

North Central Cancer Treatment Group

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

Addendum 4 – January 22, 2009

Summary

- The drug information section and consent form risks for sorafenib have been updated to reflect current drug safety information. Risk changes in this addendum have been determined to be a minor alteration in the overall risk-benefit for new patients.

New patients cannot be enrolled until this addendum has been approved by the local IRB. Patients who are newly enrolled or presently on study treatment are to be re-consented and a notation of this interaction is to be made in the patient chart or research record. Patients are to sign a revised IRB-approved informed consent form or other IRB-approved document including this information.

Determination of the level of IRB review for minor risk changes (expedited versus full board review) is at the discretion of the local IRB.

- Eliminate inpatient dose escalation of Sorafenib, if \leq grade 2 toxicity in cycle 1. Rationale: Antitumor responses were seen in all patients who received the reduced Sorafenib dose of cycle 1 and had early MRIs performed. Cycle 1 in general has been well-tolerated while all patients who received the higher Sorafenib dose in cycle 2 had toxicities, which necessitated dose omissions or delays. Therefore, inpatient Sorafenib dose escalation in cycle 2 appears to result in increased toxicity without necessarily improving efficacy; Sections 7 and 8 have been revised to eliminate the option of Sorafenib dose escalation.
- Additional correlative studies will be performed to maintain consistency with other studies utilizing Sorafenib (N054C and N0745).
- Administrative/editorial changes.

Replacement pages are included. Please incorporate into the protocol and keep this addendum with your protocol.

Title page Updated to reflect the addition of Addendum 4 and revised NCI version date.

Section 1.0 **Background**
Page 6: Due to the additional correlative studies being performed, the first sentence of Section 1.21 has been revised as follows:
Immunohistochemistry (IHC) for VEGF, VEGFR1~~2~~, VEGFR2~~+~~, **VEGFR3**, CD9, PDGFR α and β , **HIF1 α** , **HIF2 α** and microvessel density, as assessed by CD31 staining will be performed in baseline tumor tissue to assess target expression.

Due to the additional correlative studies being performed, the first sentence of Section 1.23 has been revised as follows:

Molecular biomarkers of vascular response to include circulating VEGFA, VEGFC, HGF, Angiopoietin-2 (Ang-2), PlGF, soluble VEGFR1, soluble VEGFR2, soluble KIT, bFGF and SDF1- α will be measured in peripheral blood.

Section 4.0

Test Schedule

Page 10:

An “R” has been added to the first column under Coagulation for “activated partial thromboplastin time.”

Section 7.0

Protocol Treatment

Page 15:

Due to the responses seen in patients who received the reduced Sorafenib dose of Cycle 1, the opening paragraph in Section 7.11 has been deleted as follows:

~~Cycle 1 all patients and future cycles if patient experiences a grade 3 or 4 treatment related adverse event. See Section 7.12 for future cycles if patient does not experience grade 3 or 4 treatment related adverse event.~~

Page 16:

Due to the responses seen in patients who received the reduced Sorafenib dose of Cycle 1, Section 7.12 has been deleted as follows:

~~7.12 Future cycles if patient did not experience grade 3 or 4 treatment related adverse event during Cycle 1~~

Agent	Dose Level⁴	Route	Day²
Sorafenib	200 mg /dose*	PO twice a day ¹	1 through 14
Avastin®	5 mg/kg/day	IV infusion over 90 (\pm 15) minutes ³	1

*Dose is 400 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, one each morning and one each evening (i.e., 12 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.~~

Pages 16-23: Due to the deletion of Section 7.12, repagination has occurred.

Section 8.0

Page 16:

Dosage Modification Based on Adverse Events

Due to the responses seen in patients who received the reduced Sorafenib dose of Cycle 1, Dose level 1 has been deleted in Section 8.1 as follows:

Dose Level	Sorafenib	Avastin®
+	200 mg BID (days 1 through 14)	5 mg/kg/day — no reduction
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 – no reduction

Section 14.0

Page 32:

Body Fluid Biospecimens

Due to the additional correlative studies being performed, the second to the last sentence in Section 14.412 has been revised as follows:

The plasma will be later assayed for circulating VEGFA, **VEGFC**, **HGF**, **Ang-2**, **PIGF**, soluble VEGFR1, ~~bFGF~~, soluble VEGFR2, **soluble KIT**, **bFGF**, and SDF1- α using commercially available ELISAs.

Section 15.0

Pages 37-40:

Drug Information

Section 15.12 is newly added due to the Comprehensive Adverse Events and Potential Risks List (CAEPR) for sorafenib being inserted into the protocol and the following text has been deleted in Section 15.11:

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. ~~Additional Data from Multiple Clinical Trials The following additional drug-related adverse events and laboratory abnormalities were reported from clinical trials of sorafenib in 1286 cancer patients who received sorafenib as monotherapy (very common 10% or greater, common 1 to less than 10%, uncommon 0.1% to less than 1%):~~

~~Cardiovascular: Uncommon: hypertensive crisis, myocardial ischemia and/or infarction~~

~~Dermatologic: Very common: erythema Common: exfoliative dermatitis, acne, flushing Uncommon: folliculitis, eczema, erythema multiforme~~

~~Digestive: Very common: increased lipase, increased amylase Common: mucositis, stomatitis (including dry mouth and glossodynia), dyspepsia, dysphagia Uncommon: pancreatitis, gastrointestinal reflux, gastritis~~

~~Note that elevations in lipase are very common (41%, see below); a diagnosis of pancreatitis should not be made solely on the basis of abnormal laboratory values~~

~~General Disorders: Very common: asthenia, pain (including mouth pain, bone pain, and muscle pain) Common: decreased appetite, influenza-like illness, pyrexia Uncommon: infection~~

~~Hematologic: Very common: leukopenia, lymphopenia Common: anemia, neutropenia, thrombocytopenia Uncommon: INR abnormal~~

Hypersensitivity: *Uncommon*: hypersensitivity reactions (including skin reactions and urticaria)

Metabolic and Nutritional: *Very common*: hypophosphatemia *Common*: transient increases in transaminases *Uncommon*: dehydration, hyponatremia, transient increases in alkaline phosphatase, increased bilirubin (including jaundice), hypothyroidism

Musculoskeletal: *Common*: arthralgia, myalgia

Nervous System and Psychiatric: *Common*: depression *Uncommon*: tinnitus

Reproductive: *Common*: erectile dysfunction *Uncommon*: gynecomastia

Respiratory: *Common*: hoarseness *Uncommon*: rhinorrhea

In addition, the following medically significant adverse events were reported infrequently during clinical trials of sorafenib: cerebral hemorrhage, transient ischemic attack, cardiac failure, arrhythmia, thromboembolism, acute renal failure. For these events, the causal relationship to sorafenib has not been established.

For the most recent safety update, please refer to the current sorafenib Prescribing Information.

Due to the inclusion of the CAEPR listing, all remaining sections have been renumbered. Repagination throughout the remainder of the document has also occurred.

Section 16.0

Page 56:

Statistical Considerations and Methodology

Due to the additional correlative studies being performed, sections 16.9a42 and 16.9a43 have been revised as follows:

Cellular biomarkers from blood samples (VEGFA, **VEGFC**, **HGF**, **Ang-2**, P1GF, soluble VEGFR1, ~~bFGF~~, soluble VEGFR2, **soluble KIT**, **bFGF**, and SDF1- α [see Section 14.0]) from blood samples will be evaluated at baseline and relative change from baseline at the specified time points in Section 14.0.

Tumor biomarkers (CD31, CD9, VEGF, VEGFR1, VEGFR2, **VEGFR3**, PDGFR α , PDGFR β , **HIF1 α** , **HIF2 α** , 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.

Section 17.0

Page 60:

Pathology Considerations/Tissue Biospecimens

Due to the additional correlative studies being performed, the number of unstained slides as reflected in the second row of the first column in Section 17.1 has been revised to reflect **13** rather than ~~10~~.

Page 60: Due to the additional correlative studies being performed, the number of slides reflected in the first sentence of Section 17.32 has been revised to reflect **15** rather than ~~12~~.

Due to the additional correlative studies being performed, the number of slides reflected in the first bullet has been revised to reflect **13** rather than ~~10~~.

Page 61: Due to the additional correlative studies being performed, the following have been added to the bullet items in Section 17.51:

- CD31
- VEGFR1
- VEGFR2
- **VEGFR3**
- PDGFR α
- PDGFR β
- VEGF
- CD9
- **HIF1 α**
- **HIF2 α**

Section 19.0

Page 63:

Budget

Section 19.2 has been revised for clarification as follows:

Tests to be research funded: PT/INR (~\$29 x 4 if patient is on Coumadin), **APTT (~\$37 x up to 6/patient)**, fibrinogen (~\$42 x up to 6/patient); DCE MRI (~\$2,268 x ~~42~~/patient – baseline **if needed to assess progression**, Cycle 1 Day 3, ~~prior to Cycle 3 (Day 28), and prior to Cycle 5~~ first 20 patients at Mayo Clinic Rochester only); Urine protein: creatinine ratio (~\$27 x 6/patient). Research analyses being done on the blood and tissue samples.

Appendix I

Pages 6-7:

Consent Form

In order to reflect current drug safety information for Sorafenib, the risks section of the consent form has been revised as follows:

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

- Skin rash
- ~~Dehydration~~ (*moved to Less Likely*)
- Tiredness
- Hand and foot syndrome (numbness, tingling, redness, and/or discomfort of hands or feet that may affect activity of daily living.
- ~~Skin peeling~~ **Flaking or sloughing of skin** (*reworded*)
- ~~Anorexia (loss of appetite, not feeling hungry)~~ (*moved to Less Likely*)
- ~~Dyspnea (difficult breathing)~~ (*deleted*)
- ~~Pruritus (itching)~~ (*moved to Less Likely*)
- ~~Drop in the white blood cell count which could be connected with an increased risk of infections~~ (*moved to Less Likely*)
- ~~Decreased risk of phosphorus in the blood (called hypophosphatemia)~~ (*moved to Less Likely*)
- ~~Decrease in platelet count which may result in bleeding, even potentially serious bleeding such as in the lungs, intestine, or brain~~ (*moved to Less Likely*)
- High blood pressure (*moved to Less Likely*)
- ~~Hair loss~~ (*deleted as this is also listed under Less Likely*)
- Diarrhea
- ~~Nausea, vomiting~~ (*moved to Less Likely*)
- ~~Pain (in mouth, stomach, bone, headache, or tumor pain)~~ (*moved to Less Likely and reworded*)
- ~~Possible increase in pancreas associated enzymes of amylase and lipase~~ (*deleted*)

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

- Anemia (drop in the red blood cells in the blood, which may cause tiredness and shortness of breath)
Decrease in a part of red blood cells that carries oxygen in the body (*reworded*)
- ~~Depression~~ (*deleted*)
- ~~Numbness or tingling in the nerves of the hands or feet~~ **Condition of the nervous system that causes numbness, tingling, burning** (*reworded*)
- ~~ringing in the ears~~ (*deleted*)
- ~~Hoarseness~~ (*deleted*)
- Constipation
- ~~Mouth sores~~ (*deleted*)
- Difficulty swallowing
- ~~Upset stomach~~ (*deleted*)
- Dry skin
- ~~Peeling rash~~ (*deleted as this is listed in Likely*)
- ~~Aene~~ (*deleted*)
- ~~Inflammation of the joints~~ (*deleted*)
- ~~Muscle pain~~ (*combined in category below*)
- ~~Difficulty in initiating or maintaining an erection~~ (*deleted*)
- ~~Weakness~~ (*deleted*)
- Fever
- Flu like symptoms (fever, aching joints, etc.)

- Decrease in weight
- Increase in liver function tests **Abnormal liver or bone enzyme levels** (*reworded*)
- ~~Decrease in kidney function as measured by blood tests~~ **Kidney failure** (*reworded*)
- ~~Decrease in amount of testosterone or other hormones the body makes which could lead to a decrease in sex drive, skin problems, menstrual cycles, or more~~ (*deleted*)
- ~~Teeth and bone changes~~ (*deleted*)
- Chills/shaking chills
- Excessive amounts of air and gases in the stomach
- High blood sugar
- Fluid around the lungs
- General lung damage, **inflammation of the lung** (*newly added*)
- Flushing of the skin
- Pancreatitis
- ~~Persistent runny nose~~ (*deleted*)
- Heartburn
- ~~Enlargement of breast tissue in males~~ (*deleted*)
- Hair loss
- **Allergic reactions, also known as hypersensitivity reactions** (*moved from Rare but serious*)
- **Dehydration** (*moved from Likely*)
- **Anorexia (loss of appetite, not feeling hungry)** (*moved from Likely*)
- **Pruritus (itching)** (*moved from Likely*)
- **Drop in the white blood cell count which could be connected with an increased risk of infections** (*moved from Likely*)
- **Decreased risk of phosphorus in the blood (called hypophosphatemia)** (*moved from Likely*)
- **Decrease in platelet count which may result in bleeding, even potentially serious bleeding such as in the lungs, intestine, or brain** (*moved from Likely*)
- **High blood pressure** (*moved from Likely*)
- **Nausea, vomiting** (*moved from Likely*)
- **Pain (in stomach, joints, or muscles)** (*moved from Likely and reworded*)
- **Non-threatening superficial skin cancer** (*newly added*)
- **Lightening of the skin** (*newly added*)
- **Nail changes** (*newly added*)
- **Fluid collection in the abdomen** (*newly added*)
- **Irritation or sores in the lining of the throat** (*newly added*)
- **Bleeding of areas such as the intestinal system, reproductive organs, and urinary system** (*newly added*)
- **Fever with dangerously low white blood cell count** (*newly added*)
- **Infection** (*newly added*)
- **Low levels of a blood protein called albumin** (*newly added*)
- **Abnormal digestive enzyme level** (*newly added*)
- **Abnormal level of bilirubin in the blood. Bilirubin is a bile pigment found in the liver** (*newly added*)
- **Abnormal blood level of fat-digesting enzyme** (*newly added*)
- **Decrease in oxygen supply to a tissue** (*newly added*)
- **Collection of air outside the lungs in the space surrounding the lungs** (*newly added*)
- **Elevation of blood tests such as blood elastase** (*newly added*)

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

- ~~Allergic reactions, also known as hypersensitivity reactions (moved to Less Likely)~~
- ~~Decrease in thyroid function, with symptoms of tiredness, sensitivity to cold, and slow metabolic rate (deleted)~~
- ~~Decrease in salts in the blood such as sodium (deleted)~~
- ~~Rare brain dysfunction (reversible posterior leukoencephalopathy syndrome) (deleted)~~
- ~~Heart attack (deleted)~~
- ~~Decrease in heart function or heart failure (deleted)~~
- ~~Severe increases in the blood pressure (deleted)~~
- Holes developing in the intestinal system which could be life threatening
- ~~Decreases in liver function (deleted)~~
- ~~Severe life threatening rash (deleted)~~
- ~~Prolonged blood clotting times (deleted)~~
- ~~If you are taking a blood thinner such as Coumadin or Warfarin sorafenib may change the amount of blood thinner in your blood. If this happens, you may have unexpected bleeding. Your doctor may need to do some blood tests to check the level of blood thinner in your blood. (deleted)~~

Page 10: The first paragraph under the “What are the costs of taking part in this research study” section has been revised for clarification as follows:

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, fibrinogen; ~~DCE MRI done at baseline, Cycle 1 Day 3, before Cycle 3 (Day 28), before cycle 5;~~ **(For first 20 patients at Mayo Clinic Rochester – DCE MRI at baseline [if needed at that time] and Cycle 1 Day 3); APTT;** and urine protein analysis. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Appendix VII Research Base Instructions for Biospecimen Processing in BAP Laboratory

Page 1: The second column of the second row has been revised to read ~2 mL ~~(45)~~

Due to the additional correlative studies being performed, a new third row has been added to the table for “Platelet Poor Plasma (PPP).

Page 2: Due to the additional correlative studies being performed, item #6 has been revised as follows:

At the end of the study, forward one frozen plasma aliquot **and one frozen PPP aliquot** (aliquot volume to be determined at the end of the study) to the laboratory of Dr. Shaji Kumar, Stable 6-13, Mayo Clinic Rochester (ATTN: Terry Kimlinger) for the assaying of circulating VEGFA, **VEGFC, HGF, Ang-2, P1GF, soluble VEGFR1, bFGF, soluble VEGFR2, soluble KIT, bFGF,** and SDF1- α by ELISA.. **VEGFC and SDF1- α require the PPP, whereas the remaining ELISAs require regular plasma.**