Abbreviated Title: Ph II Sunitinib CNS Sarcomas **CC Protocol #:** 18C0137

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Title: Phase II Study of Sunitinib in Sarcomas of the Central Nervous System

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Commercial Agent: Sunitinib Malate, hereafter referred to as sunitinib will be supplied by Pfizer.

Commercial Device: wGT3X-BT manufactured by Actigraph, hereafter referred to as Actigraph. AIs in the Diabetes, Endocrinology, and Obesity Branch of NIDDK will provide the actigraphy equipment.

PRÉCIS

Background:

- Gliosarcoma and primary CNS sarcomas are malignant brain tumors uniformly associated with poor outcome.
- There are no known effective medical therapies for these cancers.
- Sunitinib is an orally administered small molecule that inhibits signaling of multiple receptor tyrosine kinases including those known to be activated in CNS sarcomas.

Objectives:

To determine the anti-tumor effect of sunitinib in recurrent gliosarcomas and primary CNS sarcomas as assessed by objective response rate (ORR).

Eligibility:

- Patients with histologically proven gliosarcoma and primary CNS sarcoma at disease relapse after failing standard therapy (surgery and irradiation).
- Tumor tissue blocks or 15 unstained slides should be available
- Subjects must be ≥ 18 years old.
- Karnofsky performance status of ≥ 60.
- Patients must have adequate organ function.
- Patients must not have received tyrosine kinase inhibitor(s) in the past.

Design:

- This is a prospective, single institution, single arm, multi-cohort phase II study of sunitinib in subjects with recurrent gliosarcoma and primary CNS sarcoma that have failed prior surgery and irradiation (unless radiation therapy was contraindicated).
- Subjects will be classified into three cohorts: 1) Primary gliosarcoma; 2) Secondary gliosarcoma; 3) Primary CNS sarcoma. Cohort expansion will be carried out at indication of promising response.
- Sunitinib will be administered orally using a continuous schedule at 50 mg per day (with dose adjustments allowed for toxicity) for 2 weeks with 1 week off to constitute a 3-week cycle until disease progression or development of intolerable side-effects.
- Toxicity will be assessed every cycle by CTCAE version 5.0.

TABLE OF CONTENTS

1. INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective:

To determine the anti-tumor effect of sunitinib in recurrent gliosarcomas and primary CNS sarcomas as assessed by objective response rate (ORR).

1.1.2 Secondary Objective(s):

- To determine the 6-month and median progression-free survival rates.
- To determine the adverse event rate of sunitinib in patients with recurrent gliosarcoma and primary CNS sarcoma.
- To evaluate archival tumor tissue for activation of signaling pathways targeted by sunitinib to establish potential biomarkers of response.
- To perform broad unbiased molecular profiling of archival tumor tissues to identify potential novel biomarkers of response to sunitinib.
- To evaluate radiological parameters such as perfusion and dynamic contrast enhanced MRI before and during treatment with sunitinib.
- To longitudinally evaluate patient reported outcome measures using self-reported symptom severity and interference with daily activities using the MDASI-BT

1.1.3 Exploratory:

- Blood will be collected to evaluate presence of and changes to circulating VEGFR2, PLGF, IL-4, IL-12, HGF, basic FGF, circulating tumors cells, endothelial progenitors, mature apoptotic endothelial cells, regulatory T cells, exhausted CD8 T cells, myeloid-derived suppressor cells (MDSC), and Th1/Th2 T cells. Immunophenotyping evaluations will be performed upon availability of tumor samples.
- To assess free-living physical activity and sleep quality (Optional).

1.2 BACKGROUND AND RATIONALE

This is an Investigator-Initiated Research study to evaluate the anti-tumor effect of sunitinib in subjects with sarcomas of the central nervous system.

1.2.1 Gliosarcoma

Gliosarcoma, tumor classified as a rare variant of glioblastoma, demonstrates biphasic glial and mesenchymal differentiation. Primary gliosarcoma is a de novo neuroepithelial tumor that exhibits dual glial and sarcomatous components at initial diagnosis.[1] On occasion, glioblastoma in the recurrent setting may transition from typical glial phenotype (GFAP positive) to a tumor with reticulin rich sarcomatous-mesenchymal features (secondary gliosarcoma). These tumors are more common in men and often arise in the temporal lobes. While extra-cranial metastasis from glioblastoma is rare, gliosarcomas have a propensity to disseminate extra-cranially likely due to the sarcomatous component. Patients with gliosarcoma experience poor outcome with median survival ranging from 4 to 24 months.[2, 3]

The underlying tumor biology of gliosarcoma appears to be distinct compared to glioblastoma. Frequency of *TP53* mutation is higher and only on very rare occasion EGFR amplification is present. In addition, MGMT methylation and IDH mutations are rare in gliosarcomas.[3] Most patients that present with gliosarcoma are treated similarly to those with glioblastoma in spite of the likely differences in tumor pathogenesis and therefore therapeutic response pattern. Treatment options for patients with recurrent gliosarcoma are extremely limited. However, gliosarcomas often possess platelet-derived growth factor receptor (PDGFR), KIT/ SCF autocrine activation loops, suggesting the potential utility of certain tyrosine kinase inhibitors.[4]

1.2.2 Primary CNS sarcoma

Primary sarcomas of the CNS are rare tumors (~1.5% of all intracranial tumors) with little known concerning the underlying biology. They are believed to arise from mesenchymal tissues within the intracranial cavity such as blood vessels, meninges, or bone. As such, these tumors are histologically similar to sarcomas of soft tissue or bone. The current WHO classification recognizes specific differentiation: fibrosarcoma, solitary fibrous tumor, chondrosarcoma, osteosarcoma, liposarcoma, inflammatory malignant myofibroblastic tumor, leiomyosarcoma, rhabdomyosarcoma, angiosarcoma, and other CNS sarcomas. Although detailed studies of these tumors are limited, reports indicate they may be in part driven by vascular endothelial growth factor (VEGF).[5] Treatment consists of surgical resection when accessible, followed by irradiation. There are no known effective medical therapies for primary CNS sarcomas.

1.2.3 Sunitinib (Sutent)

Sunitinib malate is approved multinationally for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib, advanced renal cell carcinoma, and unresectable, well-differentiated metastatic pancreatic neuroendocrine tumors (NET). Sunitinib is an orally administered small molecule that inhibits multiple receptor tyrosine kinases (RTKs), some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib was evaluated for its inhibitory activity against a variety of kinases (>80 kinases) and was identified as an inhibitor of PDGFRα, PDGFRβ, VEGFR1, VEGFR2, VEGFR3, stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). Sunitinib inhibition of the activity of these RTKs has been demonstrated in biochemical and cellular assays, and inhibition of function has been demonstrated in cell proliferation assays. The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays. Sunitinib inhibited the phosphorylation of multiple RTKs (PDGFRβ, VEGFR2, KIT) in tumor xenografts expressing RTK targets in vivo and demonstrated inhibition of tumor growth or tumor regression and/or inhibited metastases in some experimental models of cancer. Sunitinib demonstrated the ability to inhibit growth of tumor cells expressing dysregulated target RTKs (PDGFR, RET, or KIT) in vitro and to inhibit PDGFRβ- and VEGFR2-dependent tumor angiogenesis in vivo. Sunitinib is clinically indicated for the treatment of advanced renal cell carcinoma, gastrointestinal stromal tumor.

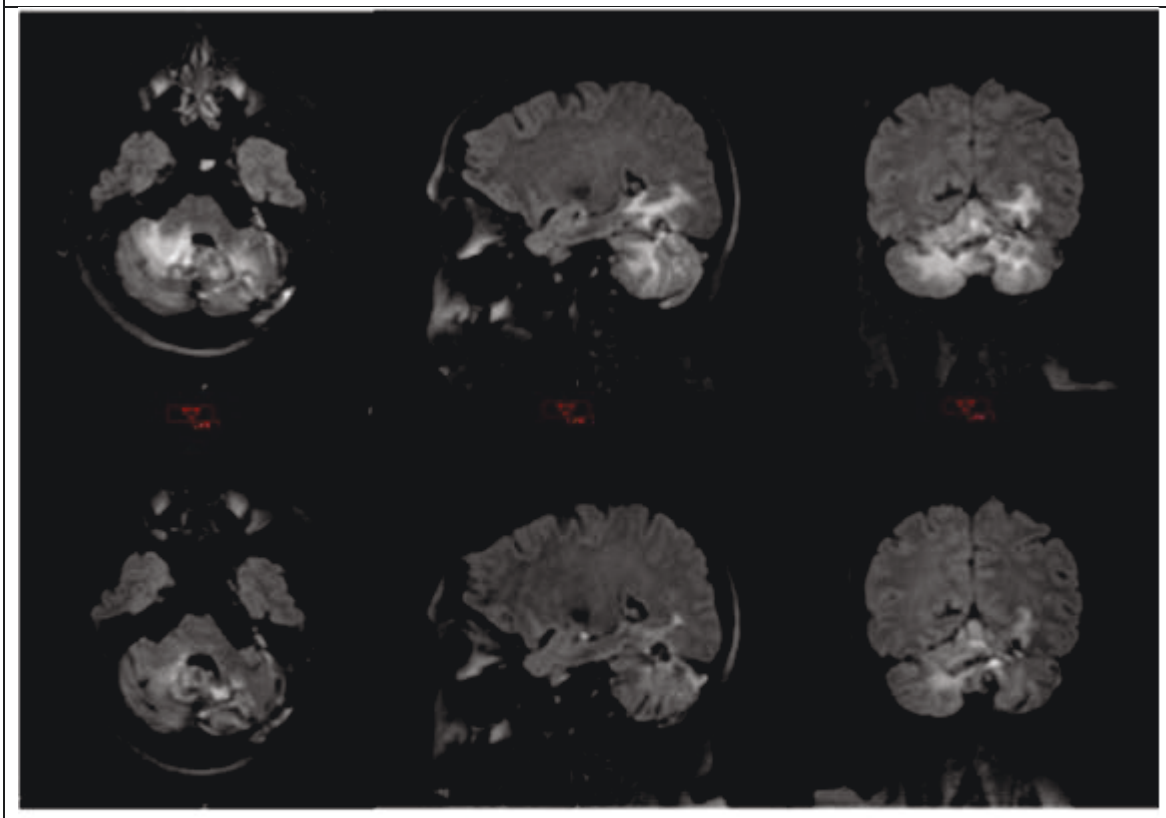
As of October 2012, 13298 subjects (including healthy subjects, subjects with renal impairment, subjects with hepatic impairment, subjects with acute myeloid leukemia, and subjects with solid

malignant tumors) in 89 completed or ongoing clinical studies had received at least one dose of sunitinib. Pharmacokinetic studies indicate sunitinib is able penetrate the blood-brain barrier.[6, 7]

1.2.4 Past Experience

A 49-year-old woman with recurrent primary CNS sarcoma was referred to the NOB Outpatient Clinic. Surgical resection was not a feasible option and she failed recent radiation therapy. Based on previous experience with CNS sarcomas, we decided to proceed with a trial of sunitinib. After 1 cycle (4 weeks) of treatment, MRI showed response (see panel below Figure **1**).

Figure 1



MRI brain, FLAIR sequence on a 49 year-old woman with cerebellar primary sarcoma. Top images (axial, sagittal and coronal) were done prior to treatment with sunitinib. Bottom images were obtained after 1 cycle of treatment with sunitinib and show striking reduction in T2 FLAIR hyperintense signal.

1.2.5 Rationale for Exploratory Studies

Serum markers of angiogenesis: A potential mechanism for sunitinib resistance is the upregulation of alternative proteins and/or pathways that could drive tumor angiogenesis and/or growth independent of VEGF. Preclinical studies, involving RCC and non-RCC models have identified a variety of candidate proteins that may be involved in resistance to VEGF therapy. Among these proteins which stimulate angiogenesis directly or indirectly are fibroblast growth factor (FGF), hepatocyte growth factor (HGF), and placental growth factor (PlGF). We propose to explore the potential utility of these proteins as biomarkers of pharmacological and clinical activity of sunitinib in CNS sarcomas. These assays will be performed in the Trepel Laboratory, DTB, NCI.

Peripheral blood immune monitoring: In addition to modulation of angiogenic activity, sunitinib also appears to regulate key anti-tumor immune response. Sunitinib has been shown to decrease the frequency of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) in metastatic renal cell carcinoma patients.[8, 9] It has been shown that development of sunitinib resistance is partly mediated by the survival of MDSCs, thereby providing sustained immune suppression and angiogenesis.[10] Sunitinib has also shown to shift T-helper cells toward a T helper 1 (Th1)-polarized response and increase the Th1 cell / T helper 2 (Th2) cell ratio. A significant decrease in the Th1/Th2 ratio was seen after sunitinib treatment in the PFS-short group in mRCC.[9, 11] Exhausted CD8+ T cells which express inhibitory receptors PD-1 and Tim-3 were found in cancer patients, and therapeutic response was correlated with decline in Tim-3+ CD8+ T cells. Peripheral blood will be collected into one 8 ml CPT tube. Peripheral blood mononuclear cells (PBMC) will be assessed using multiparameter flow cytometry for immune subsets including but not necessarily limited to CD8+ T-cells, CD4+Foxp3- T-cells, Tregs, monocyte subsets, MDSC subsets. Assessment will include functional markers, i.e. PD-1, Tim-3, CTLA-4, PD-L1, HLA-DR and/or CD40. Therefore, monitoring immune subsets in CNS sarcoma patients pre- and post-sunitinib therapy may contribute to improved understanding of sunitinib and possibly inform future studies.

Circulating Endothelial Cells (CEC) and Endothelial Progenitor Cells (CEP): CECs have emerged as a potentially useful marker to assess anti-angiogenic therapy. At least two distinct populations of CECs have been identified, bone marrow-derived CEP cells and mature CECs. CEP cells bear antigens that identify them as endothelial cells, such as VEGFR2 (Flk-1) and CD31, as well as antigens for stem cells, such as CD117, CD133, and CD34. Upon appropriate stimulation, bone marrow-derived endothelial progenitor cells migrate to the circulation, where they are referred to as CEP cells. CEP cells have been shown to infiltrate human tumors and give rise to tumor neovasculature. Further VEGFR signaling is thought to mobilize CECs which is consonant with the observation that CECs are increased in patients with active cancer. How sunitinib may affect CECs and CEPs is unclear. To explore this, pre-treated and post-treated samples will be obtained to perform CEC/CEP analyses by multi-parametric flow cytometry in the Trepel Laboratory.

1.2.6 Rationale for The Patient-Reported Outcomes:

This study seeks to establish effective therapy for sarcomas of the CNS. We hypothesize that single agent sunitinib will result in anti-tumor activity. However, given the potential toxicity of sunitinib, it will be important to determine whether any determined anti-tumor effect is

associated with improvements in symptoms or whether a worsening of symptoms offsets 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.[18] 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.[12] 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. The evaluation of symptom burden in this study will assist in finding the best possible treatment with the least toxicity.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have histologically confirmed gliosarcoma (primary or secondary) or primary central nervous system sarcoma confirmed by the Laboratory of Pathology, NCI.

2.1.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured bidimensionally by MRI (or CT scan if MRI is contraindicated). See Section **6.3** for the evaluation of measurable disease

2.1.1.3 Patients must have failed standard therapy consisting of surgery, irradiation, and chemotherapy if indicated.

2.1.1.4 Age ≥18 years.

2.1.1.5 Karnofsky ≥60%, see Appendix **13.1.**

2.1.1.6 Patients must have normal organ and marrow function as defined below:

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	within normal institutional limits
– AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal
– creatinine	within normal institutional limits
	OR
– creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

2.1.1.7 Patients must have the ability to understand and the willingness to sign a written informed consent document indicating that they are aware of the investigational nature of this study.

2.1.1.8 The effects of sunitinib on the developing human fetus are unknown. For this reason and because anti-angiogenic agents are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

2.1.1.9 Tumor tissue blocks or at least 10-15 unstained slides from the diagnosis should be available.

2.1.1.10 At the time of registration, all subjects must be removed ≥ 28 days from any investigational agents.

2.1.2 Exclusion Criteria

2.1.2.1 Patients who are receiving any other investigational agents.

2.1.2.2 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

2.1.2.3 Prior use of tyrosine kinase inhibitors or VEGF inhibition.

2.1.2.4 Patients who are receiving strong CYP450 inducers or inhibitors are ineligible.

2.1.2.5 Pregnant women are excluded from this study because sunitinib has potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with sunitinib, breastfeeding should be discontinued if the mother is treated with sunitinib.

2.1.2.6 Patients with known HIV history on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with sunitinib. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy.

2.1.2.7 Uncontrolled hypertension (>150/100 mmHg) while on antihypertensive medications.

2.1.2.8 New York Heart Association class II or greater congestive heart failure.

2.1.2.9 Serious cardiac arrhythmia requiring medication.

2.1.2.10 Baseline echocardiogram with ejection fraction < 50% or ≥ 20% decrease from a prior study.

2.1.2.11 QTc interval > 500 msec on baseline EKG.

2.1.2.12 Patients who require use of therapeutic doses of coumarin-derivative anticoagulants such as warfarin are excluded, although doses of up to 2 mg daily are permitted for

prophylaxis of thrombosis. Note: Low molecular weight heparin is permitted provided the patient's INR is ≤ 1.5.

2.1.2.13 Previous exposure to anthracyclines.

2.1.3 Recruitment Strategies

Both men and women of all races and ethnic groups are eligible for this study. Potential subjects will be identified from referrals to the Neuro-Oncology Clinic.

2.2 SCREENING EVALUATION

Documentation / confirmation of tumor diagnosis by the NCI Laboratory of Pathology is required prior to enrollment. Slides from the most recent pre-registration biopsy or resection must be submitted for review if the previous surgery was not performed at NIH.

Within 28 days prior to registration, the following assessments are required:

1. A complete history and neurological examination (to include documentation of the patient's Karnofsky Performance Status).
2. Vital signs, blood pressure
3. Neuro-imaging confirming tumor progression shall be performed on all patients. MRI is preferred over CT scan.
4. 12-lead ECG
5. Laboratory Evaluation:
    a. CBC with differential, platelets, PT, PTT, INR
    b. Total protein, albumin, calcium, phosphorus, magnesium, glucose, BUN, creatinine, sodium, potassium, alkaline phosphatase, ALT, AST, total bilirubin, direct bilirubin)
    c. Urine or serum β-HCG
6. Echocardiogram
7. Assessment of concomitant medications and treatments.

2.3 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, 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. A recorder is available during non-working hours.

2.3.1 Treatment Assignment Procedures

Cohorts

Number	Name	Description
1	Primary Gliosarcoma	Patients with primary gliosarcoma
2	Secondary Gliosarcoma	Patients with secondary gliosarcoma
3	Primary CNS sarcoma	Patients with primary CNS sarcoma

Arms

Number	Name	Description
1	Experimental therapy	Sunitinib 50 mg with ActiGraph

Arm Assignment

Patients in cohorts 1, 2, and 3 will be assigned to arm 1.

2.4 BASELINE EVALUATION

All baseline evaluation procedures should be done prior to the study treatments. They do not need to be repeated if performed within 28 days prior to study drug initiation.

- A complete history and physical [including baseline blood pressure measurement and determination of Karnofsky Performance Score (KPS)] examination.
- A baseline standard NOB Gd-DPTA enhanced MRI should be performed.
- Thyroid Function Tests (and subsequently every 2 cycles)
- Urinalysis
- MDASI-BT
- Correlative Studies Blood Collection

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 caregiver may complete the questionnaires as a patient proxy if the patient's deficits preclude self-report; however, this must be done at every assessment from baseline to end of treatment. Non-English-speaking patients will complete the questionnaire with the assistance of an interpreter during the clinic visit.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a prospective, single institution, single arm, multi-cohort phase II study of sunitinib in subjects with recurrent gliosarcoma and primary CNS sarcoma that have failed prior surgery and irradiation (unless radiation therapy was contraindicated). Subjects will be classified into three cohorts: 1) Primary gliosarcoma; 2) Secondary gliosarcoma; 3) Primary CNS sarcoma. Cohort expansion will be carried out at indication of promising response.

3.1.1 Optional Assessment of Free-Living Physical Activity and Sleep Quality

Free-living physical activity and sleep quality will be quantified continuously using a small, non-invasive, portable watch accelerometer (Actigraph Inc., Pensacola FL) at the subject's wrist. Overall physical activity levels, daily changes, sleep duration and efficiency, amount of time spent in sedentary, moderate, vigorous intensity categories and estimated activity-associated energy expenditures will be extracted using established predictive equations.

Patients will be asked to wear the Actigraph device for Cycle 1 through Cycle 6. The patient will bring the Actigraph device to each patient visit to have the battery changed. This can be done in person at each visit, or via mail. Any lapses in Actigraph monitoring due to removal of the device by the patient, dead battery, or any unforeseen situations will not constitute a protocol deviation.

3.1.1.1 Safety Considerations

Accelerometers. These small watch-like monitors may cause slight discomfort to subjects. No other known risks are associated.

3.1.2 Dose Limiting Toxicity (DLT)

Toxicities will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Toxicities that occur during Cycle 1 will be evaluated for determination of DLT.

3.2 DRUG ADMINISTRATION

Sunitinib 50 mg will be self-administered orally, once daily on an outpatient basis. Sunitinib will be administered at a dose of 50 mg daily for 2 consecutive weeks followed by 1 week of rest. Studies in patients with metastatic renal cell carcinoma, sunitinib tolerability was superior with the 2-weeks on and 1-week off compared to 4-weeks on and 2-weeks off.[13, 14] Patients should be instructed to store sunitinib at room temperature. Patient will take sunitinib once daily, with or without food, as desired. Patients should drink plenty of water or take rehydration fluids to avoid dehydration if diarrhea occurs. Patients should be alerted to the possibility that sunitinib capsules can cause a yellow discoloration of the skin on direct contact. If this happens, the patient should wash immediately with soap and water. Thyroid function will be monitored at baseline and at every two cycles. Dose reductions (to 37.5 mg and then 25 mg) will be permitted for patients experiencing grade 3 or 4 sunitinib-related toxicities.

Because hypertension is a known and potentially serious but rare adverse event associated with sunitinib treatment, patients will have their blood pressure monitored and recorded at baseline and weekly during treatment including the weeks off the investigational drug either at the doctors' office or using any calibrated electronic device.

All subjects will be evaluated with magnetic resonance imaging at baseline and after every 2 cycles of treatment. Patients will continue treatment until there is disease progression or development of intolerable side effects.

3.3 DOSE MODIFICATIONS

Dose reductions (to 37.5 mg and then 25 mg) will be permitted for patients experiencing grade 3 or 4 sunitinib-related toxicities. If treatment is delayed for more than 4 weeks due to treatment associated toxicity, the patient will be discontinued from treatment and followed until disease progression.

- Patients may continue to receive therapy provided the following criteria are met on day 1 of each cycle:
    - ANC $\geq 1.0 \times 10^9$/L
    - Platelets $\geq 75 \times 10^9$/L
    - Non-hematological toxicity recovered to < grade 2 (or tolerable grade 2 or baseline)
    - No evidence of progressive disease
- With development of adverse events possibly related to sunitinib, dose reduction is permitted (see guideline below). If an adverse event is not covered by the guideline, dose may be reduced or held at the discretion of the investigator for the subject's safety. Subjects with adverse events that are manageable with supportive therapy may not require dose reductions (e.g. nausea/vomiting may be treated with antiemetics, diarrhea may be treated with loperamide, and electrolyte abnormalities may be corrected with supplements rather than by dose reduction).
- If a patient takes 75% or more of scheduled doses during a cycle, missed doses will not be reported as deviations. If the study team instructs a patient to hold the investigational drug, it will not be considered a protocol deviation.
- Increase in BP has been reported with use of anti-VEGF agents. Guidelines for management [15] is provided in Appendix **13.5**

3.3.1 Dose Modification Guidelines for Sunitinib Associated-Toxicity

Event	AE Grade or Observation	Dose Modification
Neutropenia	Grades 1 and Grade 2 ≥ 1200	Maintain dose

Event	AE Grade or Observation	Dose Modification
	Grade 2 < 1200 and Grade 3	Hold sunitinib until ANC ≥ 1,000, then reduce 1 dose level and resume treatment
	Grade 4	Hold sunitinib until ANC ≥ 1,000, then reduce 1 dose level and resume treatment
Thrombocytopenia	Grade 1	Maintain dose
	Grades 2-4	Hold sunitinib until platelets ≥ 75,000, then reduce 1 dose level and resume treatment
Fever or flu-like symptoms	Grades 1-4	Maintain dose
Fatigue	Grades 1 and 2	Maintain dose
	Grade 3 (and severe Grade 2, at investigator discretion)	Hold sunitinib until ≤ Grade 2, then reduce 1 dose level and resume treatment
QTc prolongation **Do not use CTCAE grades**	> 450 but < 550 msec	Review patient's concomitant medications for QT interval-prolonging agents. Correct any electrolyte abnormalities. Continue sunitinib at current dose level.
	≥ 550 msec	Stop sunitinib and any other QT-interval prolonging agents immediately. Correct any electrolyte abnormalities, then: If there is a plausible explanation for AE other than sunitinib treatment and the contributing factor is removed, resume sunitinib at current dose level after the QTc returns to <550 msec. If sunitinib may have contributed to the AE: Reduce 2 dose levels and restart sunitinib. If QTc remains < 500 msec after 14 days at reduced dose, increase one dose level and continue sunitinib.
Hand-foot syndrome	Grades 1 and 2	Maintain dose
	Grade 3	Hold sunitinib until ≤ grade 1, then resume treatment at same dose or reduce 1 dose level, at the discretion of the physician.
	Grades 1 and 2	Maintain dose

Event	AE Grade or Observation	Dose Modification
AST and/or ALT elevation	Grades 3 and 4	Sunitinib should be dose delayed if elevation of ALT is >5 x ULN, AST is >5 x ULN, and/or bilirubin is >3 x ULN. Sunitinib may be re-administered when levels of ALT and AST are ≤ 5 x ULN and bilirubin is ≤ 3 x ULN. Sunitinib should not be re-administered if subjects develop ≥ grade 3 hepatic failure (CTCAEv5 definition). Patients must have LFTs checked at baseline and during each treatment cycle. LFTs should be obtained at any time when they are clinically indicated.

3.3.2 Supportive Care Guidelines

- Nausea/Vomiting: Treat as needed and consider initiation of prophylactic anti-emetic therapy. Please note: Ondansetron and related drugs are not recommended since they may interfere with the metabolism of sunitinib. Ondansetron may contribute to QT interval prolongation. Aprepitant, is a moderate CYP3A4 inhibitors that should be avoided if possible, or used with caution.
- Diarrhea: Manage with loperamide as needed (maximum = 16 mg per day).
- Hand-foot syndrome: Treat with topical emollients (e.g. Aquaphor), topical steroids, and/or anti-histamines. Vitamin B6 (pyridoxine 50-150 mg oral per day) may also be used.

3.4 QUESTIONNAIRES

The MDASI-BT will be utilized for this portion of the study. The instrument will be administered at baseline and then at the time of each evaluation that also includes imaging. Of note, the MDASI-BT will need to be given prior to informing the patients about the results of the imaging study. Full instruments are provided in the Appendix **13.3** 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 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, and those associated with the underlying disease. 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 the instrument is 5 minutes. The MDASI-BT has been translated into 18 languages, but the English language version will be

used for this study.[12] Non-English-speaking patients will complete the questionnaire with the assistance of an interpreter during the clinic visit.

3.5 STUDY CALENDAR

Procedure	Screening/ Baseline	Cycle 1			Subsequent Cycles		End of treatment Visit[9]	Post Therapy Follow-up
		Day 1	Day 8	Day 15	Day 1	Day 15		
		+/- 3			+/- 3	+/-3		
History and PE	X	X	X		X		X	
Vital signs	X	X	X		X		X	
Performance Score (KPS)	X	X	X		X		X	X
CBC w/diff, plts	X	X	X		X		X	
Serum chemistry[1]	X	X	X		X		X	
Urinalysis	X							
PT/PTT INR	X							
Thyroid function tests [2]	X				X		X	
β-HCG (serum or urine)	X							
Blood Pressure	X	X	X	X	X	X	X	
Correlative Research Studies[3]		X	X		X		X	
MDASI-BT[4]	X						X	
Cranial MRI/CT[5]	X						X	
EKG/ECHO[6]	X							
Adverse Events[7]		X	→	→	→	→	→	
Concomitant Medications[7]	X	X			X			
Actigraphy[8]	X	X	X	X	X	X		
NIH Advanced	X							

Procedure	Screening/ Baseline	Cycle 1			Subsequent Cycles		End of treatment Visit[9]	Post Therapy Follow-up
		Day 1	Day 8	Day 15	Day 1	Day 15		
Directives Form[10]								

[1]Total protein, albumin, calcium, phosphorus, magnesium, glucose, BUN, creatinine, sodium, potassium, alkaline phosphatase, ALT, AST, total bilirubin, direct bilirubin
[2]Thyroid function tests to be done at baseline, C2D1, D1 of every other cycle and at end of treatment visit
[3]Blood for correlative studies will be collected at C1D1, C1D8, C2D1 and at end of treatment visit
[4]MDASI-BT to be done at baseline, at time of imaging studies throughout treatment, and at end of treatment visit
[5]Response assessment to be done every other cycle within 7 days of initiation of odd numbered cycles, starting with Cycle 3 and at end of treatment visit. (Pre C1 MRI is done at screening. MRI is preferred.)
[6]ECHO to be done at screening, day 1 of cycle 3 and every other cycle EKG/ECHO frequency of day 1 of the third cycle and every other cycle.
[7]Adverse Event and Concomitant Medication evaluations to be documented at day 1 of each cycle and at end of treatment visit
[8] ActiGraphy to be done at baseline and during cycles 1 through 6
[9] End of treatment visit will occur approximately 30 days after the last dose of study drug. If the patient cannot return to the Clinical Center for this visit, a request will be made to collect required clinical labs from a local physician or laboratory. If this is not possible, patients may be assessed by telephone for symptoms.
*[10]As indicated in section **10.5**, all subjects ≥ age 18 will be offered the opportunity to complete an NIH advanced directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.*

3.6 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Patients may be removed from the protocol therapy and/or study at any time at their own request or may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons.

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy. The following evaluation will occur:

- KPS
- Adverse Event assessment
- Physical examination
- Vital signs and weight
- CBC with differential, comprehensive chemistry panel, thyroid function tests

- Cranial imaging
- Blood collection for correlative studies
- MDASI-BT

3.6.1 Criteria for Removal from Protocol Therapy

The reason(s) for discontinuation must be clearly documented and may include:

- Patient voluntarily withdraws from treatment (follow-up permitted)
- Completion of protocol therapy
- Progressive disease
- Unacceptable toxicity as defined in section **3.3**
- Investigator discretion
- Positive pregnancy test
- Treatment is delayed for more than 4 weeks due to treatment associated toxicity.

3.6.2 Off-Study Criteria

- Completed study follow-up period
- Participant requests to be withdrawn from study (no follow-up permitted)
- Death

3.6.3 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. A Participant Status Updates Form from the web site **(**http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

4 CONCOMITANT MEDICATIONS/MEASURES

- All prescription and over-the-counter medications at trial entry as well as any new medications started during the trial must be documented. Patient may use any ongoing medications not prohibited by the protocol.
- No other anti-cancer therapy agents are permitted while the patient is on this trial.
- Corticosteroids (inducer of CYP3A4) may be used for control of sign and symptoms of increased intracranial pressure and must be recorded. If the dose is increased during the period of 5 days before scheduled cranial imaging, the study should be delayed by at least 2 weeks.
- Use of drugs with potential proarrhythmic actions should not be used.

- Sunitinib is primarily metabolized by liver enzymes, in particular CYP3A4. Patients must not have taken potent inhibitors (azole antifungals such as ketoconazole/itraconazole; clarithromycin; erythromycin; diltiazem; verapamil) or inducers (rifampin; rifabutin; carbamazepine; phenobarbital; phenytoin; St. John's wort) of CYP3A4 enzyme within 7 and 12 days prior to drug administration respectively. Also during the study, potent inhibitors and inducers should not be administered. If usage is necessary, this must be discussed with a study team member and outcome of the discussion should be documented.
- Aprepitant, grapefruit juice, fluconazole, and voriconazole are moderate CYP3A4 inhibitors that should be avoided if possible, or used with caution.
- Ondansetron and related drugs are not recommended since they may interfere with the metabolism of sunitinib.
- Drugs known to cause prolongation of QTc should be avoided.

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH

Test/assay	**Volume blood (approx)**	**Type of tube**	**Collection point (+/- 48hrs)**	**Location of specimen analysis**
Circulating mature endothelial cells and endothelial progenitor cells Immune-monitoring	8 ml at C1D1, C1D8, C2D1	CPT citrate (blue/black)	C1D1, C1D8, C2D1 and at end of treatment visit	Trepel Lab
Circulating tumor cells	7.5 ml at C1D1, C1D8, C2D1	CellSave tube	C1D1, C1D8, C2D1 and at end of treatment visit	Trepel Lab
Immune subset analyses	8 ml at C1D1, C1D8, C2D1	CPT citrate (blue/black)	C1D1, C1D8, C2D1 and at end of treatment visit	Trepel Lab

For Trepel Lab samples, contact the lab by email: Jane Trepel Neckers (trepel@helix.nih.gov), Sunmin Lee (leesun@mail.nih.gov), Min-Jung Lee (leemin@mail.nih.gov), and Akira Yuno

(akira.yuno@nih.gov) when the patient is scheduled and by phone at 240-760-6330 when the blood has been drawn, and a Trepel Lab member will come to pick it up. Store at ambient temperature. The samples will be 2D barcoded, securely stored at the appropriate temperature, and entered into a secure patient database that can only be accessed by laboratory members. Each laboratory member can only interact with the database at their approved level of access. All laboratory members have completed courses in patient information security and computer security. Samples will only be released with approval of the Principal Investigator. No cell lines will be established.

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without IRB notification and an executed MTA.

Paraffin embedded tissue blocks and unstained slides will be stored at NCI Laboratory of Pathology located at Building 10.

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described above. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed. The PI will report any loss or destruction of samples to the NCI IRB as soon as he is made aware of such loss.

If the patient withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples or other problems associated with samples will also be reported to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. Data will be entered into the C3D Database. The MDASI-BT responses will be entered by study subjects directly into Labmatrix via Scribe. Actigraph data will be downloaded from the device using ActiLife Software. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. 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 adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Patients will be followed for adverse events for 30 days after removal from study treatment or until off-study, whichever comes first.

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

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

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.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

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

__X_ De-identified data in an NIH-funded or approved public repository.

__X_ De-identified data in BTRIS (automatic for activities in the Clinical Center)

__X_ De-identified or identified data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

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

_X__ BTRIS (automatic for activities in the Clinical Center)

_X__ Approved outside collaborators under appropriate individual agreements.

_X__ Publication and/or public presentations.

When will the data be shared?

_X__ Before publication.

_X__ At the time of publication or shortly thereafter.

6.3 RESPONSE CRITERIA

6.3.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with sunitinib.

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.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.3.2 Disease Parameters

Measurable disease: Based on RANO criteria [16]

6.3.3 RANO Criteria for Response

RANO Criteria for Response (34)				
	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥ 25% ↑[1]
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑[1]
New lesion	None	None	None	Present[1]
Corticosteroids	None	Stable or ↓	Stable or ↓	n/a†
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓[1]
Requirement for response	All	All	All	Any[1]

[1] Progression occurs when this criterion is present
†Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.
↓ = decreased, ↑ = increased,
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease. If PD is unclear based on white matter changes, patients may be kept on trial.
FLAIR, fluid-attenuated inversion recovery; NA, not applicable.

6.3.3 Evaluation of Best Overall Response

6.3.3.1 Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

6.3.3.2 The duration of overall CR: duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

6.3.3.3 Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

6.3.4 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. In cases where this might be unclear, patients may continue on trial.

6.3.5 Response Review

All subjects will be evaluated by cranial imaging every 6 weeks.

6.4 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 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 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.

7.1.2 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.

7.1.3 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.

7.1.4 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.

7.1.5 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.

7.1.6 Disability

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

7.1.7 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.

7.1.8 Protocol Deviation (NIH Definition)

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

7.1.9 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.

7.1.10 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.

7.2 NCI-IRB AND CLINICAL DIRECTOR REPORTING

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

The Protocol PI will report in 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.

7.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol 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.

7.3 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

7.3.1 Reporting of Serious Adverse Events

Within twenty-four (24) hours of first awareness of the event (immediately if the event is fatal or life-threatening), Principal Investigator will report to Pfizer by facsimile at 1-866-997-8322 any Serious Adverse Event ("SAE,"). Such SAEs are to be reported for (1) Study subjects who are assigned or (2) individuals otherwise exposed to the Pfizer Product. Principal Investigator should report SAEs as soon as they are determined to meet the definition, even if complete information is not yet available.

7.3.2 Pregnancy: Exposure or Lack of Effect

Even though there may not be an associated SAE, exposure to the Pfizer Product during pregnancy, exposure to the Pfizer Product during lactation, and occupational exposure to the Pfizer Product are reportable, and lack of effect of the Pfizer Product may also be reportable. The term SAE will be understood to include exposure during pregnancy, exposure during lactation, occupational exposure, and reportable instances of lack of effect.

7.3.3 Hy's Law Cases

Cases of potential drug-induced liver injury as assessed by laboratory test values ("Hy's Law Cases") are also reportable to Pfizer. If a Study subject develops abnormal values in aspartate aminotransferase ("AST") or alanine aminotransferase ("ALT") or both, concurrent with abnormal elevations in total bilirubin and no other known cause of liver injury, that event would be classified as a Hy's Law Case. The term SAE will be understood to also include Hy's Law Cases.

7.3.4 Reporting

7.3.4.1 Forms

Principal Investigator will report SAEs using one of the following forms: (1) a reporting form approved by the local regulatory authority, (2) a CIOMS form, (3) a Pfizer-provided *Investigator-Initiated Research Serious Adverse Event Form*, **or** (4) any other form prospectively approved by Pfizer. The *Reportable Event Fax Cover Sheet* provided by Pfizer must also be included with each SAE submitted.

7.3.4.2 SAE Reporting Period

The SAEs that are subject to this reporting provision are those that occur from after the first dose of the Pfizer Product through twenty-eight (28) calendar days after the last administration of the Pfizer Product. In addition, if Principal Investigator becomes aware of an SAE occurring any time after the administration of the last dose of the Pfizer Product, Principal Investigator should report that SAE to Pfizer if the Principal Investigator suspects a causal relationship between the Pfizer Product and the SAE.

7.3.4.3 Exclusions from SAE Reporting Requirements

Specifically excluded from the reporting requirements for SAEs under this protocol is any SAE identified in the Protocol as anticipated to occur in the Study population at some frequency independent of drug exposure, unless the Principal Investigator assesses such an event as related

to the Pfizer Product. Also, specifically excluded from the reporting requirements is any SAE judged by the Principal Investigator to represent progression of the malignancy under study, unless it results in death within the SAE Reporting Period.

7.4 DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a weekly basis 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.

8 STATISTICAL CONSIDERATIONS

8.1 GENERAL APPROACH

We monitor the ORR using the Bayesian optimal phase 2 (BOP2) design [18]. Specifically, let n denote the interim sample size and N denote the maximum sample size. Let p denote the ORR and define the null hypothesis $H_0: p \leq 0.2$, representing that the treatment is inefficacious. We will stop enrolling patients and claim that the treatment is not promising if

$$Pr(p > 0.2 \mid data) < \lambda(\frac{n}{N})^{\alpha},$$

where λ=0.85 and α=0.8 are design parameters optimized to minimize the chance of incorrectly claiming that an efficacious treatment is not promising (i.e., type II error) under the alternative hypothesis $H_1: p = 0.4$, while controlling the type I error rate at 0.1 (i.e., the chance of incorrectly claiming that an inefficacious treatment is promising is no more than 10%). Assuming a Beta(0.2,0.8) prior distribution for p, the above decision rule corresponds to the following stopping boundaries and yields a statistical power of 0.8537 under H_1:

Table 1. Stopping boundaries

# patients treated	Stop if # responses <=
16	3
24	5
32	9

Based on Table 1, we perform the interim and final analysis when the number of enrolled patients reaches 16, 24 and 32. If the number of responses fails to exceed the stopping boundary, we will suspend accrual, inspect the efficacy data and make the go/no-go decision based on both the ORR and other clinical considerations (e.g., PFS).

Below are the operating characteristics of the design based on 10000 simulations using the BOP2 web application, which is available at http://www.trialdesign.org.

ORR	Early stopping (%)	Claim promising (%)	Sample size
0.1	97.95	0.05	16.7
0.2	71.74	8.00	21.5
0.3	31.45	46.22	27.5
0.4	7.92	85.37	30.8
0.5	1.31	98.13	31.8

We monitor the rate of Dose Limiting Toxicity (DLT) independently for each cohort using the following Bayesian rule: stop enrolling patients to a cohort if Pr(DLT > 30% | data) > 0.9. That is, we will stop enrolling patients to a cohort if the data indicate that there is more than 90% chance that the true DLT rate is higher than 30%. This posterior probability is calculated based on the beta-binomial model. The decision rule gives the following stopping rule, assuming a Beta(0.1, 0.4) prior distribution for DLT rate,

Stop enrolling pts if [# of pts with DLT] / [# of pts evaluated] ≥ 4/5, 6/10, and 9/20.

Below are the operating characteristics of the toxicity monitoring rule:

	True toxicity rate				
	0.1	0.2	0.3	0.4	0.5
Early stop probability	0.008	0.018	0.145	0.440	0.771
Average sample size	31.9	31.6	29.4	24.4	17.7

8.2 Sample Size Justification

With the maximum sample size of 32 patents per cohort, the 95% confidence interval of the estimated ORR will not be wider than 0.19 in each direction. At the two-sided significance level of 0.2, we have 80% power to detect the ORR of 48% versus 30%.

8.3 Statistical Analysis

Summary statistics, including mean, standard deviation and 95% confidence interval, will be used to describe the ORR. Kaplan-Meier curve will be used to estimate the PFS. We will calculate mean, standard deviation and 95% confidence interval of PFS6 and median PFS. Safety will be assessed by reporting the grades of toxicity and the type of toxicity observed for all patients and summarizing data using the descriptive statistics, including mean, standard deviation and confidence intervals.

Treatment effect of sunitinib will be evaluated using advanced MRI of the brain. Perfusion and diffusion-based MRI parameters including but not restricted to blood volume, mean and median ADC and structural volumes will be analyzed. Results will be summarized, and mean and median values at different time points will be tabulated. Changes in such parameters will be checked for statistical significance and correlated with the disease status. The relationship between biomarkers and response will be evaluated using Spearman correlation and regression analysis; the levels of biomarkers will be compared between responders and non-responders using an exact Wilcoxon rank sum test and t test.

8.4 Patient-Reported Outcomes

Received MDASI-BT forms will be checked versus the timing schedule and considered as valid if they fall within 14 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 symptom severity 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.

9 COLLABORATIVE AGREEMENTS

9.1 Agreement Type

Sunitinib is provided by Pfizer Inc. under a Clinical Trials Agreement (CTA). CTA # 01058-17 effective 04/14/2017 which has been amended: CTA# 01058-17 Amendment #1, effective 05/25/2018.

10 HUMAN SUBJECTS PROTECTIONS

10.1 Rationale For Subject Selection

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. Men and women 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.

10.2 Participation Of Children

Because safety of sunitinib has not been established in children, subjects less than 18 years of age are excluded.

10.3 Participation Of Women Of Child-Bearing Potential

Pregnant women are excluded from this study because sunitinib has potential for teratogenic or abortifacient effects. The effects of sunitinib on the developing human fetus are unknown. For this reason and because anti-angiogenic agents are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study treatment.

10.4 Participation for HIV+ Patients

Patients with known HIV history on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with sunitinib. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy.

10.5 Participation of Subjects Unable to Give Consent

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 **10.7**), all subjects 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 and NIH HRPP SOP 14E for 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.

10.6 Evaluation of Benefits and Risks/Discomforts

The primary risk to patients participating in this research study is from toxicity of sunitinib as described in the protocol.

10.6.1 Alternative Approaches or Treatments

During the consenting process, all risks, potential benefits, treatment requirements, and alternative therapeutic approaches to participation will be discussed.

10.6.2 Procedure for Protecting Against or Minimizing Any Potential Risks

All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. This study may involve risks to patients, which are currently unforeseeable. All

patients will have blood tests, examinations and scans as described in the study calendar (Section **3.5**). Patients will also be required to have a local physician to provide long-term care and to monitor for complications. If patients suffer any physical injury as a result of participation in this study, immediate medical treatment is available at the Clinical Center, National Cancer Institute, Bethesda, Maryland. Although no compensation is available, any injury will be evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

10.7 Risks/Benefits Analysis

10.7.1 Benefits

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

10.7.2 Risks

Risk includes toxicity as a result of administered study agent. Frequent monitoring for adverse effects should help to minimize the risks associated with administration of sunitinib.

10.7.3 Risks/Benefits Analysis

The potential benefit from this therapy is disease stabilization or tumor shrinkage and a reduction in symptoms caused by the brain tumor such as neurological deficits and headache. Even with efforts to minimize risks, participation in this protocol involves greater than minimal risk, but presents the potential for direct benefit to individual subjects.

10.8 Consent 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.

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 to give their consent to continue in the study.

10.8.1 Informed Consent of Non-English Speaking Subjects

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, 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.

11 PHARMACEUTICAL AND MEDICAL DEVICE INFORMATION

11.1 RATIONALE FOR IND EXEMPTION

This investigation of sunitinib, a marketed drug is exempt from the IND requirements because all the criteria for an exemption in § 312.2(b) are met:

- The drug product is lawfully marketed in the United States.
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).
- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).
- The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

11.2 SUNITINIB MALATE /SUTENT ®

Sunitinib is an oral multitargeted tyrosine kinase inhibitor of KIT, PDGFRs, VEGFRs, RET, and FLT3, approved multinationally for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib, advanced renal cell carcinoma, and unresectable, well- differentiated metastatic pancreatic neuroendocrine tumors (NET).

11.2.1 Source

Sunitinib will be provided by Pfizer Inc. from commercial supply.

11.2.2 Toxicity

(Please see package insert for a complete list of toxicities)

In over 10,000 subjects with solid malignant tumors diarrhea (52.4%), fatigue (49.0%), nausea (42.7%), decreased appetite (38.5%), vomiting (33.9%), palmar-plantar erythrodysaesthesia syndrome (28.7%), hypertension (27.6%), stomatitis (26.0%), dysgeusia (25.9%), and mucosal inflammation (25.7%) were the most commonly reported treatment emergent adverse events. Overall, 60.3% experienced treatment-related AEs of Grade 3, 4, or 5 severity; Grade 3 in 46.9% of subjects, Grade 4 and grade 5 in 11.9% and1.6% of subjects respectively. The most commonly reported were neutropenia (13.5%), fatigue (9.2%), thrombocytopenia (8.6%), palmar-plantar erythrodysaesthesia syndrome (7.4%), diarrhea (6.3%), hypertension (5.5%), and asthenia (5.0%). Neutropenia (0.3%), fatigue (8.8%), palmar-plantar erythrodysaesthesia syndrome (7.4%), thrombocytopenia (6.8%), diarrhea (6.1%); and hypertension (5.4%) were the most commonly reported treatment-related AEs of Grade 3 severity. Neutropenia (3.2%), thrombocytopenia (1.8%), and anemia (0.9%) were the most commonly reported treatment-related AEs of Grade 4 severity. Pulmonary embolism, cardiac failure, death, cerebral hemorrhage, renal failure, myocardial infarction, hepatic failure, gastrointestinal hemorrhage, multi-organ failure, respiratory failure, pneumonia, septic shock, cardiac arrest, sepsis, sudden death, tumor hemorrhage, and hemorrhage, were among the Grade 5 treatment-related AEs reported in at least 3 subjects.

Boxed Warning:

Sunitinib has been associated with hepatotoxicity, which may result in liver failure or death. Liver failure has been observed in clinical trials (7/2281 [0.3%]) and post-marketing experience. Liver failure signs include jaundice, elevated transaminases and/or hyperbilirubinemia in conjunction with encephalopathy, coagulopathy, and/or renal failure. Monitor liver function tests (ALT, AST, bilirubin) before initiation of treatment, during each cycle of treatment, and as Abbreviated Title: Targeted Rx in Advanced NETs Version Date: 03-01-17 Confidential 78 clinically indicated. Sunitinib should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart sunitinib if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure. Safety in patients with ALT or AST >2.5 × ULN or, if due to liver metastases, >5.0 × ULN has not been established.

11.2.3 Formulation and Preparation

Hard Gelatin Capsules

Sunitinib capsules consist of hard gelatin capsules containing sunitinib equivalent to 6.25, 12.5, 25, 37.5mg and 50 mg sunitinib together with mannitol, croscarmellose sodium, povidone, and magnesium stearate. The capsules may be printed or unprinted and are color coded for potency differentiation as described in table below.

CAPSULE STRENTH AND DESCRIPTION	
6.25 mg	Light grey, Size 4 hard gelatin capsule
12.5 mg	Swedish Orange, Size 4 hard gelatin capsule
25 mg	Swedish Orange/Caramel, Size 3 hard gelatin capsule
37.5mg [1]	Standard Yellow, Size 3 hard gelatin capsule
50 mg	Caramel, Size 2 hard gelatin capsule
[1] 37.5mg capsule strength is commercially available in some markets since 2014, however this strength has not been used in clinical investigations.	

11.2.4 Stability and Storage

The sunitinib capsules are packaged in opaque plastic bottles, and should be stored at controlled room temperature (15 to 30°C).

The capsule contents, when sprinkled on applesauce or yogurt, are stable for up to 30 minutes under conditions of ambient light and temperature.

11.2.4.1 Self-Administered Study Drugs Policy

All oral self-administered investigational agents will be properly accounted for, handled, and disposed in accordance with existing federal regulations and principles of Good Clinical Practice. All oral study drugs will be recorded in the patient diaries found in Appendix **13.2**. This will be used as a memory aide for subjects. A clinical research team maintains the primary source record.

11.2.5 Incompatibilities

Concomitant administration of sunitinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 49% and 51% increase of the complex [sunitinib + primary active metabolite] C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of sunitinib in healthy volunteers. Administration of sunitinib with strong inhibitors of the CYP3A4 family (e.g., ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) may increase sunitinib concentrations. Concomitant administration with inhibitors should therefore be avoided, or the selection of an alternate concomitant medication with no, or minimal potential to inhibit CYP3A4 should be considered. If this is not possible, the dosage of sunitinib may need to be reduced.

11.3 wGT3X-BT

The use of the wGT3X-BT for investigation in this study is exempt from IDE regulations.

The wGT3X-BT is a legally marketed device that is a FDA cleared Class II within the US. The wGT3X-Bt is intended for use in applications where quantifiable measurement and storage of physical movement is desired. For this study, wGT3X-BT will be used to measure and record physical movement associated with daily activity and sleep, which is in alignment with its indication.

The wGT3X-BT does not meet the criteria of a significant risk device. It is not: 1. intended as an implant nor does it present a potential for serious risk to the health, safety, or welfare of a subject; 2. purported or represented to be for a use in supporting or sustaining human life nor presents a potential for serious risk to the health, safety, or welfare of a subject; 3. for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health nor presents a potential for serious risk to the health, safety, or welfare of a subject; or 4. It does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

11.3.1 Product Description:

The wGT3X-BT activity monitor contains a 3-axis MEMS accelerometer with a dynamic range of +/- 8 G. Acceleration data are sampled by a 12 bit analog to digital converter at user specified rates ranging from 30 Hz to 100 Hz and stored in a raw, non-filtered/accumulated format in the units of gravity (G's). Data are stored directly into a non-volatile flash memory.

11.3.2 Manufacturer: ActiGraph

11.3.3 Dimensions: 3.3x4.6x1.5 cm

11.3.4 Weight: 19 grams

11.3.5 Source:

AIs in the Diabetes, Endocrinology, and Obesity Branch of NIDDK will provide the actigraphy equipment.

11.3.6 Storage:

In order to maximize battery life, ActiGraph recommends devices be stored in a partially charged state (40 – 60% battery capacity is ideal) in low ambient temperatures. The device should never be stored lower than -10°C or higher than +45°C.

11.3.7 Administration:

Participants will be given a small, portable pager-type and watch-like accelerometers to wear at the hip or non-dominant wrist.

11.3.8 Precautions:

There are no significant risks associated with actigraphy. Some patients may find it an inconvenience to wear the device.

12 REFERENCES

1. Han, S.J., et al., *Clinical characteristics and outcomes for a modern series of primary gliosarcoma patients.* Cancer, 2010. **116**(5): p. 1358-66.
2. Han, S.J., et al., *Primary gliosarcoma: key clinical and pathologic distinctions from glioblastoma with implications as a unique oncologic entity.* J Neurooncol, 2010. **96**(3): p. 313-20.
3. Cachia, D., et al., *Primary and secondary gliosarcomas: clinical, molecular and survival characteristics.* J Neurooncol, 2015. **125**(2): p. 401-10.
4. Reis, R.M., et al., *Molecular characterization of PDGFR-alpha/PDGF-A and c-KIT/SCF in gliosarcomas.* Cell Oncol, 2005. **27**(5-6): p. 319-26.
5. McDonald, P., A. Guha, and J. Provias, *Primary intracranial fibrosarcoma with intratumoral hemorrhage: neuropathological diagnosis with review of the literature.* J Neurooncol, 1997. **35**(2): p. 133-9.
6. Patyna, S. and G. Peng, *Distribution of sunitinib and its active metabolite in brain and spinal cord tissue following oral or intravenous administration in rodents and monkeys.* Ejc Supplements, 2006. **4**(12): p. 21-21.
7. Szalek, E., et al., *The penetration of sunitinib through the blood-brain barrier after the administration of ciprofloxacin.* Acta Pol Pharm, 2014. **71**(4): p. 691-7.
8. Finke, J.H., et al., *Sunitinib reverses type-1 immune suppression and decreases T-regulatory cells in renal cell carcinoma patients.* Clin Cancer Res, 2008. **14**(20): p. 6674-82.
9. Ko, J.S., et al., *Sunitinib mediates reversal of myeloid-derived suppressor cell accumulation in renal cell carcinoma patients.* Clin Cancer Res, 2009. **15**(6): p. 2148-57.
10. Finke, J., et al., *MDSC as a mechanism of tumor escape from sunitinib mediated anti-angiogenic therapy.* Int Immunopharmacol, 2011. **11**(7): p. 856-61.
11. Kobayashi, M., et al., *Changes in peripheral blood immune cells: their prognostic significance in metastatic renal cell carcinoma patients treated with molecular targeted therapy.* Med Oncol, 2013. **30**(2): p. 556.
12. Armstrong, T.S., et al., *Validation of the M.D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT).* J Neurooncol, 2006. **80**(1): p. 27-35.
13. Atkinson, B.J., et al., *Clinical outcomes for patients with metastatic renal cell carcinoma treated with alternative sunitinib schedules.* J Urol, 2014. **191**(3): p. 611-8.
14. Kondo, T., et al., *Superior tolerability of altered dosing schedule of sunitinib with 2-weeks-on and 1-week-off in patients with metastatic renal cell carcinoma--comparison to standard dosing schedule of 4-weeks-on and 2-weeks-off.* Jpn J Clin Oncol, 2014. **44**(3): p. 270-7.

15. Brinda, B.J., et al., *Anti-VEGF-Induced Hypertension: a Review of Pathophysiology and Treatment Options.* Curr Treat Options Cardiovasc Med, 2016. **18**(5): p. 33.

16. Wen, P.Y., et al., *Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group.* J Clin Oncol, 2010. **28**(11): p. 1963-72.

13 APPENDIX

13.1 PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

13.2 PILL AND BLOOD PRESSURE DIARY

NCI Neuro-oncology Branch
9030 Old Georgetown Road, Room 233
Bethesda, MD 20892
Telephone: 240-760-6030 **Fax:** 250-541-4432

Title: Phase II Study of Sunitinib in Sarcomas of the Central Nervous System

PILL and BLOOD PRESSURE DIARY FOR SUNITINIB

Days 1 – 14 of each cycle (1 Cycle = 21 days)

Today's date: _____ Cycle Number: _____

Patient Name (or initials): _____ Patient Study ID: _____

Sunitinib Dose/Frequency: _____mg/day **Route:** Oral **Daily**				**BLOOD PRESSURE** **BASELINE** _____ **WEEKLY**			
DAY #	**DATE-**	**TIME**	**INITIALS**	**Blood Pressure**	**DATE**	**TIME**	**INITIALS**
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							

DAY #	DATE	TIME	INITIALS	Blood Pressure	DATE	TIME	INITIALS
15	Off day						
16	Off day						
17	Off day						
18	Off day						
19	Off day						
20	Off day						
21	Off day						

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

Patient's Signature: _____ Date: _____

This calendar is for you to indicate that you took the drug(s) according to the instructions. Please put a check mark or your initials after each dose. **Please sign this calendar at the end of the cycle and bring the calendar and all study drug bottle(s) back to your next clinic visit**

NOTES TO PATIENT:

- Be instructed to store Sunitinib at room temperature.
- Sunitinib should be taken once daily, with or without food, as desired.
- You should drink plenty of water or take rehydration fluids to avoid dehydration if diarrhea occurs.
- Please be aware: there is a possibility that Sunitinib capsules can cause a yellow discoloration of the skin on direct contact. If this happens, you should wash immediately with soap and water.

13.3 MD 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?**	○	○	○	○	○	○	○	○	○	○	○

13.4 ACTIGRAPHY PATIENT TEACHING TOOL

You will be asked to participate in an optional portion of the protocol to monitor your overall physical activity levels, sleep duration and efficiency, amount of time spent in sedentary, moderate, vigorous intensity categories. If you choose to participate, you will be asked to wear a small, non-invasive, watch-like device, called an ActiGraph (similar to a Fit Bit).

You will be asked to wear the ActiGraph 24 hours per day for the first 6 cycles of the protocol. You may wear it in the shower. You should remove it prior to any MRI's (as it contains metal).

At each NIH visit, we will change the batteries for you. Occasionally, you may be asked to mail it to NIH to change the batteries for you.

These small monitors may cause slight discomfort to subjects. No other known risks are associated.

13.5 MANAGEMENT OF HYPERTENSION INDUCED BY VEGF INHIBITORS