

North Central Cancer Treatment Group

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

Addendum 5 – February 6, 2009

Summary

- An additional dose level reduction has been added for sorafenib due to the hand and foot skin reaction toxicities reported at dose level -1.
- Table 8.3 has been modified in order to allow patients who experience side effects that can only be attributed to one of the two study agents, which necessitate discontinuation of this agent, to continue with the other study agent if they still derive clinical benefit from treatment.

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 5 and revised NCI version date.

Section 8.0

Page 16:

Dosage Modification Based on Adverse Events

Due to the hand and foot skin reaction toxicities seen at dose level -1 for sorafenib, an additional dose level reduction has been added to the table in Section 8.1 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 – no reduction
-2	200 mg QOD (days 1 through 14)	5 mg/kg/day – no reduction

*Starting dose

Pages 17-19: The table in Section 8.3 has been revised due to the hand and foot skin reaction toxicities seen at dose level -1 for sorafenib and to reflect that patients may continue on one of the two study agents if side effects have been attributed to either one or the other as follows:

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

CTCAE 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 and go to observation and then to event monitoring. Dose may not be re-escalated after reduction for adverse event.
Cardiac General	Hypertension	Sorafenib Avastin®	See Section 8.6 for management.
	Other: Congestive heart failure Grade 3 ----- Grade 4	Avastin®	Hold* until resolution to grade ≤1. Discontinue Avastin® and go to observation and then event monitoring.
Dermatology/ Skin	Rash: Hand/foot skin reaction Grade 2 and 3 (see Section 8.7)	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, despite dose reduction, 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 from the previous dose level. • If adverse event persists >3 weeks, discontinue sorafenib and go to observation and then to event monitoring. • Patients with grade 4 adverse events related to agent may be taken off sorafenib study at investigator discretion and go to observation and then event monitoring.
	Rash: acne/acneiform Grade 2 and 3		Discontinue sorafenib and go to observation and then event monitoring.
	Wound complication, non-infectious (dehiscence) ≥grade 2		Discontinue sorafenib and go to observation and then event monitoring.
Gastrointestinal	Fistula, GI – abdominal Any grade	Avastin®	Discontinue Avastin® and go to observation and then event monitoring.
	Leak (including anastomotic), GI Any grade		Hold* until resolution.
	Obstruction, GI Grade 2 ----- Grade 3-4		Hold* until resolution. If surgery is necessary, patient may restart ≥28 days but ≤56 days following surgery and at investigator's discretion
	Perforation, GI Any grade		Discontinue Avastin® and go to observation and then event monitoring.
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.

			<ul style="list-style-type: none"> • 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. <p>Subjects who experience a repeat Grade 3 hemorrhagic event will discontinue and go to observation and then to event monitoring.</p>
	Grade 4		Discontinue and go to observation and then to event monitoring.
Hemorrhage/ Bleeding – CNS or pulmonary	Grade 1	Sorafenib Avastin®	<p>Subjects who are also receiving full-dose anticoagulation will discontinue and go to event monitoring</p> <p>All other subjects hold until all of the following criteria are met:</p> <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 observation and then to event monitoring
Metabolic/ Laboratory	Proteinuria Grade 3 (≥3.5 g/24 hr) Grade 4 (nephritic syndrome)		<p>Hold* until proteinuria improves to ≤grade 2.</p> <p>Discontinue Avastin® and go to observation and then to event monitoring.</p>
Neurology	CNS cerebrovascular ischemia Any grade	Avastin®	Discontinue Avastin® and go to observation and then event monitoring.
	Leukoencephalopathy syndrome (radiographic findings)	Avastin®	<p>Hold* pending workup and management, including control of blood pressure. Discontinue if RPLS diagnosed and go to observation and then 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</p>
Vascular	Thrombus/embolism Grade 3 or 4 (asymptomatic thrombosis)		<p>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:</p> <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

			<ul style="list-style-type: none"> The subject must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation
	Grade 3-4 (symptomatic thrombosis)		Discontinue Avastin® and go to observation and then event monitoring.
	Peripheral arterial ischemia Any grade		Discontinue Avastin® and go to observation and then event monitoring.
	Visceral arterial ischemia Any grade		Discontinue Avastin® and go to observation and then event monitoring.
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.