

North Central Cancer Treatment Group

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

Addendum 9 – July 3, 2009

Summary

- The study team met on 05-04-09, following accrual of 19 patients, to review adverse events in the trial. There were three grade 4 non-hematologic adverse events which were felt to be at least possibly related to treatment: one patient had grade 4 amylase elevation (a rare but known side effect of sorafenib) associated with grade 3 pancreatitis, a second patient had grade 4 venous thrombosis consisting of DVT and PE (possibly related to study treatment), and a third patient had grade 4 muscle weakness and fatigue, also possibly related to treatment. As per the predetermined toxicity rule in section 16.0 of the protocol, accrual in the trial was temporarily suspended.

The observed incidence of grade 4 non-hematologic toxicity in this trial (15.7%) is slightly higher as compared to NCCTG experience in recurrent glioma trials; nevertheless, there is also early evidence of antitumor activity with an objective response rate of 55.6%. In order to capitalize on this potentially promising antitumor activity and optimize tolerance, we propose that we reopen the trial de-escalating the starting dose by one dose level, i.e., sorafenib 200 mg po daily and bevacizumab 5 mg/kg every two weeks. It is of note that approximately 30% of the study patients had to be deescalated down to the new starting dose level, with excellent tolerance.

New patients cannot be enrolled until this addendum has been approved by the local IRB.

- 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 8 revised NCI version date.

Schema
Page 4: Due to the incidence of grade 4 non-hematologic adverse events observed in this trial, the “Active Treatment” section has been revised as follows:
Sorafenib ~~BID~~ days 1 through 14 ~~5 and 8 through 12~~ (of **each** cycle 4) plus Avastin® (day 1 of **each** cycle 4)

Section 1.0
Page 5: **Background**
Due to the incidence of grade 4 non-hematologic adverse events observed in this trial, the last paragraph on Page 5 under Section 1.1 has been revised as follows:
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 will be~~ 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.**

Section 7.0 Protocol Treatment

Page 15: Due to the incidence of grade 4 non-hematologic adverse events observed in this trial, the table and footnotes * and 1 in Section 7.1 have been revised as follows:

Agent	Dose Level ⁴³	Route	Day ²
Sorafenib	200 mg /dose*	PO twice a day daily ¹	1 through 5 and 8 through 12 Daily ²
Avastin®	5 mg/kg/ day	IV infusion over 90 (± 15) minutes ³	1 every 14 days

* Dose is ~~400~~ **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 ~~one each morning and one each evening~~ **consistently at about the same time each day at a time which is convenient for the patient**, (i.e., ~~± 24~~ **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.

Also, reference to Footnote #4 has been corrected to reflect #3 in the heading of the second column “Dose Level.”

Section 8.0 Dosage Modification Based on Adverse Events

Page 16: Due to the incidence of grade 4 non-hematologic adverse events observed in this trial, the table in Section 8.1 has been revised as follows:

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 day 1 every 14 days – no reduction
-2	200 mg QOD (days 1 through 14)	5 mg/kg/day day 1 every 14 days – no reduction

Page 17: The last column “Dosage Change” for “Dermatology/Skin” has been revised as follows:

- 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, ~~despite dose reduction, hold dose~~ **discontinue sorafenib**.
 - ~~Re-evaluate at least weekly until adverse event resolved to ≤1 or tolerable grade 2.~~
 - ~~Re-treat at a one dose level reduction from the previous dose level~~
 - ~~If adverse event persists >3 weeks, discontinue sorafenib.~~

Page 18: Due to the incidence of grade 4 non-hematologic adverse events observed in this trial, the second column “Adverse Event” for “Vascular” has been revised as follows:

Vascular	Thrombus/embolism Grade 3 or 4 (asymptomatic thrombosis) 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 Discontinue Avastin®.
	Grade 3-4 (symptomatic thrombosis)	

Page 19: An editorial change has been made to the last column “Dosage Change” for “All other non-hematologic adverse events (excluding alopecia) as follows:
 If no recovery after a 3-week delay, despite institution of all clinically appropriate symptomatic treatment, discontinue one or both agents ~~according to~~ **depending on** attribution.

Section 15.0 **Drug Information**
 Pages 44-46: The Nursing Guidelines for Sorafenib (Section 15.18) are added as these were inadvertently omitted. Due to the addition of this section, repagination has occurred.

Section 16.0 **Statistical Considerations**
 Page 55: Due to the incidence of grade 4 non-hematologic adverse events observed in this trial, the following revisions have been made to Section 16.6:

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.

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

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:

- If ~~3~~ **4** or more patients in the first 20 treated patients **at a specific starting dose level** (or ~~15~~ **20%** or more after 20 patients have been accrued) experience a grade 4 or higher non-hematologic adverse event.
- 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.

Appendix I

Consent Form

Page 3:

Due to the incidence of grade 4 non-hematologic adverse events observed in this trial, the first sentence of the second to the last paragraph under “During the study” section has been revised as follows:

You will take sorafenib, one tablet by mouth ~~twice~~ **once** a day (one tablet should be taken ~~in the morning and one tablet in the evening~~ **consistently at about the same time each day at your convenience** [i.e., ~~12~~ **24** hours apart]) on days 1 through ~~5 and 8 through 12~~ **14**.

Page 5:

Due to the incidence of grade 4 non-hematologic adverse events observed in this trial, the first and third rows in the table for Cycle 1 and the second row in the table for Future Cycles have been revised as follows:

Day 1	<ul style="list-style-type: none"> • Begin taking sorafenib twice once a day. • Avastin® will be given into a vein. • Blood pressure check
Days 1-5 and 8-12 1-14	<ul style="list-style-type: none"> • Take the sorafenib on day 1 through day 5 then no sorafenib on day 6 through day 7 and then start again on day 8 through day 12 daily.
Days 1-14	<ul style="list-style-type: none"> • Keep taking sorafenib twice a day 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.

Page 7:

The following clarification has been made under the “Rare but serious” risk section for Sorafenib:

Reversible posterior leukoencephalopathy syndrome (RPSL) is a sSyndrome caused by high blood pressure characterized by headache, confusion, seizures, and vision loss associated with imaging findings

Page 8: The following clarification has been made under the “Rare but serious” risk section for Avastin:

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) ~~or similar leukoencephalopathy syndrome~~: RPLS is a **syndrome caused by high blood pressure characterized by headache, confusion, seizures, and vision loss associated with imaging findings** medical condition related to leakiness of blood vessels in the brain. RPLS can cause confusion, blindness, or vision changes, seizures and other symptoms, as well as changes in brain scans. RPLS may go away after Avastin® is stopped. In rare cases, it may be potentially life-threatening and may have long term effects on brain function.

Page 10: For clarification purposes, the following text has been added in italics to the “What are the costs of taking part in this research study” section:

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.

Appendix III Patient Medication Diary

Page I: Due to the incidence of grade 4 non-hematologic adverse events observed in this trial, the following revisions have been made:

INSTRUCTIONS TO THE PATIENT:				
1. Complete one form for each cycle. 2. You will take two one tablets at about the same time each day, one in the morning and one in the evening 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.				
Day	Date	Time morning tablet was taken	Time evening tablet was taken	Comments
1		a.m./ p.m.	p.m.	
2		a.m./ p.m.	p.m.	
3		a.m./ p.m.	p.m.	
4		a.m./ p.m.	p.m.	
5		a.m./ p.m.	p.m.	
6		a.m./ p.m.	p.m.	
7		a.m./ p.m.	p.m.	
8		a.m./ p.m.	p.m.	
9		a.m./ p.m.	p.m.	
10		a.m./ p.m.	p.m.	
11		a.m./ p.m.	p.m.	
12		a.m./ p.m.	p.m.	
13		a.m./ p.m.	p.m.	
14		a.m./ p.m.	p.m.	