

North Central Cancer Treatment Group

N0776: Phase II Trial of Avastin® in Combination with Sorafenib in Recurrent Glioblastoma Multiforme

Addendum 17 – November 25, 2011

Summary

- Due to the high quality of work performed by HistoGeneX in Belgium, a select number of IHC assessments will now be done by HistoGeneX rather than the TACMA laboratory at the Mayo Clinic Rochester. Therefore, the Pathology Considerations/Tissue Biospecimens section has been revised accordingly.
- Administrative changes.

A replacement protocol is provided. Please replace the current copy with the one attached. Please keep this addendum with your protocol

Title page Updated to reflect the addition of Addendum 17 and revised NCI version date.

Protocol Resources

Page 2: **Sanna L. McKinzie** replaces ~~John (Jack) M. Beranek~~ as the NCCTG Research Base Research Protocol Specialist.

Section 17.0 Pathology Considerations/Tissue Biospecimens

Page 64: A select number of IHC assessments will now be done by HistoGeneX. Therefore, Section 17.5 has been revised as follows:

17.51 Immunohistochemistry (IHC) on tumor samples obtained at baseline will have the following antigens analyzed in the TACMA Shared Resource at Mayo Clinic Rochester:

- ~~CD31~~
- VEGFR1
- VEGFR2
- VEGFR3
- PDGFR α
- PDGFR β
- ~~VEGF~~
- CA-9
- HIF1 α
- HIF2 α
- ~~NRP-1~~
- NRP-2
- Phospho-ERK

17.52 The following additional IHC assessments will be performed on baseline tumor samples by HistoGeneX (Antwerp, Belgium):

- CD31
- VEGFR1
- VEGFR2
- VEGFA
- NRP-1

HistoGeneX offers IHC services in a quality-driven environment. All assays are optimized, implemented and validated according to strict quality assurance standards that are based on CAP, BELAC, and CLIA guidelines. At present, HistoGeneX provides over 80 assays covering the fields of oncology and neuropathology. Five 5-micron unstained charged slides and one H&E slide will be shipped to the following address for assaying and analysis:

**HistoGeneX
Sofie Vande Velde
Campus Middelheim-Pathology
Linderdreef 1
B-2020 Antwerp
Belgium**

Pages 64-65: Due to the newly added Section 17.52, all remaining sections have been renumbered.

Pages 64-68: Repagination has occurred.

North Central Cancer Treatment Group

Phase II Trial of Avastin® in Combination with Sorafenib
in Recurrent Glioblastoma Multiforme

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please call the protocol resource person on the following page.*

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507-284-8803

Drug Availability

Bayer Corporation: Sorafenib (*IND #101750*)

Genentech/Roche Pharmaceuticals: Avastin® (*IND#101750*)

***Investigator having NCI responsibility for this protocol**

√Study contributor(s) not responsible for patient care.

June 4, 2008

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Study Participants

Date Activated

Entire NCCTG September 12, 2008

NCI Version Date: November 14, 2011

Protocol Resources

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Add 1,13,17	Protocol document, consent form, regulatory issues	Sanna L. McKinzie NCCTG <i>Research Base</i> Research Protocol Specialist Phone: (507) 538-6626 Fax: (507) 284-5280 E-mail: mckinzie.sanna@mayo.edu
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*No waivers of eligibility per NCI

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Schema

**Pre-Registration
(Central Pathology Review Submission)**



**REGISTRATION
(Central Review Confirmation)**



Active Treatment
Sorafenib days 1 through 14 (of each cycle) plus Avastin® (day 1 of each cycle)



PD at any time
Unacceptable adverse events
Patient refusal



**Event Monitoring
(28-42 days after treatment then q3 months
x 5 years followed by yearly x 10 years)**

Update 1
Add 9

Add 12

Add 12 ¹ Cycle length = 14 days

If a patient is deemed ineligible or a cancel, please refer to Section 13.0 for follow-up information.

Generic name: sorafenib	Generic name: bevacizumab
Brand name(s): Nexavar®	Brand name(s) Avastin®
NCCTG abbreviation: 439006	NCCTG abbreviation: AVASTN
Availability: North Central Research Base Pharmacy	Availability: North Central Research Base Pharmacy

1.0 Background

1.1 Treatment

Glioblastoma multiforme is the most common glioma histology and has a dismal prognosis despite the use of multimodality treatment, with a median survival of 12 to 15 months (Stupp 2005). When patients with glioblastoma multiforme develop recurrence of the disease, available treatment options have a limited impact on overall outcome. Novel therapeutics approaches for treatment of this disease are clearly needed. Although understanding the molecular pathogenesis of GBM has allowed the rational testing of molecularly targeted agents, the redundancy and overlap of signaling pathway decreases the likelihood that single targeted agents will result in meaningful improvement of outcome of recurrent GBM patients and emphasizes the importance of development of combinations of targeted agents, which may increase the likelihood of therapeutic benefit (Simpson, 2006).

Glioblastoma multiforme is characterized by intense angiogenesis, representing a key event in tumor growth and progression (Kargiotis O, Fisher I). Vascular endothelial growth factor (VEGF) represents a key growth factor in GBM neoangiogenesis. Inhibition of angiogenesis, therefore, is an important direction in development of novel therapeutics in the treatment of GBM (Rubenstein JL; Fong TA; Laird AD; Kunkel P; Goldbrunner RH). In a recently presented trial of Avastin® in combination with irinotecan, in recurrent high grade glioma patients, a 63% objective response rate and a median progression-free survival of 24 weeks was observed (Vredenburgh, 2007). Although the mechanism of action of Avastin® in this context need to be elucidated and the role of single agent Avastin® in the treatment of recurrent GBM will be further defined in ongoing trials, this initial report emphasizes angiogenesis inhibition as a direction worth exploring in the treatment or recurrent glioblastoma multiforme.

Sorafenib is a small molecule inhibitor that inhibits the kinase activity of Raf, VEGFR2 (the main VEGFR receptor in GBM) and PDGFR- β . Both VEGFR-2 and PDGFR- β play a key role in driving angiogenesis, and aberrant activation of Ras signaling is a common finding in human glioblastomas (Knobbe et al, 2004). Single agent dose of Sorafenib® in recurrent GBM patients is 600 mg bid for patients not on enzyme-inducing anticonvulsants (EIAC) and 800 mg bid for patients on EIACs. Initial efficacy analysis showed antitumor responses and prolonged time to progression in some patients, final efficacy analysis ongoing and will soon be reported (b. Nabors, personal communication).

Two phase I studies evaluating the combination of Avastin® and sorafenib have been reported during ASCO 2006 (Azad 2006, Sosman et al, 2006). Dose-limiting toxicities (DLTs) included proteinuria, hypertension and hand-foot syndrome. Other toxicities included stomatitis, elevated liver function tests (LFTs), rhinorrhea, fatigue, anorexia, and GI fistulas.

Of note, objective responses were noted in ovarian and renal cell carcinoma patients. Based on these phase I data, the original starting dose in this glioblastoma multiforme trial was sorafenib 200 mg bid for 5/7 days and Avastin® 5 mg/kg every two weeks. As of Addendum 9, the starting dose is sorafenib 200 mg daily and Avastin® 5 mg/kg every 2 weeks.

1.2 Correlative analysis

The goals of the correlative analyses will be to help us define patient populations more likely to benefit from treatment and characterize a tumor blood vessel normalization window. It is of note that the translational experiments are going to be conducted in parallel to the planned phase II trials with sorafenib/Avastin® in patients with metastatic colorectal cancer (NCCTG N054C) and hepatocellular carcinoma (N0745) to obtain a larger sample size for correlative conclusions. These planned analyses include:

Add 4,16

1.21 Immunohistochemistry (IHC) for proteins involved in regulating angiogenesis (i.e., VEGF, VEGFR1, VEGFR2, VEGFR3, carbonic anhydrase [CA-9], PDGFR α and β , HIF1 α , HIF2 α , neuropilin-1 [NRP-1], NRP-2), and for microvessel density, as assessed by CD31 staining will be performed in baseline tumor tissue to assess expression. Given preclinical data in other tumor types (hepatocellular carcinoma) indicating that phospho-ERK can predict clinical benefit following treatment with sorafenib, phospho-ERK will be assessed by IHC (Abou-Alfa GK, et al, 2006).

1.22 Cellular biomarkers of vascular response to include circulating endothelial cells and circulating endothelial progenitor cells prior to and after treatment will be evaluated in peripheral blood. Circulating endothelial cell increase has been associated with progression on treatment and circulating endothelial progenitor cell increase has been associated with progression following treatment breaks in the trial of the AZD2171 VEGF TK inhibitor (Batchelor et al, 2007).

Add 4,16

1.23 Molecular biomarkers of vascular response to include, but not limited to, circulating VEGFA, VEGFC, HGF, Angiopoietin-2 (Ang-2), PlGF, soluble VEGFR1, VEGFR2, and VEGFR3, soluble KIT, bFGF, SDF1- α , PDGFC, G-CSF, IL-8, E-selectin, and ICAM-1 will be measured with GBM progression following angiogenesis inhibition (Batchelor, et al, 2007)

2.0 Goals

2.1 Treatment

2.11 Primary

2.111 To identify any clinical efficacy of the Avastin® combination with sorafenib in recurrent glioblastoma multiforme as measured by six month progression-free survival.

2.112 To assess the safety and adverse events of the Avastin® combination with sorafenib in this patient population

2.12 Secondary

2.121 To assess time to progression and overall survival in this patient population.

2.2 Translational Research

2.21 To assess the utility of dynamic contrast enhanced MRI as predictor of response to combination treatment.

- 2.22 To determine the relationship between tumor biomarkers and circulating biomarkers of vascular response and clinical outcome in recurrent glioblastoma multiforme patients treated with the sorafenib/Avastin® combination.
- 2.23 To assess the impact of treatment on the patient's quality of life using the FACT-Br.
- 2.24 As part of ongoing research for NCCTG studies, we are banking leftover tissue and blood products (i.e., plasma, DNA, and buffy coat) for future studies.

3.0 Patient Eligibility

3.1 Pre-registration – Inclusion Criteria

- 3.11 Central pathology review submission. This review is mandatory prior to registration to confirm eligibility (see Section 17.2). **It should be initiated as soon as possible after pre-registration.**

3.2 Registration – Inclusion Criteria

- 3.21 ≥ 18 years of age.
- 3.22 Histological confirmation of glioblastoma multiforme as determined by pre-registration central pathology review. NOTE: Gliosarcomas are eligible
- 3.23 Evidence of tumor progression by MRI or CT scan following RT or following the most recent anti-tumor therapy.
- 3.24 Bidimensionally measurable or evaluable disease by MRI or CT scan.
- 3.25 ECOG Performance Status (PS) 0, 1, or 2. NOTE: This form is now on the NCCTG website <https://nctg.mayo.edu/nctg/forms/NonProtocolSpecificForms>.

Add 1 3.26 ≤ 1 chemotherapy regimen for progressive/recurrent disease.

Add 1 3.27 ≥ 12 weeks since the completion of RT.

Add 1 3.28 The following laboratory values obtained ≤ 21 days prior to registration.

- ANC ≥ 1500
- PLT $\geq 100,000$
- Hgb > 9.0 g/dL
- T. bili ≤ 1.5 x UNL
- SGOT (AST) ≤ 3 x UNL
- Creatinine \leq UNL

Add 1 3.29a UPC ratio < 1 . NOTE: Urine protein must be screened by urine analysis for Urine Protein Creatinine (UPC) ratio. For UPC ratio ≥ 1.0 , 24-hour urine protein must be obtained and the level should be < 1000 mg.

Add 1 3.29b Negative pregnancy test done ≤ 7 days prior to registration, for women of childbearing potential only.

Add 1 3.29c Ability to complete questionnaire(s) by themselves or with assistance.

- Add 1 3.29d Provide informed written consent.
- Add 1 3.29e Willingness to return to NCCTG enrolling institution for follow-up.
- Add 1 3.29f Patient willing to provide mandatory blood samples for research purposes (see Sections 6.22 and 14.0).
- Add 1 3.29g Fixed dose of corticosteroids (or no corticosteroids) ≥ 1 week prior to baseline scan.

3.3 Registration – Exclusion Criteria

- 3.31 Any of the following:
- Pregnant women
 - Nursing women
 - Men or women of childbearing potential who are unwilling to employ adequate contraception during the study and up to 6 months after the last treatment dose

NOTE: Avastin® and sorafenib are investigational agents whose genotoxic effects on the developing fetus and newborn are unknown.

- 3.32 Prior intratumoral chemotherapy, stereotactic radiosurgery or interstitial brachytherapy. EXCEPTION: Separate lesion on MRI which is not part of the previous treatment field or there is proof of recurrent disease based on biopsy, MRI spectroscopy, or PET scan.
- 3.33 Inadequately controlled hypertension (systolic blood pressure of >150 mmHg or diastolic pressure >100 mmHg on anti-hypertensive medications). NOTE: Patients with well-controlled hypertension are eligible.
- Add 3 3.34 Receiving enzyme-inducing antiepileptic drugs (EIACs; *e.g.*, phenytoin, fosphenytoin, carbamazepine, phenobarbital, or primidone) or any other potent CYP3A4 inducer such as rifampin or St. John's wort. Note: See Appendix IV for a complete list.
- 3.35 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.
- 3.36 Immunocompromised patients (other than that related to the use of corticosteroids) including patients known to be HIV positive.
- 3.37 Any condition (*e.g.*, gastrointestinal tract disease resulting in an inability to take oral medication or a requirement for IV alimentation, or prior surgical procedures affecting absorption) that impairs ability to swallow pills.
- Add 1 3.38 Receiving therapeutic anticoagulation with Coumadin. NOTE: Prophylactic anticoagulation (*i.e.*, low dose warfarin) of venous or arterial access devices is allowed, provided that INR <1.5 . Therapeutic anti-coagulation with low molecular weight heparin is allowed at time of registration and during the study if needed.

- 3.39a Evidence of bleeding diathesis (greater than normal risk of bleeding) or coagulopathy (in the absence of therapeutic anticoagulation).
- 3.39b 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.
- 3.39c Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.
- 3.39d Other active malignancy ≤ 3 years prior to registration. EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix. NOTE: If there is a history of prior malignancy, they must not be receiving other specific treatment (other than hormonal therapy) for their cancer.
- 3.39e History of myocardial infarction or unstable angina ≤ 6 months prior to registration, or congestive heart failure requiring use of ongoing maintenance therapy for life-threatening ventricular arrhythmias.
- 3.39f New York Heart Association (NYHA) \geq Class II CHF. NOTE: This form is now on the NCCTG website <https://ncctg.mayo.edu/ncctg/forms/NonProtocolSpecificForms>
- 3.39g Core biopsy or other minor surgical procedures ≤ 7 days prior to registration. NOTE: Placement of a vascular access device is allowed.
- 3.39h Major surgical procedure, open biopsy, or significant traumatic injury ≤ 28 days prior to registration or anticipation of need for major surgical procedure during the course of the study.
- 3.39i Significant vascular disease (e.g., aortic aneurysm, aortic dissection) or recent peripheral arterial thrombosis ≤ 6 months prior to registration.
- 3.39j History of hypertensive crisis or hypertensive encephalopathy.
- 3.39k Known hypersensitivity to any of the components of sorafenib or Avastin®.
- 3.39l Serious, nonhealing wounds, ulcers, or bone fractures.
- 3.39m History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess ≤ 6 months prior to registration.
- 3.39n Active or recent history of hemoptysis ($\geq \frac{1}{2}$ teaspoon of bright red blood per episode) ≤ 30 days prior to registration.
- 3.39o Prior anti-angiogenic therapy.
- 3.39p History of stroke or transient ischemic attack (TIA) ≤ 6 months prior to registration.

- Add 10 3.39q Any evidence of CNS hemorrhage on baseline CT or MRI. Note: T1 hyperintensity confined to the surgical cavity, which is felt likely due to post surgical blood contaminating the intracavity CSF or irrigation that have not yet absorbed, and which is not felt to clinically or radiographically represent new spontaneous hemorrhage, would be acceptable. Old blood products or hemosiderin, without a history of spontaneous bleeding, would also be acceptable. If there are questions or concerns, the investigator should discuss the individual situation directly with the protocol PI
- Add 10 3.39r Any of the following:
- ≤6 weeks since last day of nitrosourea-based chemotherapy and/or
 - ≤4 weeks since last day of other chemotherapy prior to registration
 - ≤2 weeks since last day of small molecule cell cycle inhibitors prior to registration

4.0 Test Schedule

4.1 Table

		Active Monitoring Phase				
Tests and procedures		Pre-reg	≤21 days prior to reg	Prior to each new cycle	Prior to 5 th cycle and then every 4 th cycle (8 weeks) thereafter (≤7 days) (e.g. end of cycles 4, 8, 12, etc.)	At PD, withdrawal, or removal
Add 12	Pathology review (see Section 17.2)	X ⁴				
Add 12	History and exam, wt, PS, blood pressure		X	X ¹²		X
Add 12	Height		X			
Add 12	Neuro history and exam		X	X ⁹		
	Adverse event assessment		X	X		X
	Blood pressure check		X ⁶	X ⁶		
	Hematology ANC, WBC, PLT, Hgb		X	X		X
Add 7	Chemistry: SGOT [AST], alk phos, T. bili, creatinine, calcium, phos, glucose, Na, K, lipase and amylase		X	X		
	Chemistry: Lipid panel		X			
Add 4,7	Coagulation PT/INR ^R		X	X ⁷		
	activated partial thromboplastin time ^R , Fibrinogen ^R		X			
Add 12	Urine protein: creatinine ratio		X ^{R,8}	X ^{R,8,9}		
Add 10	MRI with contrast or CT with contrast – tumor assessment		X ²		X ²	X ²
Add 12	DCE MRI (Mayo Rochester ONLY first 20 patients)		X ^R	X ^{R,10}	X ^{R,10}	
	ECG		X		As clinically indicated	
	Recording of steroid and anticonvulsant dose		X	X		X
	Pregnancy test		X ¹			
	Patient Medication Diary (Appendix III)			X ³		
Add 7,12	Patient Blood Pressure Diary (Appendix II)			X ¹³		
Add 10,12	Quality of Life Questionnaire (FACT-Br) (Appendices V and VI)		X	X ⁹		
Add 10,11,12	Mandatory blood sample (see Section 14.0) ^R		X ⁵	X ⁵		X ⁵
	Optional tissue sample (see Section 17.0) ^R		X ¹¹			

(See next page for footnotes)

R Research funded – see Section 19.0 for details.

1 For women of childbearing potential, ≤ 7 days prior to registration.

2 MRI preferred; however, patients who have medical contraindications are still eligible for study by substituting contrast enhanced CT.

Add 7

3 Patient completes beginning the day the patient starts taking sorafenib and then on a daily basis throughout the study and returns at next visit **OR** compliance can be documented in the medical record.

4 If materials have been previously submitted to Mayo Neuropathology for a consult review, fax a copy of this review to the NCCTG pathology coordinator (507-284-9628) to verify grade 4 astrocytoma. Then follow the pathology material procedures found in Section 18.0 so the process can be completed.

Add 2,11

5 Submission of blood for mandatory translational research will be collected: Baseline (i.e., ≤ 2 weeks before start of therapy); Cycle 1 Day 3 (± 1 day); prior to treatment Cycle 2; prior to treatment Cycle 3; prior to treatment every 4 weeks thereafter x 5 (i.e., Cycles 5, 7, 9, 11, and 13), and at disease progression, withdrawal, or removal. Kits are required for this collection. See Section 14.0.

6 Monitored weekly during first six weeks. This can be done either at the doctor's office or using any calibrated electronic device (such as those found at a local drug store or pharmacy). Patient should call the study doctor if it is elevated. Hypertensive medication should be initiated or increased per routine practice. The patient will complete a Patient Blood Pressure Diary (Appendix II). The diary should be returned at the next scheduled visit.

Add 7

7 For patients on Coumadin, repeat PT/INR weekly for the first 4 weeks, and then as clinically indicated.

Add 12

8 a) Obtain at least 4 mL of a random urine sample (does not have to be a 24-hour urine)

b) Determine protein concentration (mg/dL)

c) Determine creatinine concentration (mg/dL)

d) Divide b by c: urine protein/creatinine ratio = protein concentration (mg/dL)/creatinine concentration (mg/dL)

The UPC directly correlates with the amount of protein excreted in the urine per 24 hours (for example, a UPC of 1 should be equivalent to 1 gram protein in a 24-hour urine collection). Protein and creatinine concentrations should be available on standard reports of urinalyses, not dipsticks.

Add 12

9 To be done every second cycle.

Add 1,12

10 At baseline, Cycle 1 Day 3 (+/-1 day), prior to the 3rd cycle (Day 28) (+/-2 days), prior to the 5th cycle of treatment (+/-2 days). DCE component in subsequent MRIs is optional (see Section 4.2).

11 To be submitted ≤ 30 days following registration.

Add 12

12 Optimal control of blood pressure according to standard guidelines is recommended.

Add 7,12

13 Recorded weekly during first 3 cycles (total 6 weeks) of sorafenib therapy.

Add 10

4.2 DCE MR research testing – Mayo Rochester ONLY first 20 patients

Patients will receive standard morphological brain tumor imaging at the intervals specified, to include gadolinium chelate contrast material. Additionally, brain perfusion imaging and permeability imaging will be performed, as means of evaluating brain tumor response to therapy. Standard clinical dynamic susceptibility contrast (DSC) T2 or T2*-weighted first-pass perfusion imaging will be performed, but also T1-weighted dynamic contrast enhanced (DCE) permeability imaging will be performed, from first pass into the steady state. DSC perfusion yields relative cerebral blood volume data, which correlates with brain tumor neovascularity volume, and which is frequently used in clinical and research brain tumor imaging analysis. T1-weighted DCE yields permeability data such as k-trans, a measure of brain tumor neovascular permeability, which is frequently used in anti-angiogenesis therapy evaluation. Performing both DSC and DCE perfusion requires two separate IV bolus injections of contrast material, although the total dose of gadolinium required would only be approximately 1.5 times the routine dose (i.e., approximately 30 mL of gadolinium chelate contrast material). Patient's estimated GFR will be calculated and checked before administration of gadolinium, per standard Department of Radiology clinical protocol.

5.0 Stratification Factors: None.

6.0 Registration/Randomization Procedures

6.1 Pre-Registration (Step 1)

6.11 To pre-register a patient, access the NCCTG web page at <https://ncctg.mayo.edu/training> and enter the remote registration/randomization application. The remote registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the NCCTG Registration Office at (507)-284-4130 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for remote registration are available on the NCCTG web page and detail the process for completing and confirming patient pre-registration. Users should refer to the section titled "Pre-Registration Components" for details on how to pre-register a patient to a study. At the time of pre-registration the patient will receive an NCCTG patient identification number. This number is to be used when submitting tissue or blood samples, if applicable for the study (See Sections 14.0 and/or 17.0). Patient pre-registration via the remote system can be confirmed in any of the following ways:

- Contact the NCCTG Registration Office (507)-284-4130. If the patient was pre-registered, the Registration Office staff can access the information from the centralized database and confirm the pre-registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.12 IRB approval(s) is required for each treating site. A signed Cancer Trials Support Unit (CTSUS) IRB Certification Form is to be on file at the CTSU Regulatory Office (fax 215-569-0206). This form can be found at the following Web site: www.ctsu.org/rss2_page.asp. Guidelines can be found under Quick Fact Sheets.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the CTSU Regulatory Office (fax 215-569-0206). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the CTSU is no longer necessary.

- 6.13 Prior to accepting the pre-registration/randomization, the remote registration/randomization application will verify the following:
- IRB approval at the registering institution
 - Patient eligibility
 - Existence of a signed consent form
 - Existence of a signed authorization for use and disclosure of protected health information (*U.S.A. institutions only*)

- 6.14 The site has reviewed and understands the process listed in Section 17.0 and must account for sufficient time to complete pre-registration and registration steps.

6.2 Registration (Step 2)

- 6.21 To register a patient, access the NCCTG web page at <https://ncctg.mayo.edu/training> and enter the remote registration/randomization application. The remote registration/ randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If you are unable to access the website, call the NCCTG Registration Office at (507) 284-4130 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for remote registration are available on the NCCTG web page and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and an NCCTG subject ID number must be available as noted in the instructions.

It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the remote system can be confirmed in any of the following ways:

Contact the NCCTG Registration Office (507) 284-4130. If the patient was fully registered, the Registration Office staff can access the information from the centralized database and confirm the registration.

- Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”

- 6.22 A mandatory translational research component for blood is part of this study; the patient will be automatically registered onto this component (Sections 3.29f and 14.0).

- 6.23 An optional translational research component for tissue is part of this study. There will be an option to select if the patient is to be registered onto this component (Section 17.3).

- Patient has/has not given permission to give tissue sample(s) for research testing.

- 6.24 At the time of registration, the following will also be recorded:
- Patient has/has not given permission to keep tissue sample(s) for use in future research to learn about, prevent, or treat cancer.
 - Patient has/has not given permission to keep blood sample(s) for use in future research to learn about, prevent, or treat cancer.
 - Patient has/has not given permission to keep tissue sample(s) for use in future research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
 - Patient has/has not given permission to keep blood sample(s) for use in future research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
 - Patient has/has not given NCCTG permission to give tissue sample(s) to outside researchers.
 - Patient has/has not given NCCTG permission to give blood sample(s) to outside researchers.
 - Patient has/has not given NCCTG permission to be contacted in the future to take part in more research.
- 6.25 Treatment on this protocol must commence at the accruing membership under the supervision of a NCCTG member physician.
- 6.26 Treatment cannot begin prior to registration and must begin ≤ 14 days after registration.
- 6.27 Pretreatment tests/procedures must be completed within the guidelines specified on the test schedule.
- 6.28 All required baseline symptoms must be documented and graded.
- 6.29a Study drug availability checked.
- 6.29b Blood draw kit availability checked.
- 6.29c Patient questionnaire FACT-Br booklet availability checked; copies are not acceptable for this submission.
- 6.29d Patient has/has not agreed to be enrolled on N0392.

7.0 Protocol Treatment

7.1 Treatment Schedule

Agent	Dose Level ³	Route	Day ²
Sorafenib	200 mg /dose*	PO ¹	Days 1-14
Avastin®	5 mg/kg	IV infusion over 90 (\pm 15) minutes ³	1 every 14 days

Add 9

Add 9,
10

Add 9

Add 9

Add 9

* Dose is 200 mg total daily dose, i.e., it is not based on weight.

Cycle length = 14 days

1. Patients will take their pills at home. Patients are to swallow the tablets whole with about 250 mL (8 oz.) of water consistently at about the same time each day at a time which is convenient for the patient (i.e., 24 hours apart). Tablets should be taken without food (at least one hour before or two hours after eating). The patient will be asked to complete a patient medication diary (Appendix III). The diary should be returned at the next scheduled visit.
2. If any daily doses are missed, they will not be made up. The cycle length remains 14 days despite missed doses.
3. If well-tolerated, second dose may be administered over 60 (\pm 10) minutes. Again, if well-tolerated, subsequent doses may be administered over 30 (\pm 10) minutes. If the patient is pre-medicated for infusion reaction, maintain previous infusion rate for first pre-medicated infusion. If well-tolerated with pre-medication, the subsequent infusion time may then be decreased by 30 minutes, as long as the subject continues to be pre-medicated. If the patient experiences infusion associated adverse events with the 60-minute infusion, all subsequent infusions should be given over 90 minutes. Similarly, if a patient experiences infusion associated adverse events with the 30-minute infusion, all subsequent doses should be given over 60 minutes.

NOTE: Anticonvulsants should be used as clinically indicated. If it is necessary to switch or add anticonvulsant medications, they should be placed on another non-EIAC. If patient requires a change to an EIAC for clinical reasons, study chair **MUST** be consulted because EIACs may alter sorafenib metabolism (efficacy).

- 7.2 For this protocol, the patient must return to a NCCTG institution for evaluation at least every 14 days.
- 7.3 Treatment by an LMD is not allowed. Treatment can only be done at the NCCTG accruing institution. Treatment will be administered on an outpatient basis.

8.0 Dosage Modification Based on Adverse Events - Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

If an adverse event is not covered in the table, doses may be reduced or held at the discretion of the investigator for the subject's safety. Dose adjustments for hematological adverse events are based on the blood counts obtained in preparation for the day of treatment.

- 8.1 Dose reductions for sorafenib will be according to the table below:

Add 4

Dose Level	Sorafenib	Avastin®
0	200 mg BID (days 1 through 5 and 8 through 12)	5 mg/kg/day – no reduction
-1*	200 mg QD (days 1 through 14)	5 mg/kg day 1 every 14 days – no reduction
-2	200 mg QOD (days 1 through 14)	5 mg/kg day 1 every 14 days – no reduction

Add 9

Add 5,9

Add 9

*Starting dose as of Addendum 9

- 8.2 Following dose reduction, if the dose is maintained for 4 weeks without further dose reduction, subsequent dose escalation to prior levels may be considered.

Add 10,12

- 8.3 Dose reductions below the -2 dose level are not allowed. If any patient has further adverse event(s) that would require further reduction, or if treatment is held for more than 3 consecutive weeks because of ongoing adverse event(s), patients will be discontinued from study and will go to event monitoring unless the study chair and investigator agree that the subject should remain in the study because of evidence that the patient has, and may continue to derive, benefit from continuing study treatment.

ALERT: ADR reporting may be required for some adverse events (See Section 10)

→ → Use Common Terminology Criteria for Adverse Events (CTCAE) v3.0 unless otherwise specified ← ←

CTCAE v3.0 CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
<i>At Time of Retreatment</i>			
Blood/Bone Marrow	ANC/AGC <1500/mm ³ OR PLT <50,000/mm ³	Sorafenib	Hold dose*. Resume treatment when ANC ≥1500 and platelets ≥50,000 and decrease by one dose level. If no recovery after a 3-week delay, despite institution of all clinically appropriate symptomatic treatment, discontinue sorafenib. Dose may not be re-escalated after reduction for adverse event.
Cardiac General	Hypertension	Sorafenib Avastin®	See Section 8.4 for management.
	Other: Congestive heart failure Grade 3	Avastin®	Hold* until resolution to grade ≤1. Then resume treatment. If second recurrence, discontinue Avastin®. Discontinue Avastin®.
	Grade 4		
Dermatology/ Skin	Rash: Hand/foot skin reaction Grade 2 and 3 (see Section 8.5)	Sorafenib	Hold dose*. • Re-evaluate at least weekly until adverse event resolved to ≤1 or tolerable grade 2. • Re-treat at a one dose level reduction • If toxicity returns to grade 3, or intolerable grade 2, discontinue sorafenib. • Patients with grade 4 adverse events related to agent may be taken off sorafenib at investigator discretion.
	Rash: acne/acneiform Grade 2 and 3		
	Wound complication, non-infectious (dehiscence) ≥grade 2		
Gastrointestinal	Fistula, GI – abdominal Any grade	Avastin®	Discontinue Avastin®.
	Leak (including anastomotic), GI Any grade		
	Obstruction, GI Grade 2		Hold* until resolution of obstruction. Then resume treatment. Hold* until resolution. If surgery is necessary, patient may restart >28 days but ≤56 days following surgery and at investigator's discretion
	Grade 3-4		
Perforation, GI Any grade	Discontinue Avastin®.		
Hemorrhage/ Bleeding – non CNS, non pulmonary	Grade 3	Sorafenib Avastin®	Subjects who are also receiving full-dose anticoagulation will discontinue and go to event monitoring All other subjects hold until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. Subjects who experience a repeat Grade 3 hemorrhagic event will discontinue and go to event monitoring.

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	Grade 4	Sorafenib Avastin®	Discontinue and go to event monitoring.
Hemorrhage/ Bleeding – CNS or pulmonary	Grade 1		Subjects who are also receiving full-dose anticoagulation will discontinue and go to event monitoring All other subjects hold until all of the following criteria are met: <ul style="list-style-type: none"> • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.
	Grade ≥2		Discontinue and go to event monitoring
Metabolic/ Laboratory	Proteinuria Grade 3 (≥3.5 g/24 hr) Grade 4 (nephritic syndrome)	Avastin®	Hold* until proteinuria improves to ≤grade 2. Then resume treatment. Discontinue Avastin®.
Neurology	CNS cerebrovascular ischemia Any grade		Discontinue Avastin®.
	Leukoencephalopathy syndrome (radiographic findings)		Hold* pending workup and management, including control of blood pressure. Discontinue if RPLS diagnosed and go to event monitoring. Resumption of Avastin® may be considered in patients who have documented benefit from the agent, provided that RPLS was <u>mild</u> and has <u>completely</u> resolved clinically and radiographically within 3 weeks; decision to resume Avastin® in these patients <u>must</u> be discussed with the study chair and approved by the sponsor
Vascular	Thrombus/embolism Grade 3 or asymptomatic grade 4		Hold*. If the planned duration of full-dose anticoagulation is <2 weeks, Avastin® should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is ≥3 weeks, Avastin® may be resumed during the period of full-dose anticoagulation if all of the following criteria are met: <ul style="list-style-type: none"> • The subject must have an in-range INR (usually between 2 and 3) if on warfarin; LMWH, warfarin, or other anticoagulant dosing must be stable prior to restarting Avastin® treatment • The subject must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation
	Grade 4 (symptomatic thrombosis)		Discontinue Avastin®.
	Peripheral arterial ischemia Any grade		Discontinue Avastin®.

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	Visceral arterial ischemia Any grade		Discontinue Avastin®.
All other non-hematologic adverse events (excluding alopecia)	Grade 2-4 (excludes nausea/vomiting that has not been pre-medicated)	Sorafenib Avastin®	Hold* responsible agent/agents until resolved to grade 0-1 adverse event, then decrease by one dose level. If no recovery after a 3-week delay, despite institution of all clinically appropriate symptomatic treatment, discontinue one or both agents depending on attribution.

* **If any daily doses are missed, they will not be made up.** The cycle length remains 14 days despite missed doses. EXCEPTION: If patient has surgery for GI obstruction, see table below for treatment guidelines.

8.4 Management of Hypertension

Add 12

Add 12

Add 12

Grade (CTCAE v3.0)	Antihypertensive Therapy	Blood Pressure Monitoring	Sorafenib/Avastin® 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), beta-blocker, thiazide diuretic)	Increase frequency and monitor (by health professional) every 2 days until stabilized; continue q2d monitoring to stabilization after dosing restarted.	Hold* until symptoms resolve <u>and</u> diastolic BP ≤100 mm/Hg, and resume treatment at 1 dose level lower. If not controlled to 150/100 with medication discontinue treatment, go to event monitoring
Grade 4			Discontinue therapy go to event monitoring
* Patients requiring a delay of >3 weeks should go off protocol therapy then go to event monitoring.			
CTCAE v3.0 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)			

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- 8.5 Patients experiencing Hand-Foot syndrome should have their signs and symptoms graded according to the following system:

Grade 1	Numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort which does not disrupt normal activities. (CTCAE v3.0 definition: minimal skin changes or dermatitis [e.g., erythema] without pain)
Grade 2	Painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities (CTCAE v3.0 definition: skin changes [e.g., peeling, blisters, bleeding, edema] or pain, not interfering with function)
Grade 3	Moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living. (CTCAE v3.0 definition: ulcerative dermatitis or skin changes with pain interfering with function)

9.0 Ancillary Treatment/Supportive Care

- 9.1 Antiemetics may be used at the discretion of the attending physician.
- 9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. J Clin Oncol 24(19): 1-19 AND American Society of Clinical Oncology/American Society of Hematology 2007 Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin J Clin Oncol 25(34): 1-17. (See www.asco.org website)
- 9.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.
- 9.4 Hypertension is a known and potentially serious adverse event associated with sorafenib and Avastin® treatment. Patients will have their blood pressure monitored and recorded weekly during the first cycle of therapy, either at the doctor's office or using any calibrated electronic device (such as those found at a local drug store or pharmacy). Patients will be provided with a Patient Blood Pressure Diary (Appendix II) on which to record the measurements. An increase in blood pressure of >20 mmHg (systolic) and 10 mmHg (diastolic) should be reported to the treatment physician immediately. (See Section 8.0 for hypertension management and dose reduction guidelines)
- 9.5 Anti-platelet therapy (e.g., ≤ 325 mg/day aspirin) should be considered for the treatment of patients at high risk of developing an arterial thromboembolic event unless contraindicated and may be continued in patients receiving it at time of entry. Patients developing bleeding on study should be evaluated for possible Avastin® discontinuation as described in the protocol.

- 9.6 Patients with indwelling venous catheters may receive prophylaxis anticoagulation against catheter thrombosis in accordance with the local standard of care.
- 9.7 Hand-foot syndrome: The use of NSAIDs, corticosteroid creams, and/or antihistamines are allowed at physician discretion. Treatment with topical emollients (such as Aquaphor) for symptom relief is permitted.
- 9.8 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

- 9.9a If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed.
- 9.9b Patients who experience infusion-associated temperature elevations to $\geq 38.5^{\circ}\text{C}$ (101.3°F) or other infusion-associated symptoms may be treated symptomatically with acetaminophen, diphenhydramine, meperidine, or other medications as clinically indicated.
- 9.9c Sorafenib is metabolized by the P450 CYP3A enzyme and has been shown in preclinical studies to inhibit multiple CYP isoforms. Therefore, it is possible that sorafenib may interact with drugs that are metabolized by the P450 CYP isoenzymes or with drugs that inhibit CYP3A. Close monitoring is recommended for patients taking agents with narrow therapeutic indices and metabolized by the liver, such as warfarin, quinidine, cyclosporine, and digoxin. See Appendix IV for a complete list of Drugs Known to be Metabolized by CYP450 Isoenzymes 2D6 and 3A4.
- 9.9d Anticonvulsants should be used as clinically indicated. If it is necessary to switch or add anticonvulsant medications, they should be placed on another non-EIAC. If patient requires a change to an EIAC for clinical reasons, study chair **MUST** be consulted because EIACs may alter sorafenib metabolism (efficacy).

10.0 Adverse Event (AE) Reporting and Monitoring

- 10.1 CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized until June 30, 2011. CTCAE version 4.0 will be utilized for expedited adverse event reporting only, beginning July 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE v4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>).
- 10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE. Next, determine whether the event is expected or unexpected (refer to Section 10.12) and if the adverse event is related to the medical treatment or procedure (see Section 10.13). With this information, determine whether an adverse event should be reported as an expedited report (see Section 10.2). **Important:** All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Section 10.3 and 18.0).

Expedited adverse event reporting requires submission of an Adverse Event Expedited Reporting System (AdEERS) report(s). Other expedited reporting requirements and systems may also apply. Expedited and/or routine reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.2 and 10.3. All expedited AE reports must also be sent to the local Institutional Review Board (IRB) according to local IRB's policies and procedures.

Add 15

Effective with Addendum 15, and beginning July 1, 2011, expedited AdEERS reporting for this protocol has been updated by the NCI/CTEP to use CTCAE v4.0. Therefore:

- 1) Events reporting expedited reporting through AdEERS must be reported through the AdEERS system in CTCAE v4.0.
- 2) The events reported via AdEERS must ALSO be reported through routine reporting (i.e., Case Report Forms) using CTCAE v3.0.
- 3) Routine data collection via Case Report Forms, including the "Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form," will remain using CTCAE v3.0 for this study.

10.12 Expected vs. Unexpected

- The determination of whether an AE is expected is based on the agent-specific information provided in Section 15.0 of this protocol.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of this protocol.

10.13 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).

Probable - The adverse event *is likely related* to the agent(s).

Possible - The adverse event *may be related* to the agent(s).

Unlikely - The adverse event *is doubtfully related* to the agent(s).

Unrelated - The adverse event *is clearly NOT related* to the agent(s).

10.2 Expedited Adverse Event Reporting Requirements

10.21 Requirements for Expedited **Investigational** Reporting via AdEERS for Adverse Events That Occur Within 30 Days¹ of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 3		Grade 3		Grades 4 & 5
	Unexpected and Expected	Unexpected and Expected	Unexpected with Hospitalization	Unexpected without Hospitalization	Expected with Hospitalization	Expected without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Not Required	Not Required	Not Required ²	Not Required	Not Required ²	Not Required	Not Required ²
Possible Probable Definite	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	24-Hour; 3 Calendar Days
<p>¹ Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under an IND require reporting as follows: AdEERS 24-hour notification followed by complete report within 3 calendar days for:</p> <ul style="list-style-type: none"> • Grade 3 unexpected events with hospitalization or prolongation of hospitalization • Grade 4 unexpected events • Grade 5 expected events and unexpected events <p>² Although expedited reporting via AdEERS is not required for hospitalizations or Grade 4 or 5 events with attribution of unlikely or unrelated, other expedited <u>and</u> routine reporting requirements must be adhered to. Please refer to the sections below for related instructions.</p> <p>Please see additional instructions and/or exceptions below under section entitled “Additional Instructions or Exceptions.”</p>							

- Expedited AE reporting timelines defined:
 - “24 hours; 3 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 3 calendar days of the initial 24-hour report.
 - “7 calendar days” - A complete AdEERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.
- Any event that results in persistent or significant disability/incapacity, congenital anomaly, or birth defect must be reported via AdEERS if the event occurs following treatment with an agent under an IND.
- SECONDARY MALIGNANCIES (defined as “cancer caused by treatment for a previous malignancy,” e.g., treatment with radiation of chemotherapy) are to be reported through AdEERS, as noted in Section 10.22. Secondary malignancies are not considered metastasis of the initial neoplasm. Secondary malignancy is unrelated to the first cancer that was treated, and may occur months or even years after initial treatment.

Note: Secondary malignancy (malignancy not due to prior treatment) should not be reported through AdEERS.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all expedited reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements

- The NCCTG SAE Coordinator will forward a copy of all AdEERS reports to:
 - The NCCTG IND Coordinator who will notify the FDA as warranted by the event and stipulated in the U.S. Code of Federal Regulations.
 - Genentech (FAX: 650/225-4682 or 650/225-5288)
 - Bayer/Onyx: DrugSafety.GPV.US@bayer.com (**within 24 hours**)
- In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report **MUST** be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP web site and will **NO LONGER** be accepted.

Add 1

Add 15

10.22 Other Required Expedited Reporting

EVENT TYPE	REPORTING PROCEDURE
Secondary AML/MDS	<p>Reporting for this event required during and after completion of study treatment via AdEERS.</p> <p>Through June 30, 2011, continue using CTCAE v3.0: Report Myelodysplasia as “Blood/Bone Marrow – Myelodysplasia” and Leukemias as “Blood/Bone Marrow – Other (Specify, _____).”</p> <p>Beginning July 1, 2011, AdEERS will only accept CTCAE v4.0 for this study. Report these events using “Neoplasms benign, malignant and unspecified (incl. cysts and polyps)” and including the appropriate adverse event:</p> <ul style="list-style-type: none"> - Leukemia secondary to oncology chemotherapy OR - Myelodysplastic syndrome OR - Treatment related secondary malignancy
Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report	<p>Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form within 5 working days, using CTCAE v3.0, of the date the clinical research associate (CRA) is aware of the event(s) necessitating the form.</p> <p>If an AdEERS report has been submitted, this form does not need to be submitted.</p> <p>You must use CTCAE v3.0 for data submission with this form. The events reported on this form must also appear on the Case Report Forms (i.e., routine data) for this study.</p> <p>Submit the Non-AER form electronically via the NCCTG Remote Data Entry System within 5 working days of the date the CRA is aware of the event(s) necessitating the form.</p> <p>The NCCTG SAE Coordinator will notify the NCCTG IND Coordinator who will submit to the FDA IND as warranted by the event and stipulated in the U.S. Code of Federal Regulations.</p>

Add 15

Add 15

- 10.3 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per Common Terminology Criteria for Adverse Events (CTCAE) v3.0 grading unless otherwise stated:

Add 15

Category (CTCAE v3.0)	Adverse Event/Symptoms	Baseline	Each evaluation	
Cardiac General	Hypertension	X	X	
Constitutional Symptoms	Fatigue (lethargy, malaise, asthenia)	X	X	
	Fever (in the absence of Neutropenia, where Neutropenia is defined as ANC <1.0 x 10 ⁹ /L)		X	
	Weight loss		X	
Dermatology/Skin	Rash/desquamation	X	X	
	Rash: hand-foot skin reaction	X	X	
	Wound complication, non-infectious	X	X	
Gastrointestinal	# stools per day	X		
	Anorexia	X	X	
	Diarrhea		X	
	Mucositis/stomatitis (clinical exam)	• Oral cavity	X	X
		• Pharynx	X	X
	Mucositis/stomatitis (functional/symptomatic)	• Oral cavity	X	X
		• Pharynx	X	X
	Nausea	X	X	
Vomiting	X	X		
Infection	Febrile Neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10 ⁹ /L, fever ≥38.5°C)		X	
	Infection with unknown ANC	• Abdomen NOS		X
Pain	Gastrointestinal	X	X	
	• Abdomen NOS			
Vascular	Thrombosis/thrombus/embolism	X	X	

Add 15

- 10.31 Submit to the NCCTG Research Base via the Nadir/AE Log the following AEs using CTCAE v3.0 experienced by a patient and not specified in Section 10.3:
- 10.311 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.
- 10.312 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.313 Grade 5 AEs (Deaths)

- 10.3131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure
- 10.3132 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.32 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation

11.1 Response criteria: The neurologic examination and the MRI and/or CT at each evaluation will be scored as follows:

11.11

NEURO EXAM STATUS (compared to pre-Rx exam)	
Better:	must be on stable or decreasing dose of steroids.
Same:	failure to qualify for better or worse.
Worse:	includes patients requiring increasing steroid dose to remain stable.

11.12 MRI AND/OR CT ASSESSMENT (compared to pretreatment scan for bidimensionally measurable disease:

CR =	Total disappearance of all tumor. CR requires that patients be on no corticosteroids or on only adrenal replacement maintenance.
PR =	≥50% reduction in product of perpendicular diameters of contrast enhancement or mass with no new lesions. PR requires stable or decreasing steroid dosing.
SD =	failure to qualify for CR, PR, or PD.
PD =	>25% increase in product of perpendicular diameters of contrast enhancement or mass or appearance of new lesions.

11.13 MRI AND/OR CT ASSESSMENT (compared to pretreatment scan) for evaluable disease (i.e., contrast enhancing mass on MRI and/or CT which is not bidimensionally measurable but clearly evaluable for response to therapy.

CR =	Total disappearance of all tumor. CR requires that patients be on no corticosteroids or on only adrenal replacement maintenance.
REGR =	unequivocal reduction in size (but <50% reduction) of contrast-enhancement or decrease in mass effect as agreed upon independently by primary physician and quality control physicians; no new lesions.
SD =	failure to qualify for CR, REGR, or PROG.
PD =	unequivocal increase in size of contrast enhancement or increase in mass effect as agreed upon independently by primary physician and quality control physicians: appearance of new lesions.

11.14 Objective Status: Scored as follows for cycles with MRI and/or CT.

Add 1

NEURO STATUS	MRI and/or CT Status				
	CR	PR	REGR	SD	PD
Better					UNKN*
Same	CR	PR	REGR	SD	PD
Worse	UNKN*				

* Set the Objective Status equal to unknown. Treat one more cycle and evaluate according to the table below:

Add 1

NEURO STATUS	MRI and/or CT Status				
	CR	PR	REGR	SD	PD
Better					PD
Same	CR	PR	REGR	SD	
Worse					

12.0 Descriptive Factors

- 12.1 Prior nitrosoureas: Yes vs. no.
- 12.2 Interval since end of RT (months).
- 12.3 Corticosteroid therapy at study entry: Yes vs. no.
- 12.4 Extent of primary resection: None vs. biopsy vs. subtotal resection vs. gross total resection.
- 12.5 Prior temozolomide: None vs. adjuvant vs. recurrent vs. both.

- 12.6 Histologic type of primary tumor: Oligodendroglioma vs. oligoastrocytoma vs. astrocytoma.
- 12.7 Histologic grade of primary tumor: 2 vs. 3 vs. 4.
- 12.8 Extent of resection at recurrence: None vs. biopsy vs. subtotal resection vs. gross total resection.
- 12.9a Family history of brain tumor: Yes vs. no.
If yes, check all that apply:
- _____ Father
 _____ Mother
 _____ Brother/Sister
 _____ Child
 _____ Other (list: _____)
- 12.9b Number of prior chemotherapy regimens: 0 vs. 1 vs. ≥ 2 .

13.0 Treatment/Follow-up Decision at Evaluation of Patient

- Add 7 13.1 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).
- Add 12
 - If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
 - If the patient never received treatment, on-study material must be submitted. Event monitoring will be required per section 18.0 of the protocol.
- Add 7 13.2 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will be observed 28-42 days following discontinuation of treatment and no additional follow-up will be required after that. Event monitoring will be required per Section 18.0 of the protocol.
- 13.3 A patient is deemed a *cancel* if he/she is removed from study for any reason after pre-registration but prior to registration. The Pre-Registration Screening Failure Form must be submitted. No further data submission is necessary.
- 13.4 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.
- Add 12 13.5 Patients will continue treatment until PD, unacceptable adverse events, investigator's decision to remove patient from the study, patient refusal to continue, or alternate treatment. Treatment will then be discontinued.

Add 12

14.0 Body Fluid Biospecimens

14.1 Body Fluid Biospecimen Submission

14.11 Summary Table of Body Fluid Biospecimens for This Protocol

Type of Biospecimen to submit	Mandatory or optional	When to submit	Reason for submission (background/methodology section)	Where to find specific details for specimen submission
Blood/blood products (EDTA blood)	Mandatory	Multiple draws (see Section 14.24 for schedule)	Defined translational studies (Section 14.4)	Section 14.2

14.2 Blood/Blood Products

14.21 **Kits are required for this study.**

14.211 The kit contains supplies and instructions for collecting, processing, and shipping specimens.

14.212 Participating institutions may obtain kits by completing and faxing the Supply Order Form (found in the Forms Packet) to the number listed on the form. Because we are now being charged for all outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry.

14.213 Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.**

14.214 Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx® account number or alternate billing number for express mail. **NCCTG will not cover the cost for rush delivery of kits.**

Add 13

Add 1

14.22 All samples must be collected **Monday-Thursday ONLY.**

14.23 Label specimen tube(s) with protocol number, NCCTG patient ID number, and time and date blood drawn.

14.24 Collect and process all blood/blood products according to specific kit instructions and table below.

14.241 Summary Table of Research Blood/Blood Products to be Collected for this Protocol

Indicate if specimen is mandatory or optional	Collection tube description and/or additive (color of tube top)	Volume to collect per tube (number of tubes to be collected)	Blood product being processed and submitted at participating site	Baseline (i.e., ≤2 weeks before start of therapy)	Cycle 1, Day 3 (± 1 day) ¹	Prior to treatment Cycle 2	Prior to treatment Cycle 3	Prior to treatment every 4 weeks thereafter x 5 (i.e., Cycles 5, 7, 9, 11, and 13)	At disease progression, withdrawal, or removal	Process at site?	Storage/shipping conditions ²
Mandatory	EDTA (purple)	10 mL (3)	Whole Blood	X	X		X			No	Refrigerate/cold pack (DO NOT FREEZE)
Mandatory	EDTA (purple)	10 mL (2)	Whole Blood			X		X	X	No	Refrigerate/cold pack (DO NOT FREEZE)
Mandatory	EDTA (purple)	10 mL (2)	Plasma	X	X	X	X	X	X	Yes	Frozen/dry ice

Add 2, 10, 11

Add 2

¹ The blood sample taken on Cycle 1, Day 3 (± 1 day) may be done at the patient’s local lab. The blood draw kit should be sent with the patient to be used by that local lab.

²After all samples have been processed according to kit instructions, ship all specimens according to shipping instructions (see Section 14.25 for detailed shipping instructions).

14.25 Shipping

Add 7,13

14.251 Verify ALL sections of the Blood Specimen Submission Form (see Forms Packet), Biospecimen Accessioning and Processing (BAP) Requisition Form (provided in kit), and specimen collection labels are completed and filled in correctly. Enter information from the Blood Specimen Submission Form into the remote data entry system ≤14 days of specimen collection (see Forms Packet).

14.252 Specimens must be shipped the same day they are drawn.

14.253 Specimens will be shipped in a dual-temperature shipping container. Place the refrigerated whole blood EDTA tubes with a properly prepared cold pack in one compartment. See kit instructions for specific details for cold pack preparation (i.e., frozen or refrigerated) and proper packing of blood and cold pack to avoid freezing of specimen. Place the frozen plasma samples with dry ice in the other compartment of the dual-temperature shipping container.

Add 1,7,13

14.254 Ship specimens via Priority Overnight service, **Monday – Thursday ONLY**, to BAP. **Do not send samples on Fridays, weekends or holidays.**

Add 7,13

14.255 BAP kits will include a smart shipper label (3x5 white barcoded label) affixed to the shipping boxes. The smart shipper label is a pre-addressed return label which replaces the need for an airbill. Shipping costs will be covered by NCCTG if the shipping box provided with the BAP kits is used for shipping specimens to BAP Receiving.

Add 13

14.256 BAP Receiving will forward specimens to the NCCTG Research Base Biospecimens Accessioning and Processing (BAP) Shared Resource, Stable 13-10A, Attention: BAP Supervisor.

14.257 BAP will process specimens according to Appendix VII instructions.

14.3 Other Body Fluids: None.

14.4 Background/Methodology Information

14.41 Blood/blood product samples will be collected for the following research

To determine the relationship between tumor biomarkers and circulating biomarkers of vascular response and clinical outcome in recurrent glioblastoma multiforme patients treated with the sorafenib/Avastin® combination.

Add 2

14.411 Analysis of circulating endothelial cells (CECs) and circulating endothelial progenitor cells (CEPCs) will be performed at baseline, Cycle 1 Day 3 (\pm 1 day), prior to treatment Cycle 2, prior to treatment Cycle 3, prior to treatment every 4 weeks thereafter x 5 (i.e., prior to treatment Cycles 5, 7, 9, 11, and 13), and at disease progression, withdrawal, or removal. **Analysis has to be performed, at the latest, \leq 48 hours from sample collection for the results to be valid. Samples must be collected Monday-Thursday and shipped overnight.**

Add 10

Add 1

Add 1

Add 7

Analyses of CECs and CEPCs will be performed in the laboratory of Dr. Shaji Kumar, Stable 6-13, Mayo Clinic Rochester. Whole blood samples will be collected in 2 x 10 mL vacutainer EDTA tubes at the time points indicated above.

Add 1,7

CECs and their progenitor subpopulation (CEPs) will be evaluated as previously described (Mancuso, 2001; Khan, 2005). In brief whole blood will be lysed to remove RBC (red blood cells). A portion of the cells will be stained in BD Pharmingen Trucount© tubes for the absolute count calculation of endothelial cells by their characteristic low FWD/SSC and CD146+CD3-CD31 + phenotype. Cells will also be stained with CD133 or CD105 to evaluate

Add 7 the percentages of progenitor (CD133+) or activated (CD105+) endothelial cell subsets. Isotype control reagents will be included to account for non-specific staining and 7-Amino-actinomycin D (7-AAD) will be used to exclude dead cells from further analysis.

Add 7 We have performed reproducibility experiments using normal blood samples as well as blood samples spiked with HUVECs. The CV for the CEC counts range from 4.4% to 18%. In addition, spiking experiments using HUVECs demonstrate high degree of accuracy with ability to detect endothelial cells up to a 1:100,000 dilution. Furthermore, we have done time course experiments and have determined that CEC counts remain stable for up to 24 hours from the time of the draw. The median number of CEC as defined above in normal individuals is 99/mL. The numbers are same to higher in different malignancies which have been studied.

Add 2,16 14.412 Measurement of angiogenic proteins in plasma will be performed at baseline, Cycle 1 Day 3 (± 1 day), prior to treatment cycle 2, prior to treatment Cycle 3, and prior to treatment every 4 weeks thereafter x 5 (i.e., prior to treatment Cycles 5, 7, 9, 11, and 13). Blood will be collected in two 10 mL EDTA-containing Vacutainers processed into plasma aliquots at the participating sites and forwarded to the Research Base according to kit instructions (see Section 14.21). Molecular biomarkers of vascular response to be assayed in plasma will include, but not limited to circulating VEGFA, VEGFC, HGF, Ang-2, PlGF, soluble VEGFR1, VEGFR2, and VEGFR3, soluble KIT, bFGF, SDF1- α , PDGFC, G-CSF, IL-8, E-selectin, and ICAM-1.

Add 4,7

14.4121 Circulating bFGF, SDF1- α , HGF, soluble KIT, Ang-2, and PlGF will be assayed using commercially available ELISAs from R&D systems or similar vendors. The accuracy and precision of these assays are as published in the individual ELISA product inserts. Analyses of angiogenic proteins in plasma will be performed in the laboratory of Dr. Shaji Kumar, Stable 6-13, Mayo Clinic Rochester.

14.4122 Protein concentrations of circulating VEGFA, VEGFC, PDGFC, G-CSF, VEGFR1, VEGFR2, VEGFR3, IL-8, bFGF, E-selectin, ICAM-1, and other molecular biomarkers of response will be measured using IMPACT (Immunological MultiParameter Chip Technology), a multimarker platform developed by Roche Diagnostics GmbH. De-identified 300 uL plasma aliquots will be shipped overnight on dry ice to the following address for testing:

Dr. Julia Riedlinger
Manager Sample Bank
Roche Diagnostics GmbH
Nonnenwald 2
82377 Penzberg / Germany

This multiplex technology is based on a small polystyrene chip manufactured by proprietary procedures. The chip surface is coated with a streptavidin layer, onto which the biotinylated antibodies are then spotted for every assay. During the assay, the array is probed with specimen samples containing the specific analytes. After incubation for 12 minutes and washing of the chip with washing buffer the digoxigenylated monoclonal antibody mix is added and is incubated for additional 6 minutes to bind onto the captured analytes. The second antibody is finally detected with a reagent buffer including an anti-digoxigenin antibody conjugate coupled with fluorescent latex. Using this label, 10 individual binding events in a single spot can be detected, resulting in very high

sensitivity down to the fmol/L concentration. Chips are transported into the detection unit, and a charge coupled device (CCD) camera generates an image that is transformed into signal intensities using dedicated software. Individual spots are automatically located at predefined positions and quantified by image analysis. Assay characteristics are provided in the table below.

Examples of analyte concentration ranges:

Analytes	Concentration unit	*LDL (lower detection limit)	HDL (high detection limit)	Inter assay variability %CV
VEGFA	pg/mL	15.34	17,476	4.4 - 10.8
VEGFC	pg/mL	1.97	5,000	5.1 - 6.7
PDGFC	pg/mL	10.49	10,000	4.6 - 6.0
G-CSF	pg/mL	0.55	500	4.1 - 9.5
VEGFR1	pg/mL	23	7,314	13.1 - 18.4
VEGFR2	ng/mL	0.043	200	5.3 - 6.8
VEGFR3	ng/mL	0.69	1,000	7.5 - 9.3
IL-8	pg/mL	0.28	1,000	8.3 - 15.1
bFGF	pg/mL	0.39	1,000	8.5 - 20.0
E-Selectin	ng/mL	1.32	100	2 - 3
ICAM-1	ng/mL	3.16	5,000	3 - 4

*LDL is determined as the concentration at a signal intensity 3 standard deviations above the mean signal of 21 repetitive measurements of an analyte-free sample.

Add 2,11

14.413 DNA will be extracted at baseline and buffy coat will be collected after Cycle 1 Day 3 (\pm 1 day) and four weeks of treatment (prior to treatment Cycle 3) from whole blood collected in one 10 mL EDTA tube. DNA and buffy coat will be stored frozen at -80°C by BAP, according to patient consent information (see Section 6.24) for pharmacogenetic assays (e.g., single nucleotide polymorphism [SNP] analyses) to determine correlations with efficacy and tolerability of bevacizumab and sorafenib treatment. Pharmacogenetic studies of molecular targets of bevacizumab and sorafenib to be analyzed include, but are not limited to, VEGF, VEGF receptors, PDGFR- β , and RET, Flt3, and c-KIT SNP analyses.

14.414 Plasma will initially be analyzed according to Section 14.412 and any remaining plasma will be stored frozen at -80°C in the NCCTG Research Base BAP Shared Resource for future research depending on the patient consent permission (see Section 6.24). As protocols are developed and specific analyses are identified, they will be presented for NCCTG and IRB review and approval. (This collection is part of a general strategy of investigation for the majority of NCCTG studies.)

14.42 Return of Genetic Testing Research Results

Add 11

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians. If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

- 15.1 Sorafenib (BAY43-9006; Nexavar®; NSC 724772)
- IND: Exempt
 - Investigator brochure contact information: The most current version of the Investigator Brochure will be maintained on the secure members section of the NCCTG website until all investigations under the IND have been completed. Each investigator should obtain a copy of the Investigator's Brochure prior to initiation of the study. Updated Investigator Brochures should be obtained from the website, as they become available.

Chemical Name: *4-{4-[3-(4-chloro-3-trifluoromethyl-phenyl)ureido]-phenoxy}-pyridine-2 carboxylic acid methylamide-4-methylbenzenesulfonate.*

Other Names: BAY 54-9085 is the tosylate salt of BAY 43-9006; sorafenib

Classification: Kinase inhibitor (Raf, VEGF-R, and PDGF-R)

Mechanism of Action: The ras/raf signaling pathway is an important mediator of responses to growth signals and angiogenic factors. This pathway is often aberrantly activated in human tumors due to presence of activated ras, mutant b-raf, or over expression of growth factor receptors.

BAY 43-9006 is a potent inhibitor of c-raf, and wild-type and mutant b-raf in vitro. Additionally, further characterization of BAY 43-9006 tosylate revealed that this agent inhibits several receptor tyrosine kinases (RTKs) that are involved in tumor progression (VEGF-R, PDGF-R, Flt3, and c-KIT) and p38 α , a member of the MAPK family.

Molecular Formula: C₁₂H₁₆ClF₃N₄O₃ X C₇H₈O₃S

M.W.: BAY 43-9006 tosylate: 637 Daltons; BAY 43-9006 (free base): 465 Daltons

Approximate Solubility: 0.19 mg/100 mL in 0.1 N HCl, 453 mg/100 mL in Ethanol, and 2971 mg/100 mL in PEG 400.

How Supplied: BAY 43-9006 tosylate is supplied as an immediate-release film-coated, round, and salmon color tablet containing 200 mg of the free base, BAY 43-9006, and the excipients croscarmellose sodium, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium lauryl sulfate, and magnesium stearate. The film-coat consists of hydroxypropylmethyl cellulose, polyethylene glycol, titanium dioxide and red iron oxide. The film coating has no effect on the rate of release of the active BAY 43-9006 tosylate.

Commercial sorafenib 200 mg tablets are supplied in bottles of 120 tablets.
Study Drug BAY 43-9006 tosylate 200 mg tablets are supplied in bottles of 140 tablets.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) (see USP controlled room temperature). Store in a dry place.

Stability: Stability studies with the 200 mg dosage form are ongoing. The current shelf life is 24 months when stored at controlled room temperature.

Route(s) of Administration: Oral. The recommended daily dose of sorafenib is 200 mg taken daily, without food (at least 1 hour before or 2 hours after eating).

See package insert for more information.

15.11 Reported Adverse Events and Potential Risks

The table below shows the percent of patients experiencing treatment-emergent adverse events that were reported in at least 10% of patients who received sorafenib in TARGET Trial. CTCAE Grade 3 treatment-emergent adverse events were reported in 31% of patients receiving sorafenib compared to 22% of patients receiving placebo. CTCAE Grade 4 treatment-emergent adverse events were reported in 7% of patients receiving sorafenib compared to 6% of patients receiving placebo.

Table 4: 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 Stomatitis (including dry mouth and glossodynia) 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** Pruritus 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	Gynecomastia
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 erythrodysesthesia syndrome in MedDRA

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. CTC Grade 3 or 4 lipase elevations occurred in 12% of patients in the sorafenib group compared to 7% of patients in the placebo group. CTC 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 (CTC Grade 4) and 1 of 451 patients (CTC 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. CTC 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 CTC Grade 4 hypophosphataemia (< 1 mg/dl) reported in either sorafenib or placebo patients. The etiology of hypophosphataemia associated with sorafenib is not known.

Lymphopenia: CTC 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.

Table Below Shows Treatment-Emergent Adverse Events Reported in at Least 10% of Sorafenib -Treated Patients – TARGET Trial

Adverse Event NCI-CTCAE v3 Category/Term	Sorafenib N=451			Placebo N=451		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Any Event	95	31	7	86	22	6
Cardiovascular, General						
Hypertension	17	3	<1	2	<1	0
Constitutional symptoms						
Fatigue	37	5	<1	28	3	<1
Weight loss	10	<1	0	6	0	0
Dermatology/skin						
Rash/desquamation	40	<1	0	16	<1	0
Hand -foot skin reaction	30	6	0	7	0	0
Alopecia	27	<1	0	3	0	0
Pruritus	19	<1	0	6	0	0
Dry skin	11	0	0	4	0	0
Gastrointestinal symptoms						
Diarrhea	43	2	0	13	<1	0
Nausea	23	<1	0	19	<1	0
Anorexia	16	<1	0	13	1	0
Vomiting	16	<1	0	12	1	0
Constipation	15	<1	0	11	<1	0
Hemorrhage/bleeding						
Hemorrhage – all sites	15	2	0	8	1	<1
Neurology						
Neuropathy-sensory	13	<1	0	6	<1	0
Pain						
Pain, abdomen	11	2	0	9	2	0
Pain, joint	10	2	0	6	<1	0
Pain, headache	10	<1	0	6	<1	0
Pulmonary						
Dyspnea	14	3	<1	12	2	<1
Cough	13	<1	0	14	<1	0

The rate of adverse events (including events associated with progressive disease) resulting in permanent discontinuation was similar in both the sorafenib and placebo groups (10% of sorafenib patients and 8% of placebo patients). Safety was also assessed in a Phase 2 study pool comprised of 638 sorafenib-treated patients, including 202 patients with RCC, 137 patients with hepatocellular carcinoma, and 299 patients with other cancers. The most common drug-related adverse events reported in sorafenib-treated patients in this pool were rash (38%), diarrhea (37%), hand-foot skin reaction (35%), and fatigue (33%). The respective rates of CTC (v2.0) Grade 3 and 4 drug-related adverse events in sorafenib-treated patients were 37% and 3%, respectively.

Add 4,6,13

15.12 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Sorafenib (BAY 43-9006, NSC 724772)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with **bold** and **italicized** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'

http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_adeers for further clarification. Frequency is provided based on 2157 patients. Below is the CAEPR for sorafenib (BAY 43-9006).

Version 2.3, February 18, 2010¹

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006) (CTCAE 4.0 Term) [n= 2157]			EXPECTED AEs FOR ADEERS REPORTING Agent Specific Adverse Event List (ASAEL)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	Expected
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		Anemia
	Febrile neutropenia		
CARDIAC DISORDERS			
		Acute coronary syndrome	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
GASTROINTESTINAL DISORDERS			
Abdominal pain			Abdominal pain
	Anal mucositis		
	Ascites		
	Constipation		Constipation
Diarrhea			Diarrhea
	Gastrointestinal hemorrhage ²		Gastrointestinal hemorrhage²
		Gastrointestinal perforation ³	
	Mucositis oral		
Nausea			Nausea
	Rectal mucositis		
	Small intestinal mucositis		
	Vomiting		Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			Fatigue
	Fever		Fever
	Non-cardiac chest pain		
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis	

INFECTIONS AND INFESTATIONS		
	Infection ⁴	
INVESTIGATIONS		
	Activated partial thromboplastin time prolonged	Activated partial thromboplastin time prolonged
Alanine aminotransferase increased		Alanine aminotransferase increased
Alkaline phosphatase increased		Alkaline phosphatase increased
Aspartate aminotransferase increased		Aspartate aminotransferase increased
Blood bilirubin increased		Blood bilirubin increased
	Cholesterol high	
Creatinine increased		Creatinine increased
	GGT increased	
INR increased		INR increased
	Investigations - Other (bicarbonate, serum-low)	
Lipase increased		Lipase increased
Lymphocyte count decreased		Lymphocyte count decreased
	Neutrophil count decreased	Neutrophil count decreased
Platelet count decreased		Platelet count decreased
Serum amylase increased		Serum amylase increased
Weight loss		Weight loss
White blood cell decreased		White blood cell decreased
METABOLISM AND NUTRITION DISORDERS		
Anorexia		Anorexia
	Hypercalcemia	
Hyperglycemia		Hyperglycemia
	Hyperkalemia	Hyperkalemia
	Hypernatremia	
	Hyperuricemia	
Hypoalbuminemia		Hypoalbuminemia
Hypocalcemia		Hypocalcemia
	Hypoglycemia	Hypoglycemia
	Hypokalemia	Hypokalemia
Hyponatremia		Hyponatremia
Hypophosphatemia		Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	Arthralgia
	Back pain	Back pain
	Bone pain	
	Musculoskeletal and connective tissue disorder - Other (muscle spasms)	
	Myalgia	
	Pain in extremity	Pain in extremity

NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Headache	
		Intracranial hemorrhage
	Peripheral sensory neuropathy	
		Reversible posterior leukoencephalopathy syndrome
PSYCHIATRIC DISORDERS		
	Insomnia	
RENAL AND URINARY DISORDERS		
	Acute kidney injury	
	Hematuria	
	Renal hemorrhage	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
	Hematosalpinx	
	Ovarian hemorrhage	
	Prostatic hemorrhage	
	Spermatic cord hemorrhage	
	Testicular hemorrhage	
	Uterine hemorrhage	
	Vaginal hemorrhage	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Bronchopulmonary hemorrhage	
	Cough	
	Dyspnea	
	Epistaxis	
	Laryngeal mucositis	
	Pharyngeal mucositis	
	Tracheal mucositis	
	Voice alteration	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Alopecia		
	Dry skin	
		Erythema multiforme
Palmar-plantar erythrodysesthesia syndrome		
	Pruritus	
Rash maculo-papular		
		Stevens-Johnson syndrome
VASCULAR DISORDERS		
	Hypertension	
	Thromboembolic event	

¹This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

²Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage,

Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

³Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

⁴Includes all 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

Also reported on sorafenib (BAY 43-9006) trials but with the relationship to sorafenib (BAY 43-9006) still undetermined:

CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Chest pain - cardiac; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia

EAR AND LABYRINTH DISORDERS - Tinnitus

ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism

EYE DISORDERS - Blurred vision; Cataract; Extraocular muscle paresis

GASTROINTESTINAL DISORDERS - Abdominal distension; Dyspepsia; Dysphagia; Flatulence; Ileus; Pancreatitis; Rectal fistula; Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Flu like symptoms; Pain

IMMUNE SYSTEM DISORDERS - Allergic reaction

INVESTIGATIONS - Fibrinogen decreased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypermagnesemia; Hypertriglyceridemia; Hypomagnesemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Generalized muscle weakness

NERVOUS SYSTEM DISORDERS - Dysgeusia; Encephalopathy; Ischemia cerebrovascular; Memory impairment; Syncope

PSYCHIATRIC DISORDERS - Confusion; Depression

RENAL AND URINARY DISORDERS - Proteinuria

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Erectile dysfunction

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Hypoxia; Pleural effusion; Pneumonitis; Pneumothorax

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Hyperhidrosis; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (non-life threatening squamous cell carcinoma of skin: keratoacanthoma type); Skin hypopigmentation

VASCULAR DISORDERS - Flushing; Hypotension; Vasculitis

Note: Sorafenib (BAY 43-9006) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Sorafenib is contraindicated in patients with known severe hypersensitivity to sorafenib or any of the excipients.

Add 4

15.14 Special Warnings and Precautions for Use

Sorafenib is approved for treatment of patients with advanced renal 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 erythrodysesthesia) and rash represent the most common adverse drug reactions with sorafenib. Rash and hand-foot skin reaction are usually CTC (National Cancer Institute Common Toxicity Criteria) 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.

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 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 re-initiation 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/m² (approximately 0.5 times the AUC in cancer patients at the recommended human dose). Dogs showed tubular degeneration in the testes at 600 mg/m²/day (approximately 0.3 times the AUC at the recommended human dose) and oligospermia at 1200 mg/m²/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/m² (approximately 0.3 times the AUC at the recommended human dose), hypocellularity of the bone marrow adjoining the growth plate at 200 mg/m²/day (approximately 0.1 times the AUC at the recommended human dose), and alterations of the dentin composition at 600 mg/m²/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.

Add 4

15.15 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:** 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 PT-INR. 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.

Add 4

15.16 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.

Add 4

- 15.17 Drug procurement: Bayer Corporation will supply investigational drug to the NCCTG Coordinating Center Pharmacy. Each institution will order the drug from the NCCTG Coordinating Center Pharmacy by submitting a NCCTG Clinical Drug Order/Return Form request to:

Medical Oncology Pharmacist
 Mayo Clinic
 Gonda 10-178
 Rochester, MN 55905
 Fax (507) 284-3464

Add 8

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

Add 9

- 15.18 Nursing Guidelines

- 15.181 Due to the early investigational nature of this drug not all side effects can be known at this time. Monitor patients closely and report all adverse events per section 10.0 of the protocol.
- 15.182 Drug should be taken with at least 250 cc of water. Should be taken without food (at least 1 hour before or 2 hours after meals). Do not administer with grapefruit juice.
- 15.183 Patient may experience flu-like symptoms such as fatigue, fever. Tylenol may be beneficial for these patients.

- 15.184 Monitor CBC. Instruct patients to report signs and symptoms of infection and excessive bruising or bleeding to the MD.
- 15.185 Monitor LFT's.
- 15.186 Patients may experience diarrhea. See section 9.0 for management of diarrhea.
- 15.187 Instruct patient to report severe abdominal pain, as pancreatitis is a possibility.
- 15.188 May cause anorexia. Encourage patient to consume small frequent meals.
- 15.189 Monitor for sign/symptoms of hand/foot syndrome. See section 9.0 for appropriate management.
- 15.189a May cause alopecia, instruct patient of this possibility
- 15.189b Monitor for rash. Instruct patient to report any rash to MD.
- 15.189c Patients on Coumadin should be monitored closely, as dose may need to be adjusted secondary to CYP3A inhibition. See section 15.7 for more drug interactions with BAY 43-9006. As there are many potential drug interactions, instruct patient not to start any new medication (including OTC's or herbal products) without checking with their MD first.
- 15.189d Monitor blood pressure. Instruct patients who are self-monitoring to report any increase in their blood pressure to the study team.
- 15.189e Nausea and vomiting may occur. Administer antiemetics as necessary and monitor for their effectiveness.
- 15.189f Bleeding has been seen (GI, respiratory, CNS). Instruct patient to report any bleeding to the study team immediately. If bleeding is severe, seek out emergency medical attention.
- 15.2 Avastin® (also known as Recombinant Humanized Monoclonal Anti-VEGF Antibody, RHuMAb VEGF)
- IND: Exempt
 - Investigator's Brochure: The most current version of the Investigator Brochure will be maintained on the secure members section of the NCCTG website until all investigations under the IND have been completed. Each investigator should obtain a copy of the Investigator's Brochure prior to initiation of the study. Updated Investigator Brochures should be obtained from the website, as they become available.

- 15.21 Preparation and storage: Avastin® is supplied as a clear to slightly opalescent, sterile liquid concentrate for solution for intravenous (IV) infusion. Avastin® may be supplied in 20 mL (400 mg) glass vials containing 4 mL and 16 mL Avastin®, respectively (all at 25 mg/mL). Vials contain Avastin® with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection (SWFI) USP. Vials contain no preservatives and are intended for single use only. Avastin® vials must be refrigerated at 2-8°C (36-46°F) and should remain refrigerated until just prior to use. **DO NOT FREEZE. DO NOT SHAKE.** Avastin® vials should be protected from light. Store in the original carton until time of use. Avastin® will be diluted in a total volume of 100mL of 0.9% Sodium Chloride Injection, USP. Vials are for single use only. Vials used for 1 subject may not be used for any other subject. Open vials must be used within 8 hours. Once Avastin® has been added to the bag, the solution must be used within 8 hours.
- 15.22 Administration: The first dose of Avastin® should be given over 90 minutes. If well tolerated, second dose may be administered over 60 minutes. Again, if well tolerated, subsequent doses may be administered over 30 minutes. If the patient is pre-medicated for infusion reaction, maintain previous infusion rate for first pre-medicated infusion. If well tolerated with pre-medication, the subsequent infusion time may then be decreased by 30 minutes, as long as the subject continues to be pre-medicated. If the patient experiences infusion associated adverse events with the 60-minute infusion, all subsequent infusions should be given over 90 minutes. Similarly, if a patient experiences infusion associated adverse events with the 30-minute infusion, all subsequent doses should be given over 60 minutes.
- 15.23 Avastin® Clinical Experience

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

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

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

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

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

Add 14

15.231 Safety Profile

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Bevacizumab (rhuMAb VEGF, NSC 704865)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with **bold** and *italicized* text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_adeers for further clarification. Below is the CAEPR for bevacizumab (rhuMAb VEGF).

Version 2.1, May 4, 2010¹

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term)			EXPECTED AEs FOR ADEERS REPORTING Agent Specific Adverse Event List (ASAEL)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	Expected
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		Anemia
		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)	
CARDIAC DISORDERS			
		Acute coronary syndrome	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	Myocardial infarction
	Supraventricular tachycardia		Supraventricular tachycardia
		Ventricular arrhythmia	
		Ventricular fibrillation	
EAR AND LABYRINTH DISORDERS			
	Vertigo		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		Abdominal pain
	Colitis		
	Constipation		Constipation
Diarrhea			Diarrhea
	Dyspepsia		Dyspepsia
		Gastrointestinal fistula ²	
	Gastrointestinal hemorrhage ³		Gastrointestinal hemorrhage³
		Gastrointestinal perforation ⁴	
		Gastrointestinal ulcer ⁵	
	Ileus		
	Mucositis oral		Mucositis oral
Nausea			Nausea
Vomiting			Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			Fatigue
	Infusion related reaction		Infusion related reaction
	Non-cardiac chest pain		Non-cardiac chest pain
	Pain		Pain
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		Allergic reaction
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection ⁶		Infection⁶
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Gastrointestinal anastomotic leak	

	Wound dehiscence		Wound dehiscence
INVESTIGATIONS			
	Alanine aminotransferase increased		Alanine aminotransferase increased
	Alkaline phosphatase increased		Alkaline phosphatase increased
	Aspartate aminotransferase increased		Aspartate aminotransferase increased
	Blood bilirubin increased		Blood bilirubin increased
	Cardiac troponin I increased		
	Neutrophil count decreased		Neutrophil count decreased
	Weight loss		Weight loss
	White blood cell decreased		White blood cell decreased
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		Anorexia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		Arthralgia
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia) ⁷		
	Myalgia		
NERVOUS SYSTEM DISORDERS			
	Dizziness		Dizziness
Headache			Headache
		Intracranial hemorrhage	Intracranial hemorrhage
		Ischemia cerebrovascular	Ischemia cerebrovascular
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Hematuria		Hematuria
	Proteinuria		Proteinuria
		Renal and urinary disorders - Other (Nephrotic Syndrome)	
		Renal and urinary disorders - Other (renal failure)	
		Urinary fistula	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
		Vaginal fistula	
	Vaginal hemorrhage		Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	
	Cough		Cough
	Dyspnea		Dyspnea
	Epistaxis		Epistaxis
	Hoarseness		Hoarseness
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
	Respiratory, thoracic, and mediastinal disorders - Other		Respiratory, thoracic, and mediastinal disorders - Other

	(rhinitis)		(rhinitis)
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		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		<i>Pruritus</i>
	Skin and subcutaneous tissue disorders - Other (rash)		<i>Skin and subcutaneous tissue disorders - Other (rash)</i>
	Urticaria		<i>Urticaria</i>
VASCULAR DISORDERS			
Hypertension			<i>Hypertension</i>
	Thromboembolic event		<i>Thromboembolic event</i>
		Vascular disorders - Other (arterial thromboembolic event) ⁸	

¹This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

²Gastrointestinal fistula includes: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

³Gastrointestinal hemorrhage includes: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

⁴Gastrointestinal perforation includes: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, Small intestinal perforation, and other sites under the GASTROINTESTINAL DISORDERS SOC.

⁵Gastrointestinal ulcer includes: Duodenal ulcer, Esophageal ulcer, Gastric ulcer and other sites under the GASTROINTESTINAL DISORDERS SOC.

⁶Infection includes all 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

⁷Metaphyseal dysplasia was observed in ***young patients who still have active epiphyseal growth plates.***

⁸Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

Also reported on Bevacizumab (rhuMAb VEGF) trials but with the relationship to Bevacizumab (rhuMAb VEGF) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura); Disseminated intravascular coagulation

CARDIAC DISORDERS - Pericardial effusion

GASTROINTESTINAL DISORDERS - Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Gait disturbance; Sudden death NOS

HEPATOBIILIARY DISORDERS - Hepatic failure

INFECTIONS AND INFESTATIONS - Infections and infestations - Other (aseptic meningitis)

METABOLISM AND NUTRITION DISORDERS - Hyponatremia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone); Musculoskeletal and connective tissue disorder - Other (myasthenia gravis); Osteonecrosis of jaw

NERVOUS SYSTEM DISORDERS - Dysgeusia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure

PSYCHIATRIC DISORDERS - Confusion

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Pneumonitis; Pneumothorax; Pulmonary hypertension

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Skin ulceration

Note: Bevacizumab (rhuMAb VEGF) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

15.24 Drug procurement:

Genentech/Roche Pharmaceuticals will supply investigational drug to the NCCTG Coordinating Center Pharmacy. Each institution will order the drug from the NCCTG Coordinating Center Pharmacy by submitting an NCCTG Clinical Drug Order/Return Form request to:

Medical Oncology Pharmacist
Mayo Clinic
Gonda 10-178
Rochester, MN 55905
Fax (507) 284-3464

Add 8

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

Drug inventory records: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the investigational Avastin® received from NCCTG and used only by authorized investigators for the purposes of this trial. Drug storage and accountability are subject to verification by audit. Refer to the NCCTG Audit Manual and the NCCTG Investigator's Handbook for further information on the requirements for drug accountability and storage.

15.25 Nursing guidelines:

- 15.251 Monitor patients closely for infusion type reactions, including fever, chills, myalgias, rigors, or other allergic reactions. While this is less likely given that Avastin® is a humanized antibody, there still exists the potential for severe allergic reactions. If these signs or symptoms occur stop the infusion immediately and contact MD. Have emergency equipment nearby and be prepared to administer emergency treatment as ordered by MD.
- 15.252 Monitor urine dipstick at the beginning of each infusion therapy.
- 15.253 Evaluate IV site regularly for signs of infiltration.
- 15.254 Bleeding in the absence of thrombocytopenia is a dose limiting toxicity. Monitor patient closely for hemorrhagic events, including CNS hemorrhage, epistaxis, hematemesis and hemoptysis. Most cases of bleeding have occurred at the tumor site. Advise patient about the potential for bleeding or thrombosis.
- 15.255 In patients receiving treatment for lung cancer, hemoptysis and pulmonary hemorrhage occurred in up to 10% of patients in one study. Monitor these patients especially closely.
- 15.256 Patient may experience grade 1-2 nausea, however vomiting is uncommon. Medicate as ordered and monitor for effectiveness.
- 15.257 Monitor for skin rash, instruct patient to report to MD.
- 15.258 Monitor blood pressure. Repeat vital signs every 15 minutes during infusion. Hypertension has occurred frequently with infusion and may be severe. Administer antihypertensives as ordered by MD.
- 15.259a Monitor for signs and symptoms of DVT or PE, or MI. These have been reported with therapy. Instruct patient to report any calf pain, chest pain or SOB to MD immediately.
- 15.259b Asthenia and headache were reported commonly during therapy (in up to 70% and 50% of patients respectively). Administer acetaminophen as needed. Monitor for its effectiveness. Avoid the use of aspirin, or ibuprofen as this may interfere with the coagulation cascade and further add to the risk of bleeding.
- 15.259c Monitor CBC, including platelets. Instruct patient to report signs and symptoms of infection, unusual bruising or bleeding to the MD.
- 15.259d Patient receiving warfarin therapy for thrombosis should have their PT or INR monitored weekly until two stable therapeutic levels are attained: for patients on warfarin for venous access prophylaxis, routine monitoring is satisfactory.

- 15.259e A rare but serious complication of Avastin® is wound dehiscence. Patients who have had recent surgery or have other open wounds should be monitored carefully.
- 15.259f Gastrointestinal perforation with or without abdominal abscess is rare but possible. This may present itself as vague abdominal pain associated with constipation and vomiting. Instruct patient to report abdominal pain to the MD.
- 15.259g Reversible Posterior Leukoencephalopathy Syndrome (RPLS) is a rare (<1%) but serious condition. Presenting symptoms may include, changes in mental status, visual disturbance, seizure, or other CNS changes. Patients with this syndrome generally had HTN as well, therefore BP monitoring is important. Instruct patient to report any mental status changes, visual changes, seizures, or other CNS changes to the MD immediately. These may be a sign of RPLS or more serious condition, such as hemorrhagic event in the CNS.

16.0 Statistical Considerations and Methodology

- 16.1 Study Overview: This protocol will assess the efficacy of Avastin® in combination with sorafenib in patients with recurrent glioblastoma multiforme. A one-stage, phase II trial design will be used to evaluate the 6-month progression free survival (PFS6) in these patients.
- 16.2 Sample Size: Sample size and power are based on a three-outcome design (Sargent et al., 2001). A total of 53 patients (48 evaluable plus 5 additional patients to compensate for losses due to ineligibility, cancellation, or major protocol violations) will be enrolled unless undue adverse events are encountered. We anticipate pre-registering 75 patients to register a total of 53 patients necessary for the study design and allotted over accrual.
- 16.3 Accrual Time and Study Duration: Based on the accrual of a recent NCCTG study open to patients with recurrent glioblastoma (N047B), we anticipate an annual accrual rate of 50 patients per year. Therefore, the overall study duration is expected to be 19 months (13 months to accrue 48 evaluable patients and 6 months for follow-up).
- 16.4 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals and any other analysis.
- 16.5 Other Considerations: If a patient is declared to be a major treatment violation, the patient will be censored on the date the treatment violation was declared to have occurred. In the case of a patient starting treatment and then never returning for any evaluations, the patient will be censored for progression.
- 16.6 Adverse Events Stopping Rules: The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

A specific interim adverse event analysis will be performed once at least 20 evaluable patients have been followed for 3 months (accrual will not stop during this three-month time period).

Add 9 As of April 29, 2009, 19 patients had been accrued to this study at the starting cycle -1 dose level of Sorafenib 200 mg BID days 1-5 and 8-12 and Avastin® 5 mg/kg on day 1 with a total cycle length of 14 days. In these 19 patients, four grade 4 events at least possibly related to study treatments have occurred. One patient had a grade-4 thrombocytopenia, one had grade-4 amylase, one had grade-4 thrombosis, and one had both grade-4 fatigue and muscle weakness. These last three are grade 4+ non-hematologic and required temporarily suspending accrual to this study per the previous Adverse Event Stopping Rule. The study team met and discussed all of these adverse events and with Addendum 9, the study has been reopened at a reduced starting dose level.

Add 9 As of Addendum 9, the new Adverse Event Stopping rule is as below:

Add 9,15 Accrual to any individual cycle-1 starting dose level will be temporarily suspended if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as “possible”, “probable”, or “definite”) that satisfy either of the following (CTCAE v3.0 will be used to determine grading for these stopping rules):

- Add 9 • If 4 or more patients in the first 20 treated patients at a specific starting dose level (or 20% or more after 20 patients have been accrued) experience a grade 4 or higher non-hematologic adverse event.
- Add 9 • If 2 or more patients in the first 20 treated patients at a specific starting dose level (or more than 5% after 20 patients have been accrued) experience a grade 3 or higher CNS bleed.

We note that we will review grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.7 Adverse Events Monitoring: This study will be monitored by the Mayo Clinic Cancer Data Safety Monitoring Board. In addition, efficacy, adverse events, and administrative information for this trial will be reviewed by the study team twice per year in conjunction with production of the semiannual NCCTG Group Meeting reports. The study team will monitor the trial for evidence of severe adverse effects and feasibility problems.

16.8 Statistical Design:

16.81 Definition of Success: For design purposes an eligible patient that signs the consent form and begins therapy will be considered evaluable for assessment of treatment efficacy. To be classified as a success, an evaluable patient must be alive and progression-free 6 months after registration to the study. Patients who die prior to 6 months after study registration will be considered to have failed.

16.82 Decision Rule: The decision rules to be used for the final analysis are based on a three-outcome design for testing the null hypothesis that the proportion of success is at most 0.30 with a significance level (alpha) of 0.10. The study has 90% power of declaring the study promising (81%) or inconclusive (9%) if the true proportion of successes (PFS6) is 0.45 or greater. The combination of the two agents will be considered active in this population if at least 19 of the 48 evaluable patients are classified as successes. If 16 or fewer successes are observed in the first 48 evaluable patients, this treatment combination will be considered inactive. If either 17 or 18 successes are observed in the 48 evaluable patients, this treatment regimen will be classified as inconclusive. In this case, response rate, overall survival, progression-free survival, and adverse events will be used in addition to the primary endpoint to make the final determination if the regimen is promising.

16.9a Analyses Plans

16.9a1 Primary Endpoint: 6-month progression free survival (PFS6): The proportion of successes will be estimated using the binomial point estimator (number of successes divided by the total number of evaluable patients) and the binomial 90% confidence interval estimated.

16.9a2 Safety, Toxicity, and Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration. A specific interim adverse event analysis will be performed as specified in Section 16.6.

16.9a3 Definitions and analyses of secondary endpoints:

16.9a31 Time to progression (TTP) is defined to be the length of time from study registration to a) date of disease progression as defined by section 11.0, or b) last follow-up. If a patient dies without documentation of disease progression, the patient will be considered to have had a tumor progression at the time of death unless there is sufficient documented evidence to conclude no progression occurred prior to death.

16.9a32 Overall survival (OS) is defined as the length of time from date of registration to a) date of death due to any cause or b) last follow-up.

16.9a33 Kaplan-Meier survival curves will be used to estimate the distributions of PFS6, TTP, and OS.

16.9a34 The FACT-Br will be assessed at baseline, prior to every other cycle, and at the end of active treatment. The primary analysis will be based on the corresponding change in scores from baseline and trends over the course of treatment.

16.9a4 Definitions and analyses of translational research endpoints:

16.9a.41 The absolute and percentage changes relative to baseline for the dynamic contrast enhanced MRI (DCE-MRI) measured tumor size at baseline, Cycle 1 Day 3, prior to the 3rd cycle (Day 28), prior to the 5th cycle will be used.

16.9a.42 Cellular biomarkers from blood samples (VEGFA, VEGFC, HGF, Ang-2, P1GF, soluble VEGFR1, VEGFR2, and VEGFR3, soluble KIT, bFGF, SDF1- α , PDGFC, G-CSF, IL-8, E-selectin, ICAM-1, CECs, and CEPCs [see Section 14.0]) will be evaluated at baseline and relative change from baseline at the specified time points in Section 14.0.

Add 4,16

- 16.9a43 Tumor biomarkers (CD31, CD9, VEGF, VEGFR1, VEGFR2, VEGFR3, PDGFR α , PDGFR β , HIF1 α , HIF2 α , NPR-1, NRP-2, and P-ERK [see Section 17.0]) will be measured at baseline on appropriate scales and any determination if the levels are elevated will be made using current available standards.
- 16.9a44 We will determine the utility of DCE-MRI to predict response to this combination treatment and we will evaluate the relationship between tumor biomarkers and cellular/molecular biomarkers and the resulting clinical outcome. We will evaluate each of the tumor biomarkers and cellular/molecular biomarkers in association with clinical outcomes. Associations between continuous measures of biomarkers and PFS6 will be assessed using two-sample t-tests. Associations between categorical measures of biomarkers and PFS6 will be assessed using Fisher exact test. Associations between the change of DCE-MRI and PFS6 will be assessed using two-sample t-test. Kaplan-Meier survival curves, and logrank tests will be used to estimate and compare the equality of the overall survival and progression-time distributions of patient subsets defined by biomarker values.

16.9b Inclusion of Women and Minorities

This study will be available to all eligible patients regardless of race, gender, or ethnic group.

There is no information currently available regarding differential agent effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analyses will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for such subset analyses. A total of 53 patients may be enrolled.

Based on prior studies involving similar disease sites, we expect about 7% of patients will be classified as minorities by race and about 40% of patients to be women. Expected sizes of racial by gender subsets are shown in the following table:

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	2	2	0	4
Not Hispanic or Latino	19	30	0	49
Ethnic Category: Total of all subjects*	21	32	0	53
Racial Category				
American Indian or Alaskan Native	1	1	0	2
Asian	0	1	0	1
Black or African American	1	0	0	1
Native Hawaiian or other Pacific Islander	0	0	0	0
White	19	30	0	49
Racial Category: Total of all subjects*	21	32	0	53

*These totals must agree. Enter actual estimates (**not percentages**)

Ethnic Categories:	<p>Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”</p> <p>Not Hispanic or Latino</p>
Racial Categories:	<p>American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.</p> <p>Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)</p> <p>Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”</p> <p>Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.</p> <p>White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.</p>

17.0 Pathology Considerations/Tissue Biospecimens

NOTE: See Section 6.0 Pre-registration procedures for instructions before submitting pathology materials.

17.1 Tissue Biospecimen Submission

Type of tissue to submit	Mandatory or optional	When to submit	Reason for submission	Where to find specific details for submission
Diagnostic slides from primary and recurrent tissue	Mandatory	As soon as possible after surgery, prior to enrollment	Pre-registration requirement, confirmation of diagnosis through central review (Section 17.2)	Section 17.2
Formalin-fixed paraffin-embedded (FFPE) tissue blocks with corresponding H&E OR 13 unstained slides with 2 corresponding H&Es)	Optional*	≤30 days following registration	Correlative studies (Section 17.5)	Section 17.3

Add 1,4

If an institution is not able to provide the tissue, it does not cause the patient to be ineligible; however, the collection of these tissues is **strongly recommended.*

17.2 Diagnostic slides from all surgical biopsies need to be submitted for central review to confirm eligibility.

17.21 Clearly labeled original diagnostic slides used to make the diagnosis of glioblastoma multiforme cancer should be forwarded ***as soon as possible after pre-registration*** according to shipping instructions below.

If diagnostic slides and accompanying materials have been previously submitted to Dr. Caterina Giannini and/or associates, Mayo Clinic Rochester, for a consult review, fax a copy of this review to the NCCTG Pathology Coordinator (507-284-9628) to verify diagnosis. The Pathology Coordinator will contact you to inform you if the patient is eligible. If the patient is eligible, you may proceed with registration via the eligibility checklist. Clearly labeled diagnostic slides from all surgical biopsies will still need to be forwarded according to shipping instructions below (see Sections 17.22-17.26).

If a patient's surgery was at Mayo Clinic Rochester, you may call the Pathology Coordinator listed on the protocol Resource Page. The Pathology Coordinator will request a copy of the Surgical Pathology Report and determine patient block availability. After confirmation of block availability, the Pathology Coordinator will contact you to inform you if the patient is eligible. If the patient is eligible, you may proceed with registration via the eligibility checklist.

Add 1

- 17.22 The following materials below are mandatory (unless indicated otherwise) and required for shipment:
- Diagnostic slides from all surgical biopsies
 - Pathology Reporting Form
 - Pathology Submission Form
 - Surgical Pathology Report
 - Operative Report (*optional*)
- 17.23 The diagnostic slide(s) must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, NCCTG patient ID number, and patient initials.
- 17.24 Verify that Section 1 of the Pathology Reporting Form is completed and filled in correctly.
- 17.25 **In order to assure prompt handling, please call the NCCTG Pathology Coordinator at (507) 266-8919 to alert of the time/date sent and courier contracted.**
- 17.26 Review is being performed at the NCCTG Research Base at Mayo Clinic Rochester. Ship all diagnostic slides and accompanying materials as follows.
- 17.261 Mayo Clinic Rochester (MCR) patients only: please forward pathology material to Dr. Caterina Giannini, Hilton 11, for review.
- 17.262 For all memberships, including MCJ and MCA, ship all specimens and accompanying materials to the NCCTG Research Base:
- NCCTG Operations Office
Attn: NCCTG PC Office (Study N0776)
RO_FF_03_24-CC/NW Clinic
200 First Street SW
Rochester, MN 55905
- 17.27 The NCCTG Operations Office will forward the diagnostic slides to Dr. Caterina Giannini, Hilton 11, for central review to confirm diagnosis of glioblastoma multiforme. After the pathology materials have been reviewed, a call will be made by the Pathology Coordinator to the institution notifying them of Dr. Giannini's and/or associates' review. A copy of the Pathology Reporting Form will be faxed to the randomizing member and eligible patients can be registered.
- 17.28 The NCCTG Pathology Coordinator will enter the eligibility status of the patient into the pre-registration database. This will enable the Randomization Center to verify eligibility when the institution proceeds to step 2 of the registration.
- 17.29a One or two slides will be identified by the reviewing pathologist for inclusion in the pathology files for this study. These slides are being stored for quality assurance purposes only and no future research will be conducted on them. All remaining diagnostic slides will be returned to the submitting institution.

Add 1

17.29b If the patient does not enter the study, please notify the Pathology Coordinator listed on the Protocol Resource page and then all slides and forms will be returned to the submitting institution.

17.3 Paraffin Embedded Tissue Blocks/Slides

17.31 Submit one formalin fixed paraffin-embedded (FFPE) tumor tissue block with representative tumor from each surgical biopsy. Material obtained at the time of recurrence is preferred. **A corresponding H&E slide for each submitted block must be provided** to permit quality assessment (QA) of each tissue block. Once the QA is completed, all H&E slides will be returned, unless specified otherwise in Section 17.29a.

Add 4

17.32 The FFPE tissue block is preferred; however, **if an institution is unable to provide a tissue block**, cut 15 five micron sections and mount on charged glass slides. **Label the slides with NCCTG patient ID number, accession number, and order of sections (i.e., 1-15)**. H&E stain every 10th slide that is cut, starting with the first cut slide (i.e., slides labeled 1 and 11). These slides will be reviewed centrally under the research base's quality assessment protocol. The remaining 10 unstained slides will be processed as described in 17.5. For samples containing less than 7 square millimeters of tumor tissue, multiple sections should be mounted onto each slide to ensure that the appropriate amount of tumor tissue is available. Ideally, each slide must have a minimum of 75% tumor tissue on the slide to be deemed adequate for study. **Do not bake or place covers slips on the slides.**

Add 4

17.33 The following materials below are mandatory (unless indicated otherwise) and required for shipment:

- Paraffin Embedded Tissue Blocks with Corresponding H&E Slide (OR 13 Unstained Slides with 2 Corresponding H&E Slides)
- Tissue Specimen Submission Form
- Surgical Pathology Report

17.34 The block/slides must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, NCCTG patient ID number, and patient initials.

17.35 Tissue specimens must be shipped before or ≤ 30 days following registration.

17.36 Verify that the appropriate sections of the Tissue Specimen Submission Form are completed and filled in correctly. Enter information from the Tissue Specimen Submission Form into the remote data entry system the same day the specimen is submitted (see Forms Packet).

17.37 Ship all tissue specimens and accompanying materials to the NCCTG Research Base:

Add 1

NCCTG Operations Office
 Attn: NCCTG PC Office (Study N0776)
 RO_FF_03_24-CC/NW Clinic
 200 First Street SW
 Rochester, MN 55905

17.38 The NCCTG Operations Office will forward the block/slides to the NCCTG Research Base Tissue and Cell Molecular Analysis (TACMA) Shared Resource, Stable 13-10B, Mayo Clinic Rochester (Attn: TACMA Supervisor) for processing as outlined in Sections 17.51 and 17.52.

17.4 Frozen Tumor Tissue: None.

17.5 Study Methodology and Storage Information

Submitted tissue samples will be analyzed as follows:

Add 4, 11,
16, 17

17.51 Immunohistochemistry (IHC) on tumor samples obtained at baseline will have the following antigens analyzed in the TACMA Shared Resource at Mayo Clinic Rochester:

- VEGFR3
- PDGFR α
- PDGFR β
- CA-9
- HIF1 α
- HIF2 α
- NRP-2
- Phospho-ERK

Add 17

17.52 The following additional IHC assessments will be performed on baseline tumor samples by HistoGeneX (Antwerp, Belgium):

- CD31
- VEGFR1
- VEGFR2
- VEGFA
- NRP-1

HistoGeneX offers IHC services in a quality-driven environment. All assays are optimized, implemented and validated according to strict quality assurance standards that are based on CAP, BELAC, and CLIA guidelines. At present, HistoGeneX provides over 80 assays covering the fields of oncology and neuropathology. Five 5-micron unstained charged slides and one H&E slide will be shipped to the following address for assaying and analysis:

HistoGeneX
Sofie Vande Velde
Campus Middelheim-Pathology
Linderdreef 1
B-2020 Antwerp
Belgium

Add 11,17

17.53 DNA may be extracted from tumor tissue for pharmacogenetic assays (e.g., single nucleotide polymorphism [SNP] analyses) to determine correlations with efficacy and tolerability of bevacizumab and sorafenib treatment. Pharmacogenetic research of molecular targets of bevacizumab and sorafenib to be analyzed include, but are not limited to, VEGF, VEGF receptors, PDGFR- β , and RET, Flt3, and c-KIT SNP analyses.

Add 11,17

17.54 At the completion of the study, any unused/remaining material will be stored in the NCCTG Central Operations Office (attn: Pathology Coordinator) for future research according to the patient consent permission (see Section 6.24). Potential future research may include immunohistochemistry (IHC) analyses and/or tissue microarray (TMA) construction to analyze predictive biomarkers, changes in expression pattern with therapy, and correlation with response and/or adverse events. For TMAs, the donor block remains intact except for 6 small (0.6mm) holes where the cores were taken. This process has minimal impact on the utility of the block for future clinical diagnostic needs. When a protocol is developed, it will be presented for IRB review and approval.

Add 17

17.55 Banking of tumor tissue, according to the patient consent permission (see Section 6.24), is for future research. As protocols are developed, they will be presented for NCCTG and IRB review and approval. (This collection is part of a general strategy of investigation for NCCTG CNS studies.)

Add 17

17.56 The institutional pathologist will be notified by the NCCTG Operations Office (Pathology Coordinator) if the block may be depleted.

- Add 17 17.57 Blocks requested to accommodate individual patient management will be returned promptly upon request.
- 17.6 Return of Genetic Testing Research Results
- Add 11 Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.
- If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

18.0 Records and Data Collection Procedures

Forms	Active-Monitoring Phase (Compliance with Test Schedule)				Event-Monitoring ¹ (Completion of Active-Monitoring Phase)					At Each Occurrence			
	Pre-Reg	Initial Material	Pathology Review	Follow-up material		28-42 days after treatment discontinuation	q. 3 months for 5 years then yearly thereafter	At PD	Death	ADR/AER	New Primary	Grade 4 or 5 Non-AER Reportable Events/Hospitalization	Late Adverse Event
		≤2 weeks after registration	≤30 days after registration	At each evaluation	At end of treatment								
On-Study Form		X											
Baseline Adverse Events Form		X											
OP and Path Reports		X											
Measurement Form		X			X								
Day 3 DCE MRI Form				X ¹⁰									
Tissue Specimen Submission Form (Section 17.32)			X										
Pathology Material (see Section 17.22)	X												
Pre-Reg Screening Failure Form	X ³												
Blood Specimen Submission Form (Section 14.0)		X ⁸		X ⁸	X ⁸			X ⁸					
Event Monitoring Form					X ⁹	X	X	X	X		X		X
End of Active Treatment/Cancel Notification Form		X ²			X								
Evaluation/Treatment Form				X ⁴	X								
Blood Pressure Form		X		X ⁴	X								
Nadir/Adverse Event Form				X	X								
Concurrent Treatment Form		X		X ⁴	X								
Concurrent Steroid and Anticonvulsant Treatment Form		X		X ⁵	X								
Patient Questionnaire Booklet (FACT-Br)		X ^{5,6}		X ^{5,6}									
Patient Questionnaire Booklet Compliance Form		X ⁷		X ⁷									
ADR/AER (see Section 10.0) Notification Form									X			X	

- 1 If a patient is still alive 15 years after registration, no further follow-up is required.
2. Submit this form only if withdrawal/refusal prior to beginning protocol therapy occurs.
3. Complete only if patient is NOT registered after he/she is pre-registered.
4. Complete at each evaluation during Active Treatment (see Section 4.0).
5. Patient FACT-Br questionnaire booklets **must** be used; copies are not acceptable for this submission.
6. Every other cycle.
7. This form must be completed **only** if the quality of life questionnaires contain absolutely **NO** patient provided assessment information.
8. ≤2 weeks before start of treatment, Cycle 1 Day 3 (± 1 day), before treatment Cycle 2, before treatment Cycle 3, before treatment every 4 weeks thereafter x 5 (i.e., Cycles 5, 7, 9, 11, and 13) and at PD, withdrawal or removal to test for circulating endothelial cells only.
9. Complete if going directly to Event Monitoring (i.e., patients not entering Observation phase)
10. Day 3, Mayo Rochester only (first 20 patients) per Section 4.0. Note: All other required DCE-MRI timepoints for Mayo Rochester patients will use the Measurement Form.

19.0 Budget

19.1 Costs charged to patient: routine clinical care

Add 4,7
19.2 Tests to be research funded: PT/INR (~\$29 x 5 if patient is on Coumadin), APTT (~\$37 x 1/patient), fibrinogen (~\$42 x 1/patient); DCE MRI (~\$2,268 x 2/patient – baseline if needed to assess progression, Cycle 1 Day 3, first 20 patients at Mayo Clinic Rochester only); Urine protein: creatinine ratio (~\$27 x 6/patients). Research analyses being done on the blood and tissue samples.

19.3 Other budget concerns: Study agents will be provided free of charge.

20.0 Reference

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Appendix I

***NOTES FOR LOCAL INVESTIGATORS: [NOTE: Retain this section and asterisk item below for NCCTG model consents]**

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is <http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/>
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer...What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at <https://cissecure.nci.nih.gov/ncipubs/> or call 1-800-4-CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

**These notes for {authors and} investigators are instructional and should not be included in the informed consent form given to the prospective research participant.*

N0776: Phase II Trial of Avastin® in Combination with Sorafenib in Recurrent Glioblastoma Multiforme

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this research study because you have recurrent glioblastoma multiforme.

Why is this research study being done?

The purpose of this research study is to:

- Find out what effects, good and/or bad, the combination of Avastin® and sorafenib have on you and your cancer.
- Find out if the combination of Avastin® and sorafenib can help you get better.
- Find out if MRI testing can help tell the investigators what kind of response you might have to the treatment.
- Find out if there are individual differences and/or tumor characteristics that will affect response to treatment.
- See how treatment affects your quality of life.

The use of Avastin® and sorafenib in this study is considered investigational.

How many people will take part in the research study?

About 48 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study ...

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical history
- Complete physical exam
- Neurological history and exam
- Routine blood tests (including pregnancy tests, if necessary)
- Scans of the head with contrast (for tumor measurement)
- Electrocardiogram (ECG) (this measures how your heart is doing)

The following tests will also be done because of the drugs used in this study:

- Tests to see how your blood clots
- Random urine collection (at least 4 ml [about 1 teaspoon]). A 24-hour urine collection may be required if the results are not normal

Before you can go on study, slides made from your tumor tissue will be sent to laboratories associated with the North Central Cancer Treatment Group (NCCTG) for central review to confirm the results of your local laboratory review. **This review is mandatory.** These slides will be kept by the North Central Cancer Treatment Group. No further testing will be done on these slides.

During the study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures throughout the study. They are part of regular cancer care.

- Medical history
- Complete physical exam
- Neurological history and exam (every other cycle)
- Routine blood tests
- Scans of the head with contrast (for tumor measurement) (every 8 weeks)

Add 7

The following tests will also be done because of the drugs used in this study:

- Tests to see how your blood clots if you are on Coumadin (weekly for the first 4 weeks)
- Random urine collection (at least 4 ml [about 1 teaspoon]) (every other cycle). A 24-hour urine collection may be required if the results are not normal

You will be asked to complete a questionnaire that asks questions about how you are doing. It shouldn't take you more than 15-30 minutes to complete. You will be asked to complete this questionnaire before you start treatment and then every other visit (about every 4 weeks). This information will help the investigators better understand how patients feel during treatments and what affects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treatment cancer. If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

Add
1,7,9

Update 1

You will take sorafenib, one tablet by mouth once a day (one tablet should be taken consistently at about the same time each day at your convenience [i.e., 24 hours apart]) on days 1 through 14. A cycle of treatment covers a 14-day period of time. You will take the sorafenib tablets home with you and they need to be swallowed whole with about 8 ounces of water. Tablets should be taken without food, at least one hour before or two hours after eating. Tablets should not be taken with grapefruit/grapefruit juice. If you miss a dose, you should not make it up. A diary that keeps track of the number of tablets you take will need to be filled out every day during the time you are taking sorafenib and returned with each visit to the clinic. The treatment will continue until your disease gets worse.

You will also be given Avastin® into a vein on Day 1 every cycle.

Because high blood pressure is a side effect of taking sorafenib and Avastin®, it will be important that blood pressure be taken and recorded at least weekly during the first four weeks of treatment. The blood pressure can be done by either a health care professional (e.g. physician, physician assistant, nurse, etc), at home if you have a blood pressure monitor, at a senior center, or at a pharmacy. Take the blood pressure after you have rested at least 30 minutes. You will also be asked to record this information in a blood pressure diary that will need to be given to your study doctor each time you see him/her.

If two systolic readings (the top reading of the blood pressure value) in a row on two different days are greater than or equal to 140 mmHg OR two diastolic readings (the bottom reading of the blood pressure value) in a row on two different days are greater than or equal to 90 mmHg, you should contact your study doctor or local doctor as soon as possible. Also, contact your study doctor or local doctor if you think you are having any signs (for example, headaches) that might lead you to think your blood pressure is too high.

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.

- Research blood draw
- *Add in the following for Mayo Rochester patients only:* Research MRI at baseline, Day 3 of Cycle 1, before Cycle 3 (Day 28), and before Cycle 5.

Add 1,11

This study has mandatory laboratory tests that will be done to study small samples of blood. A blood sample (about 8-10 teaspoons) will be done by drawing some blood from a vein. Blood samples will be collected before treatment begins; Cycle 1 Day 3; before treatment Cycle 2; before treatment Cycle 3; before treatment every 4 weeks times 5 (before treatment Cycles 5, 7, 9, 11, and 13); and when your disease may worsen, you withdraw from the study, or are removed from the study.

Add 1

This study also has optional laboratory tests that will be done to study small samples of tissue. You are or will have had a biopsy to see if your cancer has returned. No additional biopsies will be done to get this tissue.

Please read the following statements and mark your choice:

1. I agree to provide tissue sample(s) to laboratories associated with NCCTG for research testing planned as part of this study.

Yes No Please initial here: _____ Date: _____

The blood and tissue will be sent to laboratories associated with North Central Cancer Treatment Group (NCCTG) where the tests will be done. These tests will be done in order to understand how your cancer responds to treatment. It is hoped that this will help investigators better understand your type of cancer. The results of these tests will not be sent to you or your study doctor and will not be used in planning your care. These tests are for research purposes only and you will not have to pay for them.

Add 12

Cycle 1 (14 days)

Day	What you do
Add 9 Add 1 Day 1	<ul style="list-style-type: none"> • Begin taking sorafenib once a day. • Avastin® will be given into a vein. • Blood pressure check
Add 1,9 Day 3	<ul style="list-style-type: none"> • Come back to the Clinic to get a research blood draw. <p><i>Add in the following for Mayo Rochester patients only: Research MRI</i></p>
Add 1,9 Days 2-14	<ul style="list-style-type: none"> • Take the sorafenib daily.
Add 1,9 Day 14	<ul style="list-style-type: none"> • Return to your doctor’s office at _____ <i>[insert appointment time]</i> for your next exam and to begin the next cycle. • Bring pill diary to this appointment.

Future cycles (each cycle is 14 days)

Day	What you do
Add 11 Day 1	<ul style="list-style-type: none"> • History and exam • Neuro history and exam every other cycle (about every 28 days) • Check to see if you have had any bad side effects • Routine blood tests • Blood pressure check – bring blood pressure diary • Urine collection every other cycle (about every 28 days) • Scans of the head with contrast (for tumor measurement) every 8 weeks • Bring in medication diary • Quality of life questionnaire every other cycle (about every 28 days) • Research blood draw (Cycles 2, 3, 5, 7, 9, 11, 13) • Avastin® will be given into a vein. <p><i>Before Cycle 3 (Day 28) and before cycle 5: Add in the following for Mayo Rochester patients only: Research MRI</i></p>
Add 7,9 Days 1-14	<ul style="list-style-type: none"> • Keep taking sorafenib daily if you have no bad side effects and cancer is not getting worse. Call the doctor at _____ <i>[insert phone number]</i> if you do not know what to do.
Add 7,9 Day 14	<ul style="list-style-type: none"> • Return to your doctor’s office at _____ <i>[insert appointment time]</i> for your next exam and to begin the next cycle. • Bring pill diary to this appointment.

How long will I be in the research study?

Add 1
You will be asked to take sorafenib and Avastin® until your tumor gets worse. After that, we would like to keep track of your medical condition indefinitely. Keeping in touch with you and checking on your condition helps us look at the long-term effects of the study.

Can I stop being in the research study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the sorafenib and Avastin® can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what followup care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the research study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the drugs in this study. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the sorafenib include those which are:

Likely risks (events occurring greater than 20% of the time)

- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
- Fatigue/tiredness
- Inflammation of the skin on the palms of the hands or soles of the feet
- Diarrhea
- Loss of appetite
- Low blood phosphate level
- Hair loss
- Nausea or the urge to vomit
- Stomach ache
- Low levels of a blood protein called albumin
- Weight loss
- High blood sugar
- Decreased total number of white blood cells (leukocytes)
- Decreased number of a type of white blood cell (lymphocyte)
- Increased blood level of a digestive enzyme level (amylase)
- High blood levels of a liver pigment (bilirubin) indicative of abnormal liver function
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver enzyme (AST/SGOT)
- Decreased number of blood cells that help to clot blood (platelet)
- Abnormal blood level of fat-digesting enzyme (lipase)
- Low blood calcium level
- Low blood sodium level

- Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)
- Increased INR (measure of the ability of the blood to clot properly) which increases the risk of bleeding
-

Add
4,6,13

Less likely (events occurring less than or equal to 20% of the time)

- Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, or burning
- Constipation
- Dry skin
- Fever
- Increased blood level of a liver enzyme (GGT)
- Low blood sugar
- Itching
- High blood pressure
- Vomiting
- Pain such as (joints, muscles, headache, legs and or arms, chest, back, bone)
- Bleeding in the reproductive organs, or urinary system such as the bladder or kidney
- Fever associated with a dangerously low white blood cell count (neutrophils)
- Infection with or without a low white blood cell count
- Irritation or sores in the lining of the voice box
- Irritation or sores in the lining of the throat
- Irritation or sores in the lining of the windpipe
- Voice change
- Difficulty sleeping or falling asleep
- Irritation or sores in the lining of the rectum
- Irritation or sores in the lining of the small bowel
- Bleeding in the digestive tract
- Bleeding of the respiratory tract
- Swelling of the arms and legs
- High blood potassium level
- Low blood potassium level
- Dizziness (or sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking)
- Cough
- Shortness of breath
- Formation of presence of a blood clot inside a blood vessel
- Lack of enough red blood cells (anemia)
- Irritation or sores in the lining of the anus
- Fluid collection in the abdomen
- Irritation or sores in the lining of the mouth
- Test that shows a problem in blood clotting
- Increased blood level of cholesterol
- Decreased blood level of carbon dioxide
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Increased blood level of calcium
- Increased blood level of sodium
- Increased blood level of uric acid, a waste material from food digestion
- Muscle spasm
- Sudden or traumatic injury to the kidney
- Shortness of breath
- Nose bleed

Add
4,6,9,13

Rare but serious (events occurring less than 2% of the time)

- A hole in a part(s) of the digestive tract
- Heart attack caused by a blockage of a blood vessel supplying part of the heart
- Decrease in the ability of the heart to pump blood during the “active” phase of the heartbeat (systole)
- Bleeding into the brain or spinal cord
- Reversible posterior leukoencephalopathy syndrome (RPSL) is a syndrome caused by high blood pressure characterized by headache, confusion, seizures, and vision loss associated with imaging findings
- Collection of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal EKG and blood tests can confirm damage to the heart.
- Serious potentially life-threatening type of allergic reaction that may cause breathing difficulty, dizziness, low blood pressure, and loss of consciousness
- Severe reaction of the skin and gut lining that may include rash and shedding or death of tissue
- Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer)

Risks and side effects related to the **Avastin®** include those which are:

Add 14 **Likely**

- Diarrhea
- Nausea or the urge to vomit
- Vomiting
- Fatigue or tiredness
- Headache or head pain
- High blood pressure

Add 14 **Less likely**

- Lack of enough red blood cells (anemia)
- Fast heartbeat usually originating in an area located above the ventricles
- Feeling of spinning or whirling
- Belly pain
- Inflammation (swelling and redness) of the large bowel (colon)
- Constipation
- Heartburn
- Bleeding in some organ(s) of the digestive tract
- Partial or complete blockage of the small and/or large bowel. Ileus is a functional rather than actual blockage of the bowel.
- Irritation or sores in the lining of the mouth
- Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
- Chest pain not heart-related
- Pain
- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.
- Infection
- Infection (collection of pus) around the rectum
- Premature opening of a wound along surgical stitches after surgery
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)

- Increased blood level of a liver enzyme (AST/SGOT)
- Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
- Increased blood level of a heart muscle protein (troponin I) indicating damage to the heart muscle
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Weight loss
- Decrease in the total number of white blood cells (leukocytes)
- Loss of appetite
- Joint pain
- Abnormal changes in the growth plate that may affect the growth of long bones in very young children. This side effect appeared to be reversible after the treatment was stopped but has not been assessed with long-term use of the bevacizumab drug.
- Muscle pain
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- Fainting
- Sudden decrease of kidney function
- Blood in the urine
- More protein leaking into the urine than usual, often a sign of kidney disease
- Bleeding in the vagina
- Cough
- Shortness of breath
- Nose bleed
- Hoarseness
- Stuffy nose
- Itching
- Skin rash
- Hives
- Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung

Add 9,14 **Rare but serious**

- Damage of or clots in small blood vessels in the kidney that can cause complications, some of which are serious including abnormal destruction of red blood cells (hemolysis) or platelets (that help to clot blood) and kidney failure
- Collection of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal EKG and blood tests can confirm damage to the heart.
- Heart failure: inability of the heart to adequately pump blood to supply oxygen to the body
- Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)
- Heart attack caused by a blockage or decreased blood supply to the heart
- Irregular heartbeat resulting from an abnormality in the one of the lower chambers of the heart (ventricle)
- Ventricular fibrillation: irregular heartbeat that involves the lower chambers of the heart (ventricles) that results in uncoordinated contraction of the heart; life threatening and potentially fatal, needing immediate attention
- Gastrointestinal fistula: Abnormal hole between an organ of the digestive tract and another organ or tissue
- Gastrointestinal perforation : A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair
- Sore (ulcer) somewhere in the digestive tract

- Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.
- Leakage from stomach due to breakdown of an anastomosis (surgical connection of two separate body structures)
- Bleeding in the brain
- Stroke caused by decreased blood flow to the brain
- Abnormal changes in the brain that can cause a collection of symptoms including headache, confusion, seizures, and vision loss associated with MRI imaging findings (RPLS)
- A condition in which the kidneys leak a large amount of protein into the urine that can cause complications including swelling and kidney failure
- Kidney failure
- Abnormal hole between part of the urinary system and another organ or tissue
- Abnormal hole between the vagina and another organ or tissue
- Abnormal hole between the lower breathing tube and the body cavity that surrounds the lungs
- Bleeding from the lungs
- Hole in the wall that separates the nostrils of the nose
- Abnormal hole between the breathing tube (windpipe) and the tube that goes from mouth to stomach through which food passes (esophagus). This is life-threatening and potentially fatal.
- Blockage or narrowing of a blood vessel (artery) that can cause damage or loss of function including a heart attack or stroke

As with any medication, allergic reactions are a possibility.

The risks of drawing blood include pain, bruising or rarely infection at the needle site.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breast feed a baby while on this study or for 6 months after your last dose of bevacizumab. It is important you understand that you need to use birth control while on this study and for at least 6 months after your last dose of bevacizumab. Check with your health care provider about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the research study?

Taking part in this study may or may not make your health better. While doctors hope the combination of treatment with sorafenib and Avastin® will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about the combination of sorafenib and Avastin® as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this research study?

You do not have to be in this study to receive treatment for your cancer.

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- North Central Cancer Treatment Group (NCCTG)
- Bayer Corporation, manufacturer of sorafenib
- Genentech/Roche Pharmaceuticals, manufacturer of Avastin®
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this research study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Those tests and procedures you will not need to pay for are the PT/INR if you are on Coumadin (*the following can be added if site feels appropriate: up to \$29.00 x 5 times per patient*), fibrinogen (*the following can be added if site feels appropriate: up to \$42.00 x 1 per patient*); (*for first 20 patients at Mayo Clinic Rochester – DCE MRI at baseline [if needed at that time] and Cycle 1 Day 3*); APTT (*the following can be added if site feels appropriate: up to \$37.00 x 1 per patient*); and urine protein analysis (*the following can be added if site feels appropriate: up to \$27.00 x 6 per patients*). Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Add
4,7,9

The sorafenib and Avastin® are being supplied to you at no cost. However, you or your health plan may need to pay for costs of the supplies and personnel who give you the sorafenib and Avastin®.

Every effort has been made to ensure adequate supplies of sorafenib and Avastin®, free of charge, for all who take part. If, however, sorafenib or Avastin® becomes FDA approved as it is used in this study, you may be asked to buy the rest of the doses of the drug. You and/or your health plan may also have to pay for other drugs or treatment that are given to help control side effects as well as the cost of tests or exams to evaluate possible side effects.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage> . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this research study?

It is important that you tell your study doctor, _____ [investigator's name(s)], if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ [telephone number].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this research study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the research study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ [name(s)] at _____ [telephone number].

For questions about your rights while taking part in this study, call the _____ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at _____ (telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [**Only applies to sites using the CIRB.*]

About Using Biological Samples for Research

We would like to keep some of the tissue and blood samples that are left over for future research. If you agree, these samples will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research (<http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf>).

Things to Think About

The choice to let us keep the left over tissue and blood for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your samples can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any samples that remain will no longer be used for research.

In the future, people who do research may need to know more about your health. While NCCTG may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes samples are used for genetic research (about diseases that are passed on in families). Even if your samples are used for this kind of research, the results will not be put in your health records.

Your samples will be used only for research and will not be sold. The research done with your samples may help to develop new products in the future.

Benefits

The benefits of research using samples include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, mark "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My tissue sample(s) may be kept for use in research to learn about, prevent, or treat cancer.

Yes

No

Please initial here: _____ Date: _____

2. My blood sample(s) may be kept for use in research to learn about, prevent, or treat cancer.

Yes No Please initial here: _____ Date: _____

3. My tissue sample(s) may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No Please initial here: _____ Date: _____

4. My blood sample(s) may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No Please initial here: _____ Date: _____

5. NCCTG can contact me in the future to take part in more research.

Yes No Please initial here: _____ Date: _____

If you want your sample(s) destroyed at any time, write to the Secretary of the _____
Institutional Review Board _____.
NCCTG has the right to end storage of the sample(s) without telling you.

The sample(s) will be the property of NCCTG. Outside researchers may one day ask for a part of your sample(s) for studies now or future studies.

How do outside researchers get the sample?

Researchers from universities, hospitals, and other health organizations do research using blood and tissue. They may call NCCTG and ask for samples for their studies. NCCTG looks at the way that these studies will be done, and decides if any of the samples can be used. NCCTG sends the samples and some information about you to the researcher. NCCTG will not send your name, address, phone number, social security number, or any other identifying information to the researcher. If you allow your sample(s) to be given to outside researchers, it will be given to them with a code number. If researchers outside NCCTG use the sample(s) for future research, they will decide if you will be contacted and, if so, they would have to contact the researchers at NCCTG. Then NCCTG will contact the clinic where you registered for this study, who will contact you.

Please read the following statements and mark your choice:

1. I permit NCCTG to give my tissue sample(s) to outside researchers:

Yes No Please initial here: _____ Date: _____

2. I permit NCCTG to give my blood sample(s) to outside researchers:

Yes No Please initial here: _____ Date: _____

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

- For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>
- For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Printed Participant Name: _____

Participant Signature: _____

Date: _____

Printed name of person obtaining informed consent:

Signature of person obtaining informed consent:

Date _____

This model informed consent form has been reviewed by the DCTD/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. Sections "What are the risks of the research study" or "What other choices do I have if I don't take part in this research study?" should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the North Central Cancer Treatment Group Operations Office for approval before a patient may be registered to this study.

Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.

Appendix III

PATIENT MEDICATION DIARY

Today's date _____
 Patient Name _____ Patient Study ID _____
 (initials acceptable)

Add 1

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle.
2. You will take one tablet at about the same time each day at a time that is convenient for you (about 24 hours apart). Tablets need to be swallowed whole with about 8 ounces of water. Tablets should be taken without food. Tablets should not be taken with grapefruit/grapefruit juice. If you miss a dose, do not make it up.
3. Record the date and the time when you took your tablet.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring your tablet bottle and this form to your physician when you go for your next appointment.

Add 7,9

Add 9

Day	Date	Time tablet was taken	Comments
1		a.m./p.m.	
2		a.m./p.m.	
3		a.m./p.m.	
4		a.m./p.m.	
5		a.m./p.m.	
6		a.m./p.m.	
7		a.m./p.m.	
8		a.m./p.m.	
9		a.m./p.m.	
10		a.m./p.m.	
11		a.m./p.m.	
12		a.m./p.m.	
13		a.m./p.m.	
14		a.m./p.m.	

Patient's Signature: _____ Date: _____

Physician's Office will complete this section:

1. Date patient started protocol treatment _____ Date patient was removed from study _____
2. Patient's planned daily dose _____ Total number of pills taken this month _____

Physician/Nurse/Data Manager's Signature _____

Appendix IV
Comprehensive List of Drugs That May Have Potential Interactions

CYP3A4

<i>Inducers</i>			
Aminoglutethimide	Nevirapine	Phenytoin	Rifapentine
Carbamazepine	Pentobarbital	Primidone	
Fosphenytoin	Phenobarbital	Rifabutin	
St. John's wort		Rifampin	

Add 3

(Adapted from Cytochrome P-450 Enzymes and Drug metabolism. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 12TH ed. Hudson, OH; LexiComp Inc. 2004: 1619-1631.)

(1) Malhorta *et al.* (2000). Clin Pharmacol Ther. 69:14-23

(2) Mathijssen *et al.* (2002). J Natl Cancer Inst. 94:1247-1249 Frye *et al.* (2004). Clin Pharmacol Ther. 76:323-329

Appendix V

Administration of FACT-Br Questionnaire Instructions for Study Staff

The instructions given below are intended to serve as a guide for the administration of the **FACT-Br** Quality of Life (QOL) questionnaire. The **FACT-Br** should be self-administered by the patient.

1. Following patient's check-in at clinic, the patient should be taken to a quiet area where he/ she may complete the questionnaire without interruption. Adequate time should be provided to the patient so that the questionnaire can be completed at the beginning of the clinic visit.
2. The patient will be given the questionnaire **PRIOR** to being seen by the physician or nursing staff or having any tests/ procedures done at the clinic visit, as indicated in the protocol.
3. The patient should be instructed to read the brief directions at the top of the page. After the patient's correct understanding has been confirmed, he/ she should be encouraged to complete every item in order. Some patients may feel that a given question is not applicable to them and will therefore skip the item altogether. **Patients should be encouraged to check the response that is most applicable.** If, for example, a patient is not currently receiving any treatment, the patient should check "not at all" to the question "I am bothered by side effects of treatment."
4. The **FACT-Br** must be completed by the patient alone, without coaching or suggestions as to the "correct" answer by health care personnel, relatives, or anyone else.

OR

If the patient has experienced cognitive deterioration during treatment, a 'significant other' (e.g., a spouse) should complete the **FACT-Br** on behalf of the patient, without coaching or suggestions as to the "correct" answer by health care personnel, other relatives, or anyone else. The respondent must sign the back of the questionnaire.

5. The study staff may provide clarification but should not rephrase questions, suggest answers, or discuss answers.
6. The study staff will collect the questionnaire as soon as it has been completed, check to see that each question has been answered, and remind the patient/respondent to answer any questions that may have been missed. If the patient/ responder declines to answer some or any of the questions, the study staff should enter an explanatory comment on the questionnaire.
7. The questionnaire must be completed in the clinic, at the beginning of the visit. The questionnaire may not be taken home nor may it be completed at a later time.

NOTE: Varying the environment in which the questionnaire is completed by allowing completion at other times than the time of the clinic visit introduces unnecessary variables into the study.

8. The information provided by the patient in the completed questionnaire is confidential and should not be discussed with, or shown to, anyone who is not a member of the study team.

Appendix V
FACT - Br (Version 4)

Below is a list of statements that other people with your illness have said are important.
By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

PHYSICAL WELL-BEING

	Not at all	A little bit	Some- what	Quite a bit	Very much
1. I have a lack of energy.....	0	1	2	3	4
2. I have nausea.....	0	1	2	3	4
3. Because of my physical condition, I have trouble meeting the needs of my family.....	0	1	2	3	4
4. I have pain.....	0	1	2	3	4
5. I am bothered by side effects of treatment.....	0	1	2	3	4
6. I feel ill.....	0	1	2	3	4
7. I am forced to spend time in bed.....	0	1	2	3	4

SOCIAL/FAMILY WELL-BEING

	Not at all	A little bit	Some- what	Quite a bit	Very much
8. I feel close to my friends.....	0	1	2	3	4
9. I get emotional support from my family.....	0	1	2	3	4
10. I get support from my friends.....	0	1	2	3	4
11. My family has accepted my illness.....	0	1	2	3	4
12. I am satisfied with family communication about my illness.....	0	1	2	3	4
13. I feel close to my partner (or the person who is my main support).....	0	1	2	3	4

Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box and go to the next section.

14. I am satisfied with my sex life.....	0	1	2	3	4
--	---	---	---	---	---

Please go to next page

FACT - Br (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

EMOTIONAL WELL-BEING

	Not at all	A little bit	Some- what	Quite a bit	Very much
15. I feel sad.....	0	1	2	3	4
16. I am satisfied with how I am coping with my illness.....	0	1	2	3	4
17. I am losing hope in the fight against my illness.....	0	1	2	3	4
18. I feel nervous.....	0	1	2	3	4
19. I worry about dying.....	0	1	2	3	4
20. I worry that my condition will get worse.....	0	1	2	3	4

FUNCTIONAL WELL-BEING

	Not at all	A little bit	Some- what	Quite a bit	Very much
21. I am able to work (include work at home).....	0	1	2	3	4
22. My work (include work at home) is fulfilling.....	0	1	2	3	4
23. I am able to enjoy life.....	0	1	2	3	4
24. I have accepted my illness.....	0	1	2	3	4
25. I am sleeping well.....	0	1	2	3	4
26. I am enjoying the things I usually do for fun.....	0	1	2	3	4
27. I am content with the quality of my life right now.....	0	1	2	3	4

Please go to next page

FACT - Br (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

ADDITIONAL CONCERNS

	Not at all	A little bit	Some- what	Quite a bit	Very much
28. I am able to concentrate.....	0	1	2	3	4
29. I have had seizures (convulsions).....	0	1	2	3	4
30. I can remember new things.....	0	1	2	3	4
31. I get frustrated that I cannot do things I used to.....	0	1	2	3	4
32. I am afraid of having a seizure (convulsion).....	0	1	2	3	4
33. I have trouble with my eyesight.....	0	1	2	3	4
34. I feel independent.....	0	1	2	3	4
35. I have trouble hearing.....	0	1	2	3	4
36. I am able to find the right words to say what I mean.....	0	1	2	3	4
37. I have difficulty expressing my thoughts.....	0	1	2	3	4
38. I am bothered by the change in my personality.....	0	1	2	3	4
39. I am able to make decisions and take responsibility.....	0	1	2	3	4
40. I am bothered by the drop in my contribution to the family.....	0	1	2	3	4
41. I am able to put my thoughts together.....	0	1	2	3	4
42. I need help in caring for myself (bathing, dressing, eating, etc.).....	0	1	2	3	4
43. I am able to put my thoughts into action.....	0	1	2	3	4
44. I am able to read like I used to.....	0	1	2	3	4
45. I am able to write like I used to.....	0	1	2	3	4
46. I am able to drive a vehicle (my car, truck, etc.).....	0	1	2	3	4
47. I have trouble feeling sensations in my arms, hands, or legs.....	0	1	2	3	4
48. I have weakness in my arms or legs.....	0	1	2	3	4
49. I have trouble with coordination.....	0	1	2	3	4
50. I get headaches.....	0	1	2	3	4

Appendix VI
PATIENT INFORMATION SHEET
Patient Completed Quality of Life Booklet

You have been given a booklet to complete for this study. The booklet contains some questions about your ‘quality of life’ as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains questions for the FACT-Br:
2. Directions on how to complete the questions are written on the top of the first set of questions.
3. Please complete the booklet during your scheduled clinical visit and return it to your nurse or your physician.

Thank you for taking the time to help us.

Appendix VII

Research Base Instructions for Biospecimen Processing in BAP Laboratory

Study Number: N0776

Summary Table of Research Blood/Blood Products to be Collected for this Protocol

Collection tube description and/or additive (color of tube top)	Volume to be collected per tube (number of tubes to be collected)	Blood product to be processed in BAP	Baseline (i.e., ≤2 weeks before start of therapy)	Cycle 1, Day 3 (± 1 day)	Prior to treatment Cycle 2	Prior to treatment Cycle 3	Prior to treatment every 4 weeks thereafter x 5 (i.e., Cycles 5, 7, 9, 11, and 13)	At disease progression, withdrawal, or removal	Further processing required by BAP?	Shipping conditions
EDTA (purple)	10 mL (2)	Whole blood	X	X	X	X	X	X	No	Cold pack
EDTA (purple)	~2 mL (4)	Plasma	X	X	X	X	X	X	No	Dry ice
EDTA (purple)	~2 mL (1)	Platelet Poor Plasma (PPP)	X	X	X	X	X	X	No	Dry ice
EDTA (purple)	10 mL (1)	DNA	X						Yes	Cold pack
EDTA (purple)	10 mL (1)	Buffy coat		X		X			Yes	Cold pack

Add 2,10, 11

Add 10

Add 4

Add 4

1. Record receipt of specimens.
2. For all time points, immediately forward 2 x 10 mL EDTA whole blood tubes to Dr. Shaji Kumar, Stable 6-13, Mayo Clinic Rochester, for CEC and CEPC analyses.

3. For all time points, frozen plasma aliquots will be stored at -80°C until the end of the study or upon request (see Step 6).
- Add 3 4. For “baseline” sample, DNA will be isolated from one EDTA tube using the protocol entitled “Extracting Samples on the AutoGen”. DNA will be stored at 4°C until a box is full and then transferred and stored in a -80°C freezer for banking.
5. For all follow-up specimens indicated, buffy coat will be isolated from one EDTA tube using the protocol entitled “Buffy Coat Preparation from Whole Blood”. Buffy coat will be stored at -80°C for banking.
- Add 1,4,16 6. At the end of the study, forward one frozen plasma aliquot and one frozen PPP aliquot (300 uL aliquot) per ELISA to the laboratory of Dr. Shaji Kumar, Stabile 6-13, Mayo Clinic Rochester (ATTN: Terry Kimlinger) for the assaying of circulating HGF, soluble KIT, bFGF, Ang-2, PIGF, and SDF1- α by ELISA. SDF1- α requires the PPP, whereas the remaining ELISAs require regular plasma.
- Add 16 7. At the end of the study, forward one frozen 300 uL plasma aliquot for the protein concentrations of circulating VEGFA, VEGFC, soluble VEGFR1, VEGFR2, and VEGFR3, bFGF, PDGFC, G-CSF, IL-8, E-selectin, and ICAM-1 by multiplex platform by Roche Diagnostics GmbH. Specimens will be shipped on dry ice to:

Dr. Julia Riedlinger
Manager Sample Bank
Roche Diagnostics GmbH
Nonnenwald 2
82377 Penzberg / Germany