improved clinically. Note: Patients with non-measurable disease cannot have a partial response. The best possible response is stable disease.

5.2.1.3.2 Partial Response (PR)

Greater than or equal to 50% decrease under baseline in the sum of products of perpendicular diameters of the two largest CE measurable lesions, sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease. If more than two clearly defined lesions exist, the remaining lesions will be considered as evaluable. No progression of evaluable or non-measurable disease. No new lesions. All measurable and evaluable lesions and sites must be assessed using the same techniques as baseline. *The steroid dose at the time of the scan evaluation should be no greater than the maximum dose used in the first 8 weeks from initiation of therapy.* Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline. Stable or improved clinically. Note: Patients with non-measurable disease cannot have a partial response. The best response possible is stable disease.

5.2.1.3.3 Partial Response, Non-Measurable (PRNM)

Not applicable.

5.2.1.3.4 Stable/No Response

Does not qualify for CR, PR, or progression. The designation of stable disease requires a minimum of 4-week duration. All measurable and non-measurable sites must be assessed using the same techniques as baseline. Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of steroids as compared to the baseline scan. In the event that the steroid dose has been increased, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

5.2.1.3.5 Progression

a. >25% increase in the sum of products of perpendicular diameters of enhancing lesions (over baseline if no decrease) on stable or increasing dose of corticosteroids.

   and/or

b. Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation or therapy, not due to co-morbid events (radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).

c. Any new lesion

d. Clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.). The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decrease in 20% of KPS or from any baseline to 50% or less be considered, unless attributable to comorbid events.

e. Failure to return for evaluation due to death or deteriorating condition.

5.2.1.3.6 Unknown

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

5.2.2 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 **5.2.1**. 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.

5.2.3 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

5.2.4 Performance Status:

Patients will be graded according to Karnofsky Performance Status (see Appendix **13.1**).

5.2.5 Time to Treatment Failure**:**

From date of registration to the date of first observation of progressive disease (as defined in Section **5.2.1**), 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.

5.2.6 Time to Death

From date of registration to date of death due to any cause.

5.2.7 Evaluability

Patients are required to receive at least 2 weeks of treatment of both agents, and the protocol defined evaluations are performed per protocol to be considered evaluable. Inevaluable patients will be replaced.

5.3 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

6.0 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

6.1 DEFINITIONS

6.1.1 Adverse Event

Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

6.1.2 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.

6.1.3 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.

6.1.4 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.

6.1.5 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.

6.1.6 Disability

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

6.1.7 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.

6.1.8 Protocol Deviation (NIH Definition)

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

6.1.9 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.

6.1.10 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.

6.2 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.

6.3 NCI-IRB AND CLINICAL DIRECTOR REPORTING

6.3.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Lead PI will report on the NIH Problem Form to the NCI-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

6.3.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The Lead 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.

6.3.3 Request for waiver from IRB reporting: Anticipated Protocol Deviations

Brief interruption and delay in the 28-day cycle may occasionally be required due to travel delays, airport closure, inclement weather, family responsibilities, security alerts and government holidays, etc. This can also extend to complications of disease not attributable to disease progression or protocol therapy. These delays will not be considered protocol deviations. We expect 1-2 anticipated delays per patient. However, any interruption more than 14 calendar days will not be permitted.

If the rate of these events exceeds the rate of more than 2 anticipated delays per patient, the events will be classified and reported as though they are unanticipated problems.

6.3.4 Multi-Institutional Guidelines

6.3.4.1 IRB Approvals

The Lead PI will provide the NCI IRB 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.

6.3.4.2 Amendments and Consents

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

6.4 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
2. Other Serious Unexpected Suspected Adverse Reactions (that did not result in death) 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
3. All protocol deviations, non-compliance and unanticipated problems	Within 5 **working** days from the time the **research team** becomes aware of event

What to Report?	When to Report?
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 **13.6**.

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.

6.5 REPORTING TO THE STUDY DRUG MANUFACTURERS

The BTTC Coordinating Center will forward all SAE reports to the NCI IRB via the Lead PI, FDA (when applicable), and Novartis and Bayer Pharmaceuticals.

The Lead Principal Investigator will report any SAEs, study drug exposure during pregnancy, and reports of misuse or abuse of study drug, including initial and follow up reports, to Novartis on a MedWatch form (including coversheet and Novartis Study Code found in M-CRADA) within 1 business day of becoming aware of such information.

The Lead Principal Investigator will forward to Novartis any findings that might alter the current benefit-risk profile of the study drug or that would be sufficient to consider changes in the study drug administration or in the overall conduct of the study within five calendar days of becoming aware of such information.

Bayer HealthCare Pharmaceuticals Inc.
FAX: (973) 709-2185 Telephone: 1-888-842-2937 Email: DrugSafety.GPV.US@bayer.com
Novartis Pharmaceuticals Corporation

Novartis Pharmaceutical U.S. DS&E Department

FAX: 877-778-9739

If above Fax # is non-functional, send to:
clinicalsafetyop.phuseh@novartis.com

6.5.1 SAEs will be forwarded to Bayer/Onyx via the BTTC Coordinating Center in accordance with the following:

All serious adverse events should be reported to Bayer/Onyx 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 Lead PI may report serious adverse drug reactions (SADRs) using either:

An ADEERS form (Adverse Event Expedited Reporting System) available at http://ctep.cancer.gov/reporting/adeers.html

OR

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

All reports shall be sent electronically to:

Electronic Mailbox: DrugSafety.GPV.US@bayer.com
Facsimile: (973) 709-2185

Address: Global Pharmacovigilance - USA
Mail only Bayer HealthCare Pharmaceuticals Inc.
P.O. Box 1000
Montville, NJ 07045-1000

Address: 340 Changebridge Road
FDX or UPS only Pine Brook, NJ 07058

Reports for all Bayer products can also be phoned in via our Clinical Communications Dept:

Phone: 1-888-842-2937

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

6.5.2 Novartis Safety Information

The Lead PI shall report any other relevant/ important safety information to Novartis in the final study report and at such other periods as Novartis may request.

The Sponsor Principal Investigator shall ensure that at a minimum the form contains:

(a) Information on the person who contacted Sponsor (i.e., the initial reporter);

(b) Information about the patient or clinical trial subject;

(c) Details of the suspected Study Drug

(d) Details on the safety events experienced by the patient

The Lead PI shall cooperate with all reasonable requests by Novartis to ensure that individual safety reports are sufficiently investigated, including requests to seek additional information relating to an individual safety reports or other relevant safety information.

The Lead PI shall perform SAE reconciliation between the Sponsor's Study database and an output of the Novartis Safety Database at the following time points:

- One year after First Patient First Visit and yearly thereafter
- At Last Patient Last Visit

The Lead PI will confirm that, for the period being reconciled, all information in the Sponsor's Study database that needed to be transferred to Novartis as per Novartis Annex, are contained in the output from the Novartis Safety Database. Where discrepancies are identified the Lead PI shall send/resend the information to Novartis DS&E as per the contact information in and using the supplied Novartis cover sheet.

Novartis U.S. Drug Safety and Epidemiology (DS&E) contact information for forwarding individual safety reports

- All reports of SAEs, drug exposure during pregnancy, study drug abuse or misuse Any Adverse Drug Reactions to Novartis products should be sent to U.S. DS&E at fax#: **877-778-9739**
- The Novartis Coversheets must be attached to all SAE submissions
- SAE Submissions must reference the Novartis Study Code.
- Should the designated SAE Fax# be non-functional please send SAEs to the designated SAE mailbox: clinicalsafetyop.phuseh@novartis.com)

The Lead PI shall provide the Novartis Medical contact listed in Novartis Annex with a written confirmation that the reconciliation was performed, the outcome of the reconciliation and documentation that, where discrepancies were identified, Novartis DS&E was informed (e.g. delivery confirmations).

6.6 GUIDELINES & PROCEDURES FOR REPORTING 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 NCI, Center

for Cancer Research is the Coordinating Center and the Lead 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 **6.1**.

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 BTTC Coordinating Center within 5 business calendar days 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 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 BTTC Coordinating Center's Research Nurse, via fax 301-451-4432, or email using the problem report form in Appendix **13.6**

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

6.7 DATA AND SAFETY MONITORING PLAN

6.7.1 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.

6.7.2 BTTC Coordinating Center Monitoring Plan

As the CCR is the coordinating center for this multi-site study, the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary study endpoints; adherence to the protocol, regulations, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

The monitoring program also extends to multi-site research when the CCR is the coordinating center.

This trial will be monitored by personnel employed by an NCI contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

6.7.3 Safety Monitoring Committee (SMC)

This protocol will require oversight from the Safety Monitoring Committee (SMC). Initial review will occur as soon as possible after the annual NCI-IRB continuing review date. Subsequently, each protocol will be reviewed as close to annually as the quarterly meeting schedule permits or more frequently as may be required by the SMC. For initial and subsequent reviews, protocols will not be reviewed if there is no accrual within the review period. Written outcome letters will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

7.0 STATISTICAL CONSIDERATIONS

7.1 PHASE I COMPONENT

A Phase I design will be used where up to 6 patients will be treated at each dose combination. For each dose combination, three patients will be treated. If none show a DLT as defined in section **3.1.3**, then the dose will be escalated for the next cohort of patients. If 2 or 3 have a DLT, then the previous dose (as defined in the cohort sequence above) is the maximum tolerated dose (MTD). If 1 of 3 patients has a DLT, then an additional 3 patients will be added to this dose. If 1 of 6 has a DLT, then the dose will be escalated. If 2 or more of 6 have a DLT, then the previous dose will be the MTD given that 6 patients have been treated in that dose. This 3+3 design has a 91% chance (70%, 17%) of dose escalating when the true toxicity rate for that dose is 10% (30%, 50%). It is expected that up to 6 dose combination will be observed, so that the expected sample size will range from 6 (if unacceptable toxicities are seen at the lowest doses) to 36 (if 6 patients per cohort are required for all 6 cohorts).

7.2 PHASE II COMPONENT

Time to progression and overall survival will be evaluated using the Kaplan-Meier product-limit survival curve methodology. Six-month Progression Free Survival (PFS) will be estimated using Kaplan-Meier estimates and associated two-sided 95% confidence intervals.

- **Group A: Recurrent glioblastoma with <u>no</u> prior exposure to bevacizumab cohort:** A maximum of 34 patients will be observed in a two-stage Simon optimum design. In the first stage, 9 patients will be accrued. If two or more patients are progression-free at 6 months (PFS6), an additional 25 patients will be accrued. We halt registering patients after 9 patients until we have at least 2 patients are progression free at six months. If 9 or more out of 34 have PFS6, then the study will be declared

promising. This study has a 5% chance of declaring promise if the PFS6 rate is at most 15%. It has an 80% chance of declaring promise if the PFS rate is at least 35%.

- **Group B: Recurrent glioblastoma with prior exposure to bevacizumab cohort:** In the group that failed bevacizumab, a maximum of 32 patients will be observed in a two-stage Simon optimum design. In the first stage, 14 patients will be accrued. If one or more patients is progression-free at 3 months (PFS3), an additional 18 patients will be accrued. We will halt registration after 14 patients until at least 1 patient is progression free at 3-months. If 2 or more out of 32 have PFS3, then the study will be declared promising. This study has a 5% chance of declaring promise if the PFS3 rate is at most 1%. It has an 80% chance of declaring promise if the PFS rate is at least 12%.
- **Group C:** A third cohort consisting of 16 patients with **anaplastic glioma** (as defined in section **2.1.1.1**) will enroll independently but will not be included in the primary endpoint assessment.

The Phase II Multicenter component of the trial will be monitored by the Study Chair, Jeffrey Raizer, MD, and the study statistician, Yuan Ying PhD, as described below.

At phase II, we will monitor the toxicity based on the combined data from the above three cohorts with a total sample size of 82. All grade 3 or greater toxicities attributable to the study treatment in the first 28-day cycle will be counted. Accrual will be temporarily suspended for analysis after each of the following interim accrual goals. We will monitor the toxicity when the accrual is 5, 10, 20, 35, 50 and 65 based on using the following stopping rule: if the posterior probability of toxicity greater than 0.3 is greater than 0.95 (i.e., Pr(toxicity>0.3|data) >0.95), we terminate the study for toxicity. Assuming the beta prior Beta(0.6, 1.4) for the toxicity, we have the following operating characteristics.

Operating characteristics of the proposed stopping rule

True toxicity probability	0.2	0.3	0.4	0.5
Stopping Probability	1.4%	14.1%	64.6%	97.2%
Average number of patients treated	82	74.9	49.9	24.9

We obtain the following stopping boundary: the study will be terminated if we observe >= 4/5, 6/10, 10/20, 16/35, 21/50, 26/65 (# of patients experienced DLTs/# of patients treated). Note that our safety monitoring starts with a small cohort size of 5, and then gradually increases to 15. Therefore, if the treatment agents are overly toxic, the trial will stop before exposing many patients to toxicities.

Patient-reported outcomes: 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.

8.0 COLLABORATIVE AGREEMENTS

8.1 AGREEMENT TYPE

There is a BTTC consortium agreement in place between all of the participating institutions listed on the title page of this study. There is a CDA in place (CDA #13471-17). In addition, there is an executed CRADA agreement with Novartis (#03235) and an executed CRADA with Bayer (#03195) who support this study.

9.0 HUMAN SUBJECTS PROTECTIONS

9.1 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. High grade gliomas occur in patients of all races and although there is a slight predominance in men, this is a disease that is also common in women. The molecular targets of the everolimus and sorafenib 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.

9.2 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 the everolimus and sorafenib are not as prevalent in pediatric malignant gliomas and therefore, the efficacy of this regimen will be initially determined in the adult population before consideration of its use in pediatrics.

9.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT (NCI)

For adults who are or may be unable to consent: All research protocols should state whether adults who are unable to provide initial informed consent are excluded or are eligible to enroll, and the conditions, if any, under which adults who lose the ability to provide on-going consent subsequent to giving initial consent, may continue to participate.

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **9.6.3**), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MAS Policy 87-4 f and NIH HRPP SOP 14E or appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

9.4 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT (BTTC)

Each institution will follow their own procedure for re-consenting subjects unable to re-consent and will notify the Coordinating Center at time of continuing review of these occurrences. At time of Amendment C, Version 10-04-2017, subjects enrolled at non-NCI sites are off treatment.

9.5 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

The primary risk to patients participating in this research study is from the toxicity of sorafenib, everolimus, or both drugs. Both are investigational agents in the treatment of gliomas, although bevacizumab is an FDA-approved drug for the treatment of colorectal carcinoma. The protocol provides for detailed and careful monitoring of all patients to assess for toxicity. Toxicity data from the current dose level will be collected and reviewed to ensure that there were no severe toxicities that would preclude further patient enrollment. Patients will be treated with therapeutic intent and response to the therapy will be closely monitored.

9.6 RISKS/BENEFITS ANALYSIS

9.6.1 Benefits

The potential benefit to a patient on this study is a reduction in the bulk of their tumor and improvement in cancer lesions, which may or may not have favorable impact on symptoms and/or survival.

9.6.2 Risks

Risks include the possible occurrence of any of a range of side effects which are listed in the Consent Document or this protocol document. Frequent monitoring for adverse effects will help to minimize the risks associated with administration of the study agents.

9.6.3 Risks/Benefits Analysis

The potential benefits from this therapy are disease stabilization or shrinkage and a reduction in symptoms caused by the brain tumor such as neurological deficits and headache. Given the efforts

to minimize risk with the administration of this combination, this protocol involves greater than minimal risk, but presents the potential for direct benefit to individual subjects.

9.7 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

All patients who are being considered for this trial will undergo informed consent prior to being enrolled on the trial. The PI or associate investigator will perform the consenting process. Patients and family members when applicable will be asked to read the consent and will be encouraged to ask questions. It will be stated clearly that participation in the research study is voluntary and that participants can withdraw from the study without losing benefits they would otherwise be entitled to. Patients will be enrolled after the consent document has been signed. Separate consents will be obtained for any surgical procedures performed. The informed consent process will be documented in the patient's medical record and on the informed consent document. This process will be performed by the local Principal Investigator or designee.

If new safety information results in significant changes in the risk/ benefit assessment, the consent form will be reviewed and updated as necessary. All subjects (including those already being treated) will be informed of the new information, be given a copy of the revised form, and be asked give their consent to continue in the study.

9.7.1 Reconsent via phone (at NCI)

The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator.

9.7.2 Informed Consent of non-English speaking subjects (at NCI)

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OHSRP SOP 12, and 45 CFR 46.117 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation (using either the long translated form or the short form). Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process for non-English speaking subjects and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

10.0 PHARMACEUTICAL INFORMATION

There will be no IND obtained for the use of Sorafenib or Everolimus for this study.

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.

10.1 SORAFENIB

10.1.1 Drug Name:

Sorafenib tosylate

10.1.2 Chemical Name:

4-(4-{3-[4-chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-N2-methylpyridine-2-carboxamide-4methylbenzenesulfonate

10.1.3 Molecular Formula:

$C_{21}H_{16}ClF_3N4O_3$ X $C_7H_8O_3S$

10.1.4 Molecular Weight:

637.0

10.1.5 Appearance:

White to yellowish or brownish solid.

10.1.6 How supplied:

Sorafenib tablets are supplied as round, biconvex, red film-coated tablets, debossed with the "Bayer cross" on one side and "200" on the other side, each containing sorafenib tosylate equivalent to 200 mg of sorafenib. Bottles of 120 tablets NDC 50419-488-58.

10.1.7 Formulation:

Red, round, biconvex, film coated tablet. Each tablet contains 274 mg sorafenib tosylate equivalent to 200 mg sorafenib and the inactive ingredients cellulose microcrystalline, croscarmellose sodium, hypromelose, magnesium stearate, and sodium lauryl sulfate. The coating material consists of hypromellose, macrogol (synthetic polyethylene glycol), titanium dioxide, and ferric oxide-red.

10.1.8 Storage and Stability:

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Store in a dry place.

10.1.9 Mechanism of Action:

Sorafenib is a kinase inhibitor that decreases tumor cell proliferation in vitro. Sorafenib was shown to inhibit multiple intracellular (CRAF, BRAF and mutant BRAF) and cell surface kinases (KIT, FLT-3, RET, VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR-ß). Several of these kinases are thought to be involved in tumor cell signaling, angiogenesis, and apoptosis. Sorafenib inhibited tumor growth and angiogenesis of human hepatocellular carcinoma and renal cell carcinoma, and several other human tumor xenografts in immunocompromised mice.

10.1.10 Pharmacology:

After administration of sorafenib-containing tablets, the drug's mean elimination half-life is between 25 and 48 h. Sorafenib reaches peak plasma levels f3 h after oral administration. With a high-fat meal, sorafenib bioavailability was reduced 29% compared with fasting bioavailability. In vitro binding of sorafenib to human plasma proteins is 99.5%. Sorafenib is metabolized primarily in the liver; oxidative metabolism is mediated by CYP3A4, and glucuronidation is mediated by UGT1A9. Sorafenib accounts for 70% to 85% of the circulating analytes in plasma at steady state. Following oral administration of a 100 mg sorafenib dose in a solution formulation, 77% of the dose was excreted in feces, and 19% was excreted in urine as glucuronidated metabolites. Unchanged sorafenib, which accounted for 51% of the dose, was found in feces but not in urine.

Analyses of demographic data suggest that no dose adjustments are necessary based on patient age or gender. No pharmacokinetic data exist for pediatric patients. In patients with mild (Child-Pugh A, n = 14 patients) or moderate (Child-Pugh B, n = 8) hepatic impairment, drug exposure values were within the range observed in patients with no hepatic impairment. Sorafenib's pharmacokinetics has not been studied in patients with severe (Child-Pugh C) hepatic impairment. In four phase 1 clinical trials, sorafenib was evaluated in patients with normal renal function, mild renal impairment (creatinine clearance >50-80 mL/min, n = 24), and moderate renal impairment (creatinine clearance = 30-50 mL/min, n = 4). No relationship was observed between renal function and steady-state sorafenib area under the curve at doses of 400 mg twice daily. The drug's pharmacokinetics has not been studied in patients with severe renal impairment (creatinine clearance <30 mL/min) or in patients undergoing dialysis.

Steady-state dosing of ketoconazole (400 mg), a potent inhibitor of cytochrome P450 3A4 (CYP3A4) did not alter the mean area under the curve of an oral dose of sorafenib. Administration of sorafenib tablets did not alter the exposure of concomitantly given midazolam (CYP3A4 substrate), dextromethorphan (CYP2D6 substrate), or omeprazole (CYP2C19 substrate). The possible effect of sorafenib on the CYP2C9 substrate warfarin was assessed indirectly by measuring the PT-INR. Mean changes from baseline in PT-INR were not higher in patients administered sorafenib tablets compared with patients given a placebo. Although not studied clinically, inducers of CYP3A4 activity are expected to increase metabolism of sorafenib and thus decrease sorafenib concentrations.

Sorafenib tablets have been given with the antineoplastic agent's gemcitabine, oxaliplatin, doxorubicin, and irinotecan. Concomitant treatment with sorafenib resulted in a 21% increase in the area under the curve of doxorubicin. When given with irinotecan, whose active metabolite

SN-38 is further metabolized by the UGT1A1 pathway, sorafenib produced a 67% to 120% increase in the area under the curve of SN-38 and a 26% to 42% increase in the area under the curve of irinotecan. Because sorafenib inhibits CYP2B6 and CYP2C8 in vitro, systemic exposure to substrates of CYP2B6 and CYP2C8 might be expected to increase when co-administered with sorafenib. Similarly, although not studied clinically, sorafenib inhibits glucuronidation by the UGT1A1 and UGT1A9 pathways, and systemic exposure to substrates of UGT1A1 and UGT1A9 may increase when co-administered with sorafenib. CYP1A2 and CYP3A4 activities were not altered after treatment of cultured human hepatocytes with sorafenib, indicating that sorafenib is unlikely to be an inducer of CYP1A2 and CYP3A4 in vivo.

10.1.11 Pre-clinical Toxicology:

Repeat-dose animal toxicology was generally predictive of the toxicities observed in humans as indicated by the clinical adverse events. In the repeat-dose toxicology studies, findings included cirrhotic changes, glomerulopathy and renal tubular dilation, gastrointestinal hemorrhage, adrenal necrosis and hemorrhage, hypothyroidism, pancreatitis, and changes in serum a-amylase. Osteodystrophy of the jaw was noted in rats. Young animals showed incomplete epiphyseal closure, thickening of growth plates, and dentin alteration. Potential cardiotoxicity was evidenced by positive findings in the in vitro hERG and action potential assays and inflammation/congestion/hemorrhage in the heart and increased creatine kinase in the chronic dog toxicity study. Changes in coagulation values were inconclusive. Sorafenib can cross the blood-brain barrier. Based on a safety pharmacology study, sorafenib may cause sensory neuropathy.

Sorafenib is teratogenic. Embryo-fetal toxicities, observed in rats and rabbits, occurred at subtherapeutic exposures and included increased post-implantation loss, fetal malformations, and necrotic placentas. Although fertility and early developmental studies were not conducted, adverse findings in the reproductive organs in the repeat dose toxicity studies suggest that sorafenib has the potential to impair reproductive function and fertility in males and females. Pharmacokinetic studies in rats with radiolabeled sorafenib indicated that sorafenib is excreted into the milk.

10.1.12 Human Toxicity:

Likely (occurring in more than 20% of patients)[*]

Fatigue, rash/desquamation, hand/foot reaction, alopecia, diarrhea, nausea, anorexia, abdominal pain.

Laboratory abnormalities include hypophosphatemia, elevated lipase, elevated amylase, and lymphopenia.

[*]Information obtained from sorafenib package insert

Common (occurring in 3 – 20% of Patients)

Hypertension, weight loss, pruritis, dry skin, vomiting, constipation, hemorrhage (all sites, including gastrointestinal tract and respiratory tract), sensory neuropathy, joint pain, headache, dyspnea, mucositis, stomatitis (including dry mouth and glossodynia), myalgia, depression, renal failure, erectile dysfunction, hoarseness.

Laboratory abnormalities include neutropenia, thrombocytopenia, and transaminase elevation.

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

Hypertensive crisis, myocardial ischemia and/or infarction, congestive heart failure, keratoacanthomas/squamous cell cancer of skin, pancreatitis, gastrointestinal perforation, cerebral hemorrhage, hypersensitivity reactions (including skin reactions and urticaria, and reversible posterior encephalopathy.

The overall safety profile of sorafenib is based on 1286 cancer patients, who received sorafenib as single agent. This table will be used to determine the "expectedness" of ADRs used for reporting of adverse events to Regulatory Agencies from clinical studies. It is not a complete list of adverse events reported in clinical trials.

Adverse Drug Reactions in patients in multiple clinical trials (MedDRA coded)

System Organ Class	Very Common ≥ 10%	Common ≥ 1% to < 10%	Uncommon ≥ 0.1% to < 1%
Infections and infestations			Folliculitis infection
Blood and lymphatic system disorders	Lymphopenia	Leucopenia Neutropenia Anemia Thrombocytopenia	
Immune system disorders			Hypersensitivity reactions (including skin reactions and urticaria)
Endocrine disorders			Hypothyroidism
Metabolism and nutrition disorders	Hypophosphatemia	Anorexia	Hyponatremia Dehydration
Psychiatric disorders		Depression	
Nervous system disorders		Peripheral sensory neuropathy	Reversible posterior leukoencephalopathy*
Ear and labyrinth disorders		Tinnitus	
Cardiac disorders			Myocardial ischemia and infarction* Congestive heart failure*

Vascular disorders	Hemorrhage (including gastrointestinal* and respiratory tract* and cerebral hemorrhage*) Hypertension		Hypertensive crisis*
Respiratory, thoracic and mediastinal disorders		Hoarseness	Rhinorrhea
Gastrointestinal disorders	Diarrhea Nausea Vomiting	Constipation Stomatis (including dry mouth and glossodynea) Dyspepsia Dysphagia	Gastro esophageal reflux disease Pancreatitis Gastritis Gastrointestinal perforation*
Hepato-biliary disorders			Increase in bilirubin and jaundice
Skin and subcutaneous tissue disorders	Rash Alopecia Hand-foot reaction** Pruritis Erythema	Dry skin Dermatitis exfoliative Acne Skin desquamation	Eczema Erythema multiforme minor
Musculoskeletal, connective tissue and bone disorders		Arthralgia Myalgia	
Reproductive system and breast disorders		Erectile dysfunction	Gynaecomastia
General disorders and administration site conditions	Fatigue Pain (inc. mouth, abdominal, bone pain, headache and tumor pain)	Asthenia Fever Influenza-like illness	
Investigations	Increased amylase Increased lipase	Weight decreased Transient increase in transaminases	Transient increase in blood alkaline phosphatase, INR abnormal, prothrombin level abnormal

* Events may have a life-threatening or fatal outcome. Such events are uncommon.

** Palmar plantar erythrodysaethesia syndrome in MedDRA

In combination with cytotoxic agents, myelosuppression leading to febrile neutropenia has also been observed. Such events may have a life-threatening or fatal outcome.

10.1.12.1 Laboratory Abnormalities

The following laboratory abnormalities were observed in the phase III advanced RCC (TARGETS) trial:

Elevated lipase and amylase: Elevated lipase and amylase levels were very commonly reported. CTCAE Grade 3 or 4 lipase elevations occurred in 12% of patients in the sorafenib group compared to 7% of patients in the placebo group. CTCAE Grade 3 or 4 amylase elevations were reported in 1% of patients in the sorafenib group compared to 3% of patients in the placebo group. Clinical pancreatitis was reported in 2 of 451 sorafenib treated patients (CTCAE Grade 4) and 1 of 451 patients (CTCAE Grade 2) in the placebo group.

Hypophosphatemia: Hypophosphataemia was a common laboratory finding, observed in 45% of sorafenib treated patients compared to 12% of placebo patients. CTCAE Grade 3 hypophosphataemia (1–2 mg/dl) occurred in 13% on sorafenib treated patients and 3% of patients in the placebo group. There were no cases of CTCAE Grade 4 hypophosphataemia (< 1 mg/dl) reported in either sorafenib or placebo patients. The etiology of hypophosphataemia associated with sorafenib is not known.

Lymphopenia: CTCAE Grade 3 or 4 were reported for lymphopenia in 13% of sorafenib treated patients and 7% of placebo patients, for neutropenia in 5% of sorafenib treated patients and 2% of placebo patients, for anemia in 2% of sorafenib treated patients and 4% of placebo patients and for thrombocytopenia in 1% of sorafenib treated patients and 0% of placebo.

Anemia: Observed in 44% of sorafenib-treated patients and 49% of placebo patients. CTCAE Grade 3 or 4 anemia was reported in 2% of sorafenib-treated patients and 4% of placebo patients.

Thrombocytopenia: Observed in 12% of sorafenib-treated patients and 5% of placebo patients. CTCAE Grade 3 or 4 thrombocytopenia was reported in 1% of sorafenib-treated patients and 0% of placebo patients.

Special Warnings and Precautions for Use

Sorafenib (Nexavar®) is approved for treatment of patients with advanced renal cancer and unresectable hepatocellular cancer. Because this is a novel agent, current knowledge of the adverse events associated with this compound is limited. As with any new chemical entity, there is always potential for unexpected adverse events.

Pregnancy: Women should avoid becoming pregnant while on therapy.

Women of childbearing potential must be apprised of the potential hazard to the fetus, which includes severe malformation (teratogenicity), failure to thrive and fetal death (embryotoxicity).

Sorafenib should not be used during pregnancy. Prescribers may only consider it to be used, if the potential benefits justify the potential risks to the fetus.

Based on the proposed mechanism of multikinase inhibition and multiple adverse effects seen in animals at exposure levels significantly below the clinical dose, sorafenib should be assumed to cause fetal harm when administered to a pregnant woman.

Breastfeeding should be discontinued during sorafenib therapy.

Dermatological Toxicities: Hand-foot skin reaction (palmar-plantar erythrodysaesthesia) and rash represent the most common adverse drug reactions with sorafenib. Rash and hand-foot skin reaction are usually CTCAE Grade 1 and 2 and generally appear during the first six weeks of treatment with sorafenib. Management of dermatologic toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of sorafenib, or in severe or persistent cases, permanent discontinuation of sorafenib. Patients who take sorafenib should be suggested to avoid long exposure to hot water such as washing dishes, long showers, or tub bath, and to avoid the activities to cause excessive pressure and friction on the soles of the feet or palms of hands such as jogging, aerobics, power walking, jumping, and/or using garden and household tools. Hand-foot syndrome may be treated with topical emollients (such as Aquaphor®), topical/systemic steroids, and/or antihistamine agents. Vitamin B6 (pyridoxine; 500-1250 mg orally each day) may also be used.

Hypertension: An increased incidence of hypertension was observed in sorafenib-treated patients. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was amenable to management with standard antihypertensive therapy. Blood pressure should be monitored regularly and treated, if required, in accordance with standard medical practice. In cases of severe or persistent hypertension, or hypertensive crisis despite adequate antihypertensive therapy, permanent discontinuation of sorafenib should be considered.

Hemorrhage: An increase in the risk of bleeding may occur following sorafenib administration. The incidence of severe bleeding events is uncommon. If any bleeding event necessitates medical intervention, it is recommended that permanent discontinuation of sorafenib should be considered.

Wound healing complications: No formal studies of the effect of sorafenib on wound healing have been conducted. In patients undergoing major surgical procedures, temporary interruption of sorafenib therapy is recommended for precautionary reasons. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume sorafenib therapy following a major surgical intervention should be based on clinical judgment of adequate wound healing.

Cardiac Ischemia and/or Infarction: In the Phase 3 Advanced RCC study (TARGETS), the incidence of treatment-emergent cardiac ischemia/infarction events was higher in the sorafenib group (2.9%) compared with the placebo group (0.4%). Patients with unstable coronary artery disease or recent myocardial infarction were excluded from this study. Temporary or permanent discontinuation of sorafenib should be considered in patients who develop cardiac ischemia and/or infarction.

Gastrointestinal perforation: Gastrointestinal perforation is an uncommon event and has been reported in less than 1% of patients taking sorafenib. In some cases this was not associated with apparent intra-abdominal tumor. Sorafenib therapy should be discontinued in patients with GI perforation.

Effects on ability to drive and use machines: No studies on the effects of sorafenib on the ability to drive or use machines have been performed. There is no evidence that sorafenib affects the ability to drive or operate machinery.

Patients with Hepatic Impairment: *In vitro* and *in vivo* data indicate that sorafenib is primarily metabolized by the liver. Systemic exposure and safety data were comparable in patients with

Child-Pugh A and B hepatic impairment. Sorafenib has not been studied in patients with Child-Pugh C hepatic impairment. No dose adjustment is necessary when administering sorafenib to patients with Child-Pugh A and B hepatic impairment.

Patients with Renal Impairment: Sorafenib has not been studied in patients with severe renal impairment (CrCl <30 mL/min) or in patients undergoing dialysis.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies have not been performed with sorafenib. Sorafenib was clastogenic when tested in an *in vitro* mammalian cell assay (Chinese Hamster Ovary) in the presence of metabolic activation. Sorafenib was not mutagenic in the *in vitro* Ames bacterial cell assay or clastogenic in an *in vivo* mouse micronucleus assay. One intermediate in the manufacturing process, which is also present in the final drug substance (<0.15%), was positive for mutagenesis in an *in vitro* bacterial cell assay (Ames test) when tested independently. No specific studies with sorafenib have been conducted in animals to evaluate the effect on fertility. However, results from the repeat-dose toxicity studies suggest there is a potential for sorafenib to impair reproductive performance and fertility. Multiple adverse effects were observed in male and female reproductive organs, with the rat being more susceptible than mice or dogs. Typical changes in rats consisted of testicular atrophy or degeneration, degeneration of epididymis, prostate, and seminal vesicles, central necrosis of the corpora lutea and arrested follicular development. Sorafenib-related effects on the reproductive organs of rats were manifested at daily oral doses ≥30 mg/m^2 (approximately 0.5 times the AUC in cancer patients at the recommended human dose). Dogs showed tubular degeneration in the testes at 600 mg/m^2/day (approximately 0.3 times the AUC at the recommended human dose) and oligospermia at 1200 mg/m^2/day of sorafenib. Adequate contraception should be used during therapy and for at least 2 weeks after completing therapy.

Pediatric Use: The safety and effectiveness of sorafenib in pediatric patients have not been studied. Repeat dosing of sorafenib to young and growing dogs resulted in irregular thickening of the femoral growth plate at daily sorafenib doses ≥600 mg/m^2 (approximately 0.3 times the AUC at the recommended human dose), hypocellularity of the bone marrow adjoining the growth plate at 200 mg/m^2/day (approximately 0.1 times the AUC at the recommended human dose), and alterations of the dentin composition at 600 mg/m^2/day. Similar effects were not observed in adult dogs when dosed for 4 weeks or less.

Geriatric Use: In total, 32% of RCC patients treated with sorafenib were age 65 years or older, and 4% were 75 and older. No differences in safety or efficacy were observed between older and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10.1.12.2 Interaction with Other Medications

Drug-Drug Interactions: Caution is recommended when administering sorafenib together with compounds that are metabolized/ eliminated predominantly by the UGT1A1 pathway (e.g. irinotecan).

- **CYP3A4 inducers:** There is no clinical information on the effect of CYP3A4 inducers on the pharmacokinetics of sorafenib. Inducers of CYP3A4 activity (e.g. rifampicin, Hypericum perforatum also known as St. John's wort, phenytoin, carbamazepine,

phenobarbital, and dexamethasone) may increase metabolism of sorafenib and thus decrease sorafenib plasma concentrations.

- **CYP3A4 inhibitors:** Ketoconazole, a potent inhibitor of CYP3A4, administered once daily for 7 days to healthy male volunteers did not alter the mean AUC of a single 50 mg dose of sorafenib. Therefore, clinical pharmacokinetic interactions of sorafenib with CYP3A4 inhibitors are unlikely.
- **CYP2C9 substrates:** The possible effect of sorafenib on the metabolism of the CYP2C9 substrate warfarin was assessed indirectly by measuring PTINR. The mean changes from baseline in PT-INR were not higher in sorafenib patients compared to placebo patients, suggesting that sorafenib did not inhibit warfarin metabolism *in vivo*. However, patients taking warfarin should have their INR checked regularly.
- **CYP isoform-selective substrates:** Concomitant administration of midazolam, dextromethorphan and omeprazole, which are substrates of cytochromes CYP3A4, CYP2D6 and CYP2C19, respectively, following 4 weeks of sorafenib administration did not significantly alter the exposure of these agents. This indicates that sorafenib is neither an inhibitor nor a clinically meaningful inducer of these cytochrome P450 isoenzymes.
- **Combination with other anti-neoplastic agents:** In clinical studies, sorafenib has been administered together with a variety of other antineoplastic agents at their commonly used dosing regimens, including gemcitabine, oxaliplatin, doxorubicin, and irinotecan. Sorafenib had no effect on the pharmacokinetics of gemcitabine or oxaliplatin. Concomitant treatment with sorafenib resulted in a 21% increase in the AUC of doxorubicin. When administered with irinotecan, whose active metabolite SN-38 is further metabolized by the UGT1A1 pathway, there was a 67-120% increase in the AUC of SN-38 and a 26-42% increase in the AUC of irinotecan. The clinical significance of these findings is unknown. However, caution is recommended when administering sorafenib with doxorubicin and with compounds that are metabolized/eliminated predominantly by the UGT1A1 pathway (e.g. irinotecan).
- **Warfarin:** Infrequent bleeding events or elevations in the International Normalized Ratio (INR) have been reported in some patients taking warfarin while on sorafenib therapy. Patients taking warfarin concomitantly should be monitored regularly for changes in prothrombin time, INR and for clinical bleeding episodes.

10.1.12.3 Pregnancy and Lactation

Pregnancy: Women should avoid becoming pregnant while on therapy. Women of childbearing potential must be apprised of the potential hazard to the fetus, which includes severe malformation (teratogenicity), failure to thrive and fetal death (embryotoxicity). Sorafenib should not be used during pregnancy. Prescribers may only consider it to be used, if the potential benefits justify the potential risks to the fetus.

- There are no adequate and well-controlled studies in pregnant women using sorafenib. Studies in animals have shown reproductive toxicity including malformations. In rats, sorafenib and its metabolites were demonstrated to cross the placenta and sorafenib is anticipated to inhibit angiogenesis in the fetus.

- Women should avoid becoming pregnant while on therapy. Women of childbearing potential must be apprised of the potential hazard to the fetus, which includes severe malformation (teratogenicity), failure to thrive and fetal death (embryotoxicity).
- Sorafenib should not be used during pregnancy. Prescribers may only consider it to be used, if the potential benefits justify the potential risks to the fetus.
- In animals, sorafenib has been shown to be teratogenic and embryotoxic. Adequate contraception should be used during therapy and for at least 2 weeks after completion of therapy.

Breastfeeding should be discontinued during sorafenib therapy.

- It is not known whether sorafenib is excreted in human milk. In animals, sorafenib and/or its metabolites were excreted in milk. Because many drugs are excreted in human milk and because the effects of sorafenib on infants have not been studied, woman should discontinue breastfeeding during sorafenib treatment.

Effects on fertility: Results from animal studies indicate that sorafenib can impair male and female fertility.

10.1.13 Clinical Pharmacokinetic Properties:

After administration of sorafenib tablets, the mean relative bioavailability is 38-49% when compared to an oral solution. The mean elimination half-life of sorafenib is approximately 25-48 hours. Multiple dosing of sorafenib for 7 days resulted in a 2.5-to 7-fold accumulation compared to single dose administration.

Steady-state plasma sorafenib concentrations are achieved within 7 days, with a peak-to-trough ratio of mean concentrations of less than 2.

10.1.13.1 Absorption and Distribution

Following oral administration, sorafenib reaches peak plasma levels in approximately 3 hours. When given with a moderate-fat meal (30% fat; 700 calories), bioavailability was similar to that in the fasted state. With a high-fat meal (50% fat; 900 calories), sorafenib bioavailability was reduced by 29% compared to administration in the fasted state. It is recommended that sorafenib be administered without food. Mean Cmax and AUC increased less than proportionally beyond doses of 400 mg administered orally twice daily. In vitro binding of sorafenib to human plasma proteins is 99.5%.

10.1.13.2 Metabolism and Elimination

Sorafenib is metabolized primarily in the liver, undergoing oxidative metabolism, mediated by CYP3A4, as well as glucuronidation mediated by UGT1A9. Sorafenib accounts for approximately 70-85% of the circulating analytes in plasma at steady-state. Eight metabolites of sorafenib have been identified, of which five have been detected in plasma. The main circulating metabolite of sorafenib in plasma, the pyridine N-oxide, shows in vitro potency similar to that of sorafenib. This metabolite comprises approximately 9-16% of circulating analytes at steady-state. Following oral administration of a 100 mg dose of a solution formulation of sorafenib, 96% of the dose was recovered within 14 days, with 77% of the dose excreted in feces, and 19% of the dose excreted in urine as glucuronidated metabolites. Unchanged sorafenib, accounting for 51% of the dose, was found in feces but not in urine.

10.1.13.3 Special Populations

Age: Analyses of demographic data suggest that no dose adjustments are necessary for age.

Gender: Analyses of demographic data suggest that no dose adjustments are necessary for gender.

Race: A study of the pharmacokinetics of sorafenib indicated that the mean AUC of sorafenib in Asians (N=78) was 30% lower than in Caucasians (N=40).

Pediatric: There are no pharmacokinetic data in pediatric patients.

Hepatic Impairment: Sorafenib is cleared primarily by the liver. Comparison of data across studies suggests that in HCC patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, 400 mg doses of sorafenib appear to be associated with AUC values that were 23 to 65% lower than those of other subjects without hepatic impairment. The AUC of sorafenib is similar between HCC patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment. The pharmacokinetics of sorafenib have not been studied in patients with severe (Child-Pugh C) hepatic impairment.

Renal Impairment: In a study of drug disposition after a single oral dose of radiolabeled sorafenib to healthy subjects, 19% of the administered dose of sorafenib was excreted in urine. In a clinical pharmacology study, the pharmacokinetics of sorafenib were evaluated following administration of a single 400 mg dose to subjects with normal renal function, and in subjects with mild (CrCl > 50-80 ml/min), moderate (CrCl 30-50 ml/min), or severe (CrCl <30 ml/min) renal impairment, not undergoing dialysis. There was no relationship observed between sorafenib exposure and renal function. No dosage adjustment is necessary based on mild, moderate or severe renal impairment not undergoing dialysis. Monitoring of fluid balance and electrolytes in patients at risk of renal dysfunction is advised.

10.1.14 Administration:

400 mg (2 tablets) orally twice daily without food (at least 1 hour before or 2 hours after a meal).

10.1.15 Supplier:

Bayer Pharmaceuticals

10.1.16 Unused or defective agent:

Refer to the detailed instructions described in Section **10.2.18** Unused or defective drug will be destroyed. Bayer Pharmaceuticals should be notified of this action.

10.2 EVEROLIMUS

10.2.1 Drug Name:

Everolimus

10.2.2 Chemical Name:

(1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18- dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.04,9]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone.

10.2.3 Molecular Formula:

$C_{53}H_{83}NO_{14}$

10.2.4 Molecular Weight:

958.2

10.2.5 Appearance:

- 2.5 mg tablet White to slightly yellow, elongated tablets with a beveled edge and no score, engraved with "LCL" on one side and "NVR" on the other.
- 5 mg tablet - White to slightly yellow, elongated tablets with a beveled edge and no score, engraved with "5" on one side and "NVR" on the other.
- 7.5 mg tablet White to slightly yellow, elongated tablets with a beveled edge and engraved with "7P5" on one side and "NVR" on the other.
- 10 mg tablet - White to slightly yellow, elongated tablets with a beveled edge and no score, engraved with "UHE" on one side and "NVR" on the other.

10.2.6 How supplied:

Each carton contains 4 blister cards of 7 tablets per card, total 28 tablets per carton.

Store everolimus tablets at 25° C (77°F); excursions permitted between 15°–30°C (59°–86°F). [See USP Controlled Room Temperature.] Store in the original container, protect from light and moisture. Keep this and all drugs out of the reach of children. Procedures for proper handling and disposal of anticancer drugs should be considered. Everolimus tablets should not be crushed. Direct contact of crushed tablets with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly. Personnel should avoid exposure to crushed tablets.

10.2.7 Formulation:

Everolimus is supplied as tablets for oral administration containing everolimus together with butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone and lactose anhydrous as inactive ingredients.

10.2.8 Storage and Stability:

Current stability data permits a shelf-life of 36 months at storage conditions below 30°C and maintenance in the original packs.

10.2.9 Mechanism of Action:

Everolimus is an inhibitor of mTOR (mammalian target of rapamycin), a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers. Everolimus binds to an intracellular protein, FKBP-12, resulting in an inhibitory complex formation and inhibition of mTOR kinase activity. Everolimus reduced the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP), downstream effectors of mTOR, involved in protein synthesis. In addition, everolimus inhibited the expression of hypoxia-inducible factor (e.g., HIF-1) and reduced the expression of vascular endothelial growth factor (VEGF). Inhibition of mTOR by everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in in vitro and/or in vivo studies.

10.2.10 Pharmacology:

10.2.10.1 Drug Interactions

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump PgP. In vitro, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

10.2.10.1.1 Agents that may Increase Everolimus Blood Concentrations

CYP3A4 Inhibitors and PgP Inhibitors: In healthy subjects, compared to everolimus treatment alone there were significant increases in everolimus exposure when everolimus was co-administered with:

- ketoconazole (a strong CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 3.9- and 15.0-fold, respectively.
- erythromycin (a moderate CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 2.0- and 4.4-fold, respectively.
- verapamil (a moderate CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 2.3-and 3.5-fold, respectively.

Concomitant strong or moderate inhibitors of CYP3A4 and PgP inhibitors should not be used.

10.2.10.1.2 Agents that may Decrease Everolimus Blood Concentrations

CYP3A4 Inducers: In healthy subjects, co-administration of everolimus with rifampin, a strong inducer of CYP3A4, decreased everolimus AUC and Cmax by 64% and 58% respectively, compared to everolimus treatment alone. Consider a dose increase of everolimus when co-administered with strong inducers of CYP3A4 or PgP if alternative treatment cannot be administered.

Agents whose Plasma Concentrations may be Altered by Everolimus Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between everolimus and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate) and population pharmacokinetic analyses also detected no influence of simvastatin (a CYP3A4 substrate) on the clearance of everolimus.

Patients will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator. At each visit, the investigator will ask the patient about any new medications he/she is or has taken after the start of the study drug.

All Concomitant medications/Significant non-drug therapies taken ≤ 30 days prior to start and after start of study drug, including physical therapy and blood transfusions, should be recorded.

- Growth factors (e.g. G-CSF, GM-CSF, erythropoietin, platelets growth factors etc.) are not to be administered prophylactically but may be prescribed by the investigator for rescue from severe hematologic events, if this is thought to be appropriate.
- Concurrent administration of everolimus and strong CYP3A4 inhibitors (such as ketoconazole, itraconazole, ritonavir) and inducers (such as rifampin, rifabutin) should be

avoided. Provided there is no alternative treatment available, patients should be closely monitored for potential toxicities.

- Concurrent administration of everolimus and moderate CYP3A4 inhibitors (such as erythromycin, fluconazole, calcium channel blockers, benzodiazepines) and moderate CYP3A4 inducers (e.g. carbamazepine, phenobarbital) should also be avoided if possible, or used subject to caution (e.g. increased frequency of safety monitoring, temporary interruption of everolimus).
- Competitive inhibition could occur when everolimus is combined with drugs which are also CYP3A4 substrates. Therefore caution should be exercised in such cases.
- Co-administration with substrates, inducers, or inhibitors of P-glycoprotein should be avoided, if possible, or used subject to caution (e.g. increased frequency of safety monitoring, temporary interruption of everolimus).
- Grapefruit and grapefruit juice affect cytochrome P450 and P-glycoprotein activity and should therefore be avoided.
- In addition, patients should avoid Seville oranges and star fruit, as well as the juice of these fruits, which are potent CYP3A4-inhibitors.
- No chronic treatment with immunosuppressive agents. Topical or inhaled corticosteroids are allowed.
- Everolimus may affect the response to vaccinations making the response to the vaccination less effective. Live vaccines should be avoided while a patient is treated with everolimus.

Oral anticoagulants such as warfarin are CYP2C9 substrates and, as such, no interaction with everolimus is expected. However, drug-drug interaction studies between macrolide antibiotics and warfarin have produced mixed outcomes and the disparity in these findings has led to the conclusion that multiple factors may alter the clearance of warfarin. The co-administration of everolimus and oral anticoagulants is possible but should be subject to verification of coagulation (INR) once steady state is reached (after one week's treatment).

Examples are provided in **Table 3-3**. A comprehensive list of cytochrome P450 isoenzymes and CYP3A4 inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/flockhart. This website is continually revised and should be checked frequently for updates.

10.2.11 Pre-clinical Toxicology:

In safety pharmacology studies, Everolimus was devoid of relevant effects on vital functions including the cardiovascular, respiratory and nervous systems. Everolimus had no influence on QT interval prolongation. Furthermore, everolimus showed no antigenic potential. Although everolimus passes the blood-brain barrier, there was no indication of relevant changes in the behavior of rodents, even after single oral doses up to 2000mg/kg or after repeated administration at up to 40 mg/kg/day. Based on these findings, the potential of everolimus to affect vital functions in patients is considered to be low. Everolimus is considered to have no genotoxicity or carcinogenicity potential. All significant adverse events observed in preclinical toxicology studies with everolimus in mice, rats, monkeys and minipigs were consistent with its anticipated pharmacologic action as an antiproliferative and immunosuppressant and at least in part reversible after a 2- or 4-week recovery period with the exception of the changes in male reproductive organs,

most notably testes. Ocular effects (lenticular disorders) observed in rats were not observed in any other species and are considered to be a species-specific disorder.

10.2.12 Human Toxicity:

Hypersensitivity to the active substance, to other rapamycin derivatives, or to any of the excipients. Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain, or angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus and other rapamycin derivatives.

WARNINGS AND PRECAUTIONS

10.2.12.1 Non-infectious Pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including everolimus. In the randomized study, non-infectious pneumonitis was reported in 14% of patients treated with everolimus. The incidence of CTCAE grade 3 and 4 non-infectious pneumonitis was 4% and 0%, respectively. Fatal outcomes have been observed.

Consider a diagnosis of non-infectious pneumonitis in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, or dyspnea, and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations. Advise patients to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue everolimus therapy without dose alteration. If symptoms are moderate, consider interrupting therapy until symptoms improve. The use of corticosteroids may be indicated. Everolimus may be reintroduced at 5 mg daily.

For cases where symptoms of non-infectious pneumonitis are severe, discontinue everolimus therapy and the use of corticosteroids may be indicated until clinical symptoms resolve. Therapy with everolimus may be re-initiated at a reduced dose of 5 mg daily depending on the individual clinical circumstances.

10.2.12.2 Infections

Everolimus has immunosuppressive properties and may predispose patients to infections, especially infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections and invasive fungal infections, such as aspergillosis or candidiasis, have occurred in patients taking everolimus. Some of these infections have been severe (e.g., leading to respiratory failure) or fatal. Physicians and patients should be aware of the increased risk of infection with everolimus, be vigilant for signs and symptoms of infection and institute appropriate treatment promptly. Complete treatment of pre-existing invasive fungal infections prior to starting treatment with everolimus. If a diagnosis of invasive systemic fungal infection is made, discontinue everolimus and treat with appropriate antifungal therapy.

Reactivation of Hepatitis B (HBV) has been observed in patients with cancer receiving chemotherapy. Sporadic cases of Hepatitis B reactivation have also been seen in this setting with everolimus. Use of antivirals during anti-cancer therapy has been shown to reduce the risk of Hepatitis B virus reactivation and associated morbidity and mortality. A detailed assessment of Hepatitis B/C medical history and risk factors must be done for all patients at screening, with testing performed prior to the first dose of everolimus.

10.2.12.3 Oral Ulceration

Mouth ulcers, stomatitis, and oral mucositis have occurred in patients treated with everolimus. In the randomized study, approximately 44% of everolimus treated patients developed mouth ulcers, stomatitis, or oral mucositis, which were mostly CTCAE grade 1 and 2. In such cases, topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed.

10.2.12.4 Renal Function

Elevations of serum creatinine, usually mild, have been reported in clinical trials. Monitoring of renal function, including measurement of blood urea nitrogen (BUN) or serum creatinine, is recommended prior to the start of everolimus therapy and periodically thereafter.

10.2.12.5 Blood Glucose and Lipids

Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported in clinical trials. Monitoring of fasting serum glucose and lipid profile is recommended prior to the start of everolimus therapy and periodically thereafter. When possible, optimal glucose and lipid control should be achieved before starting a patient on everolimus.

10.2.12.6 Hematological Parameters

Decreased hemoglobin, lymphocytes, neutrophils, and platelets have been reported in clinical trials. Monitoring of complete blood count is recommended prior to the start of everolimus therapy and periodically thereafter.

10.2.12.7 CYP3A4 Interactions

Due to significant increases in exposure of everolimus, co-administration with strong or moderate inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, amprenavir, indinavir, nelfinavir, delavirdine, fosamprenavir, voriconazole, aprepitant, erythromycin, fluconazole, grapefruit juice, verapamil or diltazem) or P-glycoprotein (PgP) should be avoided.

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump PgP. In vitro, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

10.2.12.7.1 Agents that may Increase Everolimus Blood Concentrations CYP3A4 Inhibitors and PgP Inhibitors:

In healthy subjects, compared to everolimus treatment alone there were significant increases in everolimus exposure when everolimus was coadministered with:

- ketoconazole (a strong CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 3.9- and 15.0-fold, respectively.
- erythromycin (a moderate CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 2.0- and 4.4-fold, respectively.
- verapamil (a moderate CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 2.3-and 3.5-fold, respectively.

Concomitant strong or moderate inhibitors of CYP3A4 and PgP inhibitors should not be used.

10.2.12.7.2 Agents that may Decrease Everolimus Blood Concentrations CYP3A4 Inducers:

In healthy subjects, co-administration of everolimus with rifampin, a strong inducer of CYP3A4, decreased everolimus AUC and Cmax by 64% and 58% respectively, compared to everolimus treatment alone. Consider a dose increase of everolimus when co-administered with strong inducers of CYP3A4 or PgP if alternative treatment cannot be administered.

10.2.12.7.3 Agents whose Plasma Concentrations may be Altered by Everolimus

Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between everolimus and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate) and population pharmacokinetic analyses also detected no influence of simvastatin (a CYP3A4 substrate) on the clearance of everolimus.

10.2.12.8 Adverse Reactions

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to everolimus (n=274) and placebo (n=137) in a randomized, controlled trial in patients with metastatic renal cell carcinoma who received prior treatment with sunitinib and/or sorafenib. The median age of patients was 61 years (range 27-85), 88% were Caucasian, and 78% were male. The median duration of blinded study treatment was 141 days (range 19-451) for patients receiving everolimus and 60 days (range 21-295) for those receiving placebo.

The most common adverse reactions (incidence ≥30%) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common grade 3/4 adverse reactions (incidence ≥3%) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common laboratory abnormalities (incidence ≥50%) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common grade 3/4 laboratory abnormalities (incidence ≥3%) were lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia. Deaths due to acute respiratory failure (0.7%), infection (0.7%) and acute renal failure (0.4%) were observed on the everolimus arm but none on the placebo arm. The rates of treatment-emergent adverse events (irrespective of causality) resulting in permanent discontinuation were 14% and 3% for the everolimus and placebo treatment groups, respectively. The most common adverse reactions (irrespective of causality) leading to treatment discontinuation were pneumonitis and dyspnea.

Infections, stomatitis, and pneumonitis were the most common reasons for treatment delay or dose reduction. The most common medical interventions required during everolimus treatment were for infections, anemia, and stomatitis.

Likely (occurring in more than 20% of patients)

Adverse events most frequently observed with everolimus are rash, stomatitis/oral mucositis, fatigue, anorexia, nausea, diarrhea, peripheral edema, asthenia, cough, dyspnea, ocular toxicity and infections. Infections include nasopharyngitis (6%), pneumonia (6%), urinary tract infection (5%), bronchitis (4%), sinusitis (3%), aspergillosis (<1%), candidiasis (<1%), and sepsis (<1%).

Laboratory abnormalities include anemia, neutropenia, thrombocytopenia, lymphopenia, hypercholesterolemia, and/or hypertriglyceridemia, hyperglycemia, hypophosphatemia, aspartate and alanine transaminase elevation. The majority of these AEs have been of mild to moderate severity (CTCAE grade 1-2).

Common (occurring in 3 – 20% of Patients)

Adverse events occurring in 3-20% of patients include vomiting, pyrexia, mucosal inflammation, epistaxis, pneumonitis (includes pneumonitis, interstitial lung disease, lung infiltration,, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis), pruritus, dry skin, headache, dysgeusia, pain in extremity, abdominal pain, dry mouth, hemorrhoids, dysphagia, chest pain, chills, pleural effusion, pharyngolaryngeal pain, rhinorrhea, hand-foot syndrome, nail disorder, erythema, onychoclasis, skin lesion, acneiform dermatitis, insomnia, dizziness, paresthesia, eyelid edema, hypertension, renal failure, tachycardia, jaw pain, and hemorrhage.

Laboratory abnormalities include increased bilirubin (<1% grade 3 or 4).

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

Acute respiratory failure and acute renal failure.

10.2.12.9 Pregnancy and Breast Feeding

There are no adequate and well-controlled studies of everolimus in pregnant women. However, based on mechanism of action, everolimus may cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures at the recommended dose of 10 mg daily. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use highly effective methods of contraception while receiving everolimus and for up to 8 weeks after ending treatment.

In animal reproductive studies, oral administration of everolimus to female rats before mating and through organogenesis induced embryo-fetal toxicities, including increased resorption, pre-implantation and post-implantation loss, decreased numbers of live fetuses, malformation (e.g., sternal cleft) and retarded skeletal development. These effects occurred in the absence of maternal toxicities. Embryo-fetal toxicities occurred at approximately 4% the exposure (AUC0-24h) in patients receiving the recommended dose of 10 mg daily. In rabbits, embryotoxicity evident as an increase in resorptions occurred at an oral dose approximately 1.6 times the recommended human dose on a body surface area basis. The effect in rabbits occurred in the presence of maternal toxicities.

In a pre- and post-natal development study in rats, animals were dosed from implantation through lactation. At approximately 10% of the recommended human dose based on body surface area, there were no adverse effects on delivery and lactation and there were no signs of maternal toxicity. However, there was reduced body weight (up to 9% reduction from the control) and slight reduction in survival in offspring (~5% died or missing). There were no drug-related effects on the developmental parameters (morphological development, motor activity, learning, or fertility assessment) in the offspring.

Doses that resulted in embryo-fetal toxicities in rats and rabbits were ≥0.1 mg/kg (0.6 mg/m2) and 0.8 mg/kg (9.6 mg/m2), respectively. The dose in the pre- and post-natal development study in rats that caused reduction in body weights and survival of offspring was 0.1 mg/kg (0.6 mg/m2).

10.2.12.10 Nursing Mothers

It is not known whether everolimus is excreted in human milk. Everolimus and/or its metabolites passed into the milk of lactating rats at a concentration 3.5 times higher than in maternal serum. Therefore, women who are taking everolimus should not breastfeed during treatment and for 2 weeks after the last dose.

10.2.13 Clinical Pharmacokinetic Properties:

Absorption

In patients with advanced solid tumors, peak everolimus concentrations are reached 1 to 2 hours after administration of oral doses ranging from 5 mg to 70 mg. Following single doses, Cmax is dose-proportional between 5 mg and 10 mg. At doses of 20 mg and higher, the increase in Cmax is less than dose-proportional, however AUC shows dose-proportionality over the 5 mg to 70 mg dose range. Steady-state was achieved within two weeks following once-daily dosing. Food effect: Based on data in healthy subjects taking 10 mg everolimus tablets, a high-fat meal reduced Cmax and AUC by 54% and 22%, respectively.

Distribution

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5000 ng/mL, is 17% to 73%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given everolimus 10 mg/day. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment.

Metabolism

Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, everolimus is the main circulating component in human blood. Six main metabolites of everolimus have been detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus. These metabolites were also identified in animal species used in toxicity studies, and showed approximately 100-times less activity than everolimus itself. In vitro, everolimus competitively inhibited the metabolism of CYP3A4 and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan. The mean steady state Cmax following an oral dose of 10 mg daily is more than 12-fold below the Ki-values of the in vitro inhibition. Therefore, an effect of everolimus on the metabolism of CYP3A4 and CYP2D6 substrates is unlikely.

Excretion

No specific excretion studies have been undertaken in cancer patients. Following the administration of a 3 mg single dose of radiolabelled everolimus in patients who were receiving cyclosporine, 80% of the radioactivity was recovered from the feces, while 5% was excreted in the urine. The parent substance was not detected in urine or feces. The mean elimination half-life of everolimus is approximately 30 hours.

Patients with Renal Impairment

Approximately 5% of total radioactivity was excreted in the urine following a 3 mg dose of [14C]-labeled everolimus. In a population pharmacokinetic analysis which included 170 patients with advanced cancer, no significant influence of creatinine clearance (25 – 178 mL/min) was detected on oral clearance (CL/F) of everolimus.

Patients with Hepatic Impairment

The average AUC of everolimus in eight subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in eight subjects with normal hepatic function. AUC was positively correlated with serum bilirubin concentration and with prolongation of prothrombin time and negatively correlated with serum albumin concentration. A dose reduction for patients with Child-Pugh class B hepatic impairment is recommended. Everolimus should not be used in patients with severe (Child-Pugh class C) hepatic impairment as the impact of severe hepatic impairment on everolimus exposure has not been assessed.

Effects of Age and Gender

In a population pharmacokinetic evaluation in cancer patients, no relationship was apparent between oral clearance and patient age or gender.

Ethnicity

Based on a cross-study comparison, Japanese patients (n = 6) had on average exposures that were higher than non-Japanese patients receiving the same dose. Based on analysis of population pharmacokinetics, oral clearance (CL/F) is on average 20% higher in Black patients than in Caucasians. The significance of these differences on the safety and efficacy of everolimus in Japanese or Black patients has not been established.

10.2.14 Administration:

Everolimus should be taken whole by mouth with a full glass of water as instructed by the investigator. Everolimus should be taken by the patient in a fasting state or with no more than a light fat-free meal. Patients should take their tablets at the same time of the day and at the same time in relation to meals. Patients should avoid eating grapefruit and/or grapefruit juice for the entire duration of the study. All patients should be instructed to contact the investigator if he/she is unable to take the study drug as prescribed for any reason.

10.2.15 **Supplier**: Novartis

10.2.16 Unused or defective agent: Refer to the detailed instructions described in Section **10.2.18.2** below.

10.2.17 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 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.

10.2.17.1 BTTC Procedures for Agent Accountability and Storage

- Each investigational agent should be stored separately by protocol. If an agent is used for more than one protocol, there should be separate physical storage for each protocol. Remember that agents are provided and accounted for on a protocol-by-protocol basis.
- Each agent should be accounted for separately by protocol. If an agent is used for more than one protocol, there should be a separate Drug Accountability Record Form (DARF) for each protocol, http://ctep.cancer.gov/forms/index.html. There should be a separate DARF for each agent in a multi-agent protocol.
- Separate accountability forms should be maintained for each different strength or dosage form of a particular agent (e.g., an agent with a 1-mg vial and a 5-mg vial would require a different DARF for the 1-mg vial than for the 5-mg vial).
- The DARF has been designed for use at each location where agents are stored, e.g., main pharmacy, satellite pharmacy, physician's office, or other dispensing areas.
- The DARF is also designed to accommodate both dispensing records and other agent transaction documentation (e.g., receipt of agent, returns, broken vials, etc.). A copy of the DARF may be found at http://ctep.cancer.gov/forms/index.html.
- Unauthorized inter-institutional transfer of BTTC investigational agents from one **participating** institution to another is not permitted. For some protocols the **lead** institution may enter into contractual agreements to forward agents to participating institutions (see BTTC Operations Manual).

Verification of Compliance

Investigators are reminded that compliance with procedures to ensure proper agent usage will be reviewed during site visits conducted under the monitoring program. Specifically, site visitors will check that the agent accountability system is being maintained, and will spot-check the agent accountability records by comparing them with the patients' medical records to verify that the agents were administered to a patient entered in the recorded protocol

10.2.18 Returning or destroying unused and/or defective Agent:

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). Investigators/Designees must return unused supplied agent as directed in the protocol when:

- The agent is no longer required because the study is completed.
- Agent is outdated. Investigators/designees should only return outdated agents with a firm expiration date or if they have received written notification that an agent has expired and should be returned.
- The agent is damaged or unfit for use. Investigators/designees should contact the supplier prior to returning investigational agents because of stability concerns, (e.g. loss of refrigeration or exposure to elevated temperatures). Do **NOT** return broken vials. Broken vials should be destroyed at the clinical site. Follow the appropriate agent accountability guidelines.

General Guidelines

- Regulations require that all agents received be returned to the supplier for accountability and disposition.
- Return only unused vials/bottles. Do **NOT** return opened or partially used vials/bottles unless specifically requested otherwise in the protocol.
- Return only supplied agents. Do **NOT** ship agents received from other sources to the supplier.

10.2.18.1 Sorafenib Return Procedure

All unused and returned sorafenib may be destroyed on site. The site must follow their local drug destruction policy and procedure. A copy of the drug destruction record must be submitted to Bayer Pharmaceuticals using the Bayer form provided (attached as a separate form).

Contact: **Amanda Rozner**

Bayer Healthcare, US Medical Affairs
Investigator Sponsored Studies & Medical Education
100 Bayer Boulevard, P.O. Box 915
Bldg 200, 4th Floor
Whippany, NJ 07981-0915
Phone: 1-862-404-5842
Email: amanda.rozner@bayer.com

10.2.18.2 Everolimus Return Procedure

All unused and returned everolimus may be destroyed on site. The site must follow their local drug destruction policy and procedure. A copy of the drug destruction record must be submitted to Novartis.

Contact: **Krystal Saintil**
Novartis Pharmaceuticals Corporation
USEH
One Health Plaza
Building 345
East Hanover, NJ 07936-1080
USA

Phone: +1 862778 7169
Email: krystal.saintil@novartis.com

10.2.18.3 Handling of study medication: Pharmacists should use appropriate precautions in handling and disposal of hazardous agents.

10.2.18.4 Notice of Defect or Non-Conformity:

The Sponsor (NCI) shall ensure that any notice of defect or non-conformity is sent to Novartis within ten (10) days from receipt of Study Drug. The failure to provide such notice shall be deemed an acceptance of Study Drug by the Sponsor or its Subcontractors. Latent defects which are detected later shall be immediately reported to Novartis for further processing within Novartis.

11.0 MULTICENTER PROCEDURES

11.1 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.

11.2 PRINCIPAL INVESTIGATORS

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).

11.3 PROCEDURES FOR SITE REGISTRATION

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

- Submit all required regulatory documents to the BTTC Coordinating Center 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

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.

11.4 INSTITUTIONAL REVIEW

Each cooperating center will submit the protocol to its own IRB. Documentation of the IRB approval will be forwarded to the BTTC Coordinating 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.

11.5 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.

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13.0 APPENDICES

13.1 APPENDIX: KARNOFSKY PERFORMANCE STATUS 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
☐	B	Baseline

13.2 APPENDIX: EIAEDS AND NON-EIAEDS

EIAED

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

Non-EIAEDs:

Valproic acid	(Depakote, Depakene)
Gabapentin	(Neurontin)
Lamotrigine	(Lamictil)
Topriamate	(Topamax)
Tiagabine	(Gabatril)
Zonisamide	(Zonegran)
Levatriacetam	(Keppra)
Clonazepam	(Klonopin)
Clonozam	(Frisium)

13.3 APPENDIX: DRUGS KNOWN TO BE METABOLIZED BY CYP450 ISOENZYMES 2D6 AND 3A4

CYP3A3/4	
Substrates	
Acetaminophen	Chlorpromazine
Aifentanil	Cimetidine
Alosetron	Cisapride
Alprazolam	Citałopram
Amiodarone	Clarithromycin
Amitriptyline (minor)	Clindamycin
Amlodipine	Clomipramine
Anastrozole	Clonazepam
Androsterone	Clozapine
Antipyrine	Cocaine
Astemizole	Codeine (demethylation)
Atorvastatin	Cortisol
Benzphetamine	Cortisone
Bepridil	Cyclobenzaprine (demethylation)
Bexarotene	Cyclophosphamide
Bromazepam	Cyclosporine
Bromocriptine	Dapsone
Budesonide	Dehydroepiandrostendione
Bupropion (minor)	Delavirdine
Buspirone	Desmethyldiazepam
Busutfan	Dexamethasone
Caffeine	Dextromethorphan (minor, N-demethylation)
Cannabinoids	Diazepam (minor; hydroxylation, N-demethylation)
Carbamazepine	Nefazodone
Cevimeline	Nelfinavir
Cerivastatin	Nevirapine
Digitoxin	Nicardipine
Diltiazem	Nifedipine
Disopyramide	Niludipine
Docetaxel	Nimodipine
Dolasetron	Nisoldipine
Donepezil	Nitrendipine
Doxorubicin	Omeprazole (sulfonation)
Doxycycline	Ondansetron
Dronabinol	Oral contraceptives
Enalapril	Orphenadrine
Erythromycin	Paclitaxel
Estradiol	Pantoprazole
Ethinyl estradiol	Pimozide
Ethosuximide	Pioglitazone
Etoposide	Pravastatin
Exemestene	
Dofetilide (minor)	

Felodipine	Prednisone
Fentanyl	Progesterone
Fexotenadine	Proguanil
Finaxteride	Propafenone
Fluoxetine	Quercetin
Flutamide	Quetiapine
Glyburide	Quinidine
Granisetron	Quinine
Halofantrine	Repaglinide
Hydrocortixone	Retinoic acid
Hydroxyarginine	Rifampin
lfosfamide	Risperidone
lmipramine	Ritonavir
lndinavir	Salmeterol
lsradipine	Saquinavir
ltraconazole	Sertindole
Ketoconazole	Sertraline
Lansoprazole (minor)	Sibutramine
Letrozole	Sildenafil citrate
Levobupivicaine	Simvastatin
Lidocaine	Sirolimus
Loratadine	Sufentanil
Losartan	Tacrolimus
Lovastatin	Tamoxifen
Methadone	Temazepam
Mibefradil	Teniposide
Miconazole	Terfenadine
Midazolam	Testosterone
Mifepristone	Tetrahydrocannabinol
Mirtazapine (N-demethylation)	Theophylline
Montelukast	Tiagabine
Navelbine	Tolterodine
Toremifene	Vincristine
Trazodone	Warfarin (R-warfarin)
Tretinoin	Yohimbine
Triazolam	Zaleplon (minor pathway)
Troglitazone	Zatoestron
Troleandomycin	Zileuton
Venlafaxine (N-demethylation)	Ziprasidone
Verapamil	Zolpidem
Vinblastine	Zonisamide
Inducers	
Carbamazepine	Phenytoin
Dexamethasone	Primidone
Ethosuximide	Progesterone

Glucocorticoids Griseofulvin Nafcillin Nelfinavir Nevirapine Oxcarbazepine Phenobarbital Phenylbutazone	Rifabutin Rifampin Rofecoxib (mild) St John's wort Sulfadimidine Sulfinpyrazone Troglitazone
Inhibitors	
Amiodarone Anastrozole Azithromycin Cannabinoids Cimetidine Clarithromycin Clotrimazole Cyclosporine Danazol Delavirdine Dexamethasone Diethyldithiocarbamate Diltiazem Dirithromycin Disulfiram Entacapone (high dose) Erythromycin Ethinyl estradiol Fluconazole (weak) Fluoxetine Fluvoxamine Gestodene Grapefruit juice lndinavir lsoniazid ltraconazole	Ketoconazole Metronidazole Mibefradil Miconazole (moderate) Nefazodone Nelfinavir Nevirapine Norfloxacin Norfluoxetine Omeprazole (weak) Oxiconazole Paroxetine (weak) Propoxyphene Quinidine Quinine Quinupristin and dalfopristin Ranitidine Ritonavir Saquinavir Sertindole Sertraline Troglitazone Troleandomycin Valproic acid (weak) Verapamil Zafirlukast Zileuton

(Adapted from Cytochrome P-450 Enzymes and Drug metabolism. In : Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 8th ed. Hudson, OH; LexiComp Inc. 2000: 1364-1371)

Table 13-1: Examples of clinically relevant drug interaction: substrates, inducers and inhibitors of isoenzyme CYP3A.

Substrates (competitive inhibition)	

Antibiotics[1]: clarithromycin* erythromycin telithromycin* Anti-arrhythmics: quinidine Benzodiazepines: alprazolam diazepam midazolam triazolam Immune Modulators: cyclosporine tacrolimus (FK506) HIV Protease Inhibitors: indinavir* ritonavir* saquinavir* Prokinetic: cisapride Antihistamines: astemizole chlorpheniramine90	Calcium Channel Blockers: amlodipine diltiazem felodipine nifedipine nisoldipine nitrendipine verapamil HMG CoA Reductase Inhibitors[2]: atorvastatin cerivastatin lovastatin simvastatin Miscellaneous: aprepitant buspirone haloperidol methadone pimozide quinine sildenafil tamoxifen trazodone vincristine
Inducers	
Carbamazepine Phenobarbital Phenytoin* Rifabutin*	Rifampin* St John's wort Troglitazone
Inhibitors	
Amiodarone Cimetidine Clarithromycin Delaviridine Diltiazem Erythromycin Fluvoxamine* Grapefruit juice Sevilla orange	Indinavir Itraconazole* Ketoconazole* Voriconazole* Posaconazole* Mibefradil Nefazodone* Nelfinavir* Troleandomycin Verapamil

Based on: Ingelman-Sundberg M, Human drug metabolising cytochrome P450 enzymes: properties and polymorphisms, Naunyn Schmiedebergs Arch Pharmacol. 2004 Jan;369(1):89-104. and [http://www.medicine.iupui.edu/flockhart/clinlist.htm as of July 13, 2006]

* asterisk denotes strong inhibition/ induction

Please note:

- strong inhibitor implies that it can cause ≥5-fold increase in AUC or ≥80% decrease in clearance of sensitive CYP substrates
- moderate inhibitor implies that it can cause 2 to 5-fold increase in AUC values or 50-80% decrease in clearance of sensitive CYP substrates.

  (Distinction is not always categorical as interaction can vary according to conditions).

1. Macrolide antibiotics: Azithromycin is not a CYP3A substrate. It may therefore be employed where antibiotherapy with a macrolide is desirable in a patient being treated with everolimus
2. Statins: Atorvastatin and pravastatin may be associated with everolimus, since a PK interaction study has shown that there is no relevant PK interaction.

13.4 APPENDIX: M.D. ANDERSON SYMPTOM INVENTORY (MDASI-BT)

Date: _____ Institution: _____

Participant Initials: _____ Hospital Chart #: _____

Participant Number: _____

MD Anderson Symptom Inventory - Brain Tumor (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 you to rate how severe the following symptoms have been *in the last 24 hours.* Please select a number 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 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your **weakness** on one side of the body at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your difficulty **understanding** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your difficulty **speaking (finding the words)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Date: _____ **Institution:** _____

Participant Initials: _____ **Hospital Chart #:** _____

Participant Number: _____

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
17. Your **seizures** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your difficulty **concentrating** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your **vision** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your change in **appearance** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your change in **bowel pattern (diarrhea or constipation)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your **irritability** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

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***? Please select a number from 0 (symptoms have not interfered) to 10 (symptoms interfered completely) for each item.

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
23. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
24. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
25. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
26. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
27. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
28. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

13.5 APPENDIX: PILL DIARY AND PILL COUNT DOCUMENTATION FORM

13.5.1 The Pill Diary

NCI BTTC Coordinating Center
9030 Old Georgetown Road, Room 211
Bethesda, MD 20892
Telephone: 301-443-7976 Fax: 301-480-2246

BTTC09-01: A Phase I-II trial Everolimus and Sorafenib in Patients with Recurrent High-Grade Gliomas

PILL DIARY FOR SORAFENIB AND EVEROLIMUS

Patient (Name) Initials: _____ **Patient ID#:** _____ **Cycle #:** _____

SORAFENIB	EVEROLIMUS
Dose/Frequency: _____mg (_____tabs) AM _____mg (_____tabs) PM	**Dose:** _____mg
Route: Oral **7 days ON, 7 days OFF**	**Route:** Oral **Frequency:** Daily

DAY #	DATE	TIME-AM	TIME-PM	INITIALS	DAY #	DATE	TIME	INITIALS
1					1			
2					2			
3					3			
4					4			
5					5			
6					6			
7					7			
8	off day				8			
9	off day				9			
10	off day				10			
11	off day				11			
12	off day				12			
13	off day				13			
14	off day				14			
15					15			
16					16			
17					17			
18					18			
19					19			
20					20			
21					21			
22	off day				22			
23	off day				23			
24	off day				24			
25	off day				25			
26	off day				26			
27	off day				27			
28	off day				28			

My signature signifies that the study drug(s) have been taken as indicated:

Patient's Signature: _____ **Date:** _____

Version Date: 7/01/2015

13.5.2 The Pill Count Documentation Form A and B

NCI BTTC Coordinating Center
9030 Old Georgetown Road, Room 211
Bethesda, MD 20892
Telephone: 301-443-7976 Fax : 301-480-2246

BTTC09-01 PILL COUNT DOCUMENTATION

TO BE COMPLETED BY CLINICAL RESEARCH STAFF

PATIENT INITIALS: _____ **BTTC ID #:** _____ **CYCLE#:** _____

Dose of EVEROLIMUS prescribed:_____**mg PO DAILY**
(for 28 days EVERY cycle)

(Everolimus (Afinitor) is supplied in Tablet strength(s)_____mg)

DATE DISPENSED: _____
(mm/dd/yyyy)

QUANTITY OF CARDS/BOXES DISPENSED: _____

QUANTITY OF_____**MG TABLETS DISPENSED:** _____

NUMBER OF TABLETS PER DAY REQUIRED TO ACHIEVE PRESCRIBED DOSE: _____

************DO NOT RETURN UNUSED TABLETS TO THE PATIENT**************

RETURN PILL COUNT DATE: _____
(mm/dd/yyyy)

Has the patient taken the dose scheduled for this date? YES NO

QUANTITY OF CARD(S)/BOX RETURNED: _____

QUANTITY OF TABLETS RETURNED: _____

COMMENTS: _____

_____

_____ _____
SIGNATURE OF PHARMACY OR RESEARCH STAFF **DATE**

PHONE # _____

Version Date: 7/01/2015

NCI BTTC Coordinating Center
9030 Old Georgetown Road, Room 211
Bethesda, MD 20892
Telephone: (301-443-7976 Fax : 301-480-2246

BTTC09-01 PILL COUNT DOCUMENTATION
TO BE COMPLETED BY CLINICAL RESEARCH STAFF

PATIENT INITIALS: _____ **BTTC ID #:** _____ **CYCLE#:** _____

Dose of SORAFENIB prescribed: _____ **mg PO BID**
7 days ON 7 days OFF (in a 28 day cycle)

(Sorafenib (Nexavar) is supplied in Tablet strength(s) 200 mg)

DATE DISPENSED: _____
(mm/dd/yyyy)

QUANTITY OF BOTTLES DISPENSED: _____

QUANTITY OF 200 MG TABLETS DISPENSED: _____

NUMBER OF 200 MG TABLETS PER DAY REQUIRED TO ACHIEVE PRESCRIBED DOSE: _____

************DO NOT RETURN UNUSED TABLETS TO THE PATIENT************

RETURN PILL/BOTTLE COUNT DATE: _____
(mm/dd/yyyy)

Has the patient taken the dose scheduled for this date? YES NO

QUANTITY OF BOTTLES RETURNED: _____

QUANTITY OF TABLETS RETURNED: _____

COMMENTS: _____

_____ _____
SIGNATURE OF PHARMACY OR RESEARCH STAFF **DATE**

PHONE # _____

Version Date: 7/01/2015

13.6 APPENDIX: CCR PROBLEM REPORT FORM

<table>
<tr><td>NCI Protocol #:</td><td>Protocol Title:</td></tr>
<tr><td></td><td>Report version: (select one)
____Initial Report
____Revised Report
____Follow-up</td></tr>
<tr><td>Site Principal Investigator:</td><td></td></tr>
<tr><td>Date of problem:</td><td>Location of problem: (e.g., patient's home, doctor's office)</td></tr>
<tr><td colspan="2">Who identified the problem? (provide role (not name of person): nurse, investigator, monitor, etc…)</td></tr>
<tr><td>Brief Description of Subject (if applicable)
(Do NOT include personal identifiers)</td><td>Sex: ___ Male ___ Female Age:
___ Not applicable (more than subject is involved)</td></tr>
<tr><td colspan="2">Diagnosis under study:</td></tr>
<tr><td colspan="2">Name the problem: (select all that apply)
[ ] Adverse drug reaction
[ ] Abnormal lab value
[ ] Death
[ ] Cardiac Arrest/ code
[ ] Anaphylaxis
[ ] Sepsis/Infection
[ ] Blood product reaction
[ ] Unanticipated surgery/procedure
[ ] Change in status (e.g. increased level of care required)
[ ] Allergy (non-medication)
[ ] Fall
[ ] Injury/Accident (not fall)
[ ] Specimen collection issue
[ ] Informed consent issue
[ ] Ineligible for enrollment
[ ] Breach of PII
[ ] Tests/procedures not performed on schedule
[ ] Other, brief 1-2 word description: _____</td></tr>
</table>

Detailed Description of the problem: (*Include any relevant treatment, outcomes or pertinent history*):
***Is this problem unexpected?** *(see the definition of unexpected in the protocol))* __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? (*select all that apply*) [ ] An Unanticipated Problem* that is: [ ] Serious [ ] Not Serious [ ] A Protocol Deviation that is: [ ] Serious [ ] Not Serious [ ] Non-compliance **Note if the 3 criteria starred above are answered, "YES", then this event is also a UP.*
Is the problem also *(select one)* [ ] 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: (*select all that apply*) [ ] Local IRB [ ] Study Sponsor [ ] Manufacturer : _____ [ ] Institutional Biosafety Committee [ ] Data Safety Monitoring Board [ ] Other: _____ [ ] None of the above, not applicable

INVESTIGATOR'S SIGNATURE:	**DATE:**

13.7 APPENDIX: UNUSED STUDY DRUG DISPOSITION FORM – BAYER

Bayer HealthCare

Unused Study Drug Disposition Form
Destruction or Return Confirmation

Study Drug Provided	Study Drug Unused	Study Drug Destroyed	Study Drug Returned

I hereby confirm that the product described above was **destroyed** or returned (select one) to Bayer on (date) _____at
(address)_____.

Witness (Pharmacist or PI): _____
(Print Name)

Witness: _____
Signature

Telephone Number: _____

Fax Number: _____

E-Mail: _____

Please return this form to Amanda Rozner Amanda.rozner@bayer.com, Bayer HealthCare Pharmaceuticals, *NEW ADDRESS* 100 Bayer Boulevard, P.O. Box 915 Whippany, NJ 07981-0915