

North Central Cancer Treatment Group

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

Addendum 7 – March 20, 2009

Summary

- Treatment off protocol with this drug combination is not allowed. Safety with this combination in glioma patients has not yet been established and the efficacy is unclear. Therefore, clarification has been made in Section 13 (Treatment/Follow-up Decision at Evaluation of Patient).

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 7 revised NCI version date.

Protocol Resources

Page 2: The title for Butch Kvittum has been revised as follows:
Quality Control Assurance Specialist

Roxann Neumann replaces ~~Jaqueline M. Lafky~~ as the NCCTG *Research Base* Biospecimen Resource Manager.

Section 4.0 **Test Schedule**

Page 10: Under the “Chemistry” group, the duplicate entry for glucose has been deleted.

For clarification purposes, the “activated partial thromboplastin time^R” and Fibrinogen^R entries under Coagulation have been separated out as these tests are done at baseline only.

Reference to footnote #7 for “Coagulation” in the column “≤21 days prior to reg” has been deleted as this was an error.

For clarification purposes, reference to footnote #3 for the “Patient Blood Pressure Diary” in the column “Prior to each new cycle” has been deleted and replaced with new footnote #14.

Page 11: Footnote #3 has been revised for clarification as follows:

~~Must begin the day the patient starts taking sorafenib and be completed on a daily basis throughout the study. Compliance should be documented in the medical record.~~ **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.**

Page 11: Footnote #7 has been revised for clarification as follows:
~~PT/INR at baseline.~~ For patients on Coumadin, repeat **PT/INR** weekly for the first 4 weeks, and then as clinically indicated.

Page 11: Footnote #14 is newly added as follows:
Recorded weekly during first 3 cycles (total 6 weeks) of sorafenib therapy.

Section 8.0 Dosage Modification Based on Adverse Events

Pages 17-19: For clarification purposes, the following revisions have been made in the table in Section 8.3:

- For the Congestive heart failure under the Cardiac General category, the last column now reads “Hold* until resolution to grade ≤1. **Then resume treatment. If second recurrence, discontinue Avastin®.**”
- For the Obstruction, GI Grade 2 under the Gastrointestinal category, the last column now reads “Hold* until resolution **of obstruction. Then resume treatment.**”
- For the Proteinuria Grade 3 under the Metabolic/Laboratory category, the last column now reads “Hold* until proteinuria improves to ≤grade 2. **Then resume treatment.**”

All other non-hematologic adverse events (excluding alopecia)	Grade 2-4 (excludes nausea/vomiting that has not been pre-medicated)	Sorafenib Avastin®	Hold* 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 the agent the event is clearly related to. If it cannot be determined to which agent the event is related to, discontinue treating, go to observation, and then to event monitoring.
	Grade 3-4 (excludes nausea/vomiting that has not been pre-medicated)		Discontinue the agent the event is clearly related to. If it cannot be determined to which agent the event is related to, discontinue treating, go to observation, and then to event monitoring.

Section 13.0 Treatment/Follow-up Decision at Evaluation of Patient

Page 28: The second sentence in Section 13.1 has been deleted as follows as the safety and efficacy of this combination has not yet been determined:

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 may continue treatment off protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered.~~ The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

Page 28: The fourth sentence in Section 13.2 has been deleted as follows as the safety and efficacy of this combination has not yet been determined:
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. ~~The patient may continue treatment off protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered.~~ Event monitoring will be required per Section 18.0 of the protocol.

Section 14.0 **Body Fluid Biospecimens**

Page 30: For clarification purposes, the first sentence of Section 14.251 has been revised as follows:

Verify ALL sections of the Blood Specimen Submission Form (**see Forms Packet**), ~~MCTS MML~~ Requisition Form (**provided in kit**), and specimen collection labels are completed and filled in correctly.

Page 31: The following updates have been made to Sections 14.254, 14.255, 14.256:
14.254 Ship specimens via Priority Overnight service, Monday – Thursday ONLY, to Mayo ~~Clinical Trial Services~~ Medical Laboratories (**MCTS MML**). Do not send samples on Fridays, weekends or holidays.
14.255 Use kit mailing labels for shipment to **MCTS MML**.
14.256 **MCTS MML** will receive the samples and forward specimens ~~within two hours of accessioning~~ to the NCCTG Research Base Biospecimens Accessioning and Processing (BAP) Shared Resource, Stabile 13-10A, Attention: BAP Supervisor.

A typographical error has been corrected in the last sentence of the second paragraph in Section 14.411 as follows:

Whole blood samples will be collected in a 2 x 10 mL vacutainer EDTA tubes at the time points indicated above.

The second sentence of the third paragraph in Section 14.411 has been corrected as follows:

In brief, ~~a minimum of eight ml of~~ whole blood will be lysed to remove RBC (red blood cells).

Page 32: The last sentence of the third paragraph in Section 14.411 has been revised for clarification as follows:

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.

Page 32:

A new fourth paragraph in Section 14.411 is newly added for clarification as follows:
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.

The following text has been added to Section 14.412 for clarification as follows:
 The plasma will be later assayed for circulating VEGFA, VEGFC, HGF, Ang-2, PlGF, soluble VEGFR1, soluble VEGFR2, soluble KIT, bFGF, and SDF1- α 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.

Section 19.0

Page 63:

Budget

Due to the tests that are done at baseline only (activated partial thromboplastin time^R and Fibrinogen^R) Section 19.2 has been revised as follows:

Tests to be research funded: PT/INR (~\$29 x **45** if patient is on Coumadin), APTT (~\$37 x up to **61**/patient), fibrinogen (~\$42 x up to **61**/patient); DCE MRI (~\$2,268 x 2/patients – 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.

Appendix I

Page 3:

Consent Form

The fifth bullet under the “During the study” section has been revised for clarification as follows:

Scans of the head with contrast (for tumor measurement) (every ~~other cycle~~ **8 weeks**)

Page 3:

The second and third paragraphs under the “During the study” section have been combined and revised for clarification as follows:

You will take sorafenib, one tablet by mouth twice a day (**one tablet should be taken in the morning and one tablet in the evening [i.e., 12 hours apart]**) on days 1 through 5 and 8 through 12. A cycle of treatment covers a 14-day period of time. You will take the sorafenib tablets home with you. The tablets 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.

Page 5: The seventh bullet in the “Future cycles” table for Day 1 has been revised for clarification as follows:
Scans of the head with contrast (for tumor measurement) every ~~other cycle (about every 28 days)~~ **8 weeks**

Per Addendum 4, dose escalation for sorafenib was eliminated. Therefore, the second bullet in the “Future cycles” table for Days 1-14 has been deleted as follows:
~~If you had bad side effects during cycle 1, you will keep taking sorafenib on day 1 through day 5 and day 8 through day 12.~~

Page 10: In order to fully explain the costs that the patient will not have to pay for, the first paragraph under the “What are the costs of taking part in this research study” section has been revised 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 (**up to \$29.00 x 5 times per patient**), fibrinogen (**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 (**up to \$37.00 x 1 per patient**); and urine protein analysis (**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.

Appendix III Patient Medication Diary

Page 1: The second sentence of Instruction #2 has been revised for clarification as follows:
Tablets ~~may~~ **should** be taken ~~with or~~ without food. Tablets should not be taken with grapefruit/grapefruit juice.