



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: October 10, 2008

To: NCCTG Primary Clinical Research Associates

From: Janis Wobschall
Protocol Development Coordinator

Re: N0572, A Phase I/II Study of Sorafenib and CCI-779 in Patients with Recurrent Glioblastoma

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with BAY 43-9006 for a study where the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) is distributing this agent. You may have also received this communication directly from DCTD.

AE_1820686_F1

Please note that all risks currently cited in the NCCTG consent form cannot be omitted; it is at the discretion of your local IRB as to whether they wish to add risks based on the enclosed information. If a determination has been made by the NCCTG Research Base that a protocol amendment is necessary, you will receive the NCI-approved protocol addendum at a later date; for purposes of cross-reference, this communication will cite the adverse event noted above.

Please submit this adverse event to your Institutional Review Board.

If you have any questions concerning this communication, please contact Janis Wobschall at wobschall.janis@mayo.edu or 507/284-4852.

JW/kjm
enclosure



DATE: September 8, 2008
FROM: *R. Austin Doyle (for Dr. Wright)*
John Wright, M.D., Ph.D., Investigational Drug Branch, CTEP, DCTD, NCI
Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: BAY 43-9006 Tosylate (BAY 54-9085; Sorafenib Tosylate) and Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# **1820686**
TO: Investigators Using Sorafenib (NSC 724772) and Bevacizumab (NSC 704865)

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. Please find attached a copy of an IND Safety Report recently submitted to the FDA for the CTEP-sponsored investigational agents sorafenib and bevacizumab.

The following must be completed by all investigators using sorafenib under NCI IND 69896 and bevacizumab under NCI INDs 11460 and 7921:

- Send a copy of the IND Safety Report to your Institutional Review Board (IRB) according to your local IRB's policies and procedures.
- File a copy of the IND Safety Report in your protocol file.

If your study is not covered under INDs 69896, 11460, and 7921, it is strongly recommended that you follow the instructions above.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

Based on CTEP's assessment of the current information in light of previous experience with sorafenib and bevacizumab, there does not appear to be a change in the risk-benefit ratio for sorafenib and bevacizumab studies; therefore, CTEP is not requiring a protocol amendment at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The attached Adverse Events Assessment describes the adverse event(s) (synopsis provided below), relevant previous experience under these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 55-year-old female with recurrent metastatic uterine cancer died suddenly while on a phase 1 trial using the investigational agent sorafenib in combination with bevacizumab.

ADVERSE EVENTS ASSESSMENT

IND 69896 NSC 724772 704865 BAY 43-9006 Bevacizumab tosylate (BAY 54- (rhuMAb VEGF) 9085; sorafenib tosylate) AE: 1820686	ADVERSE EXPERIENCE REPORT NO. 32 IND Safety Report: # 1 Event: Gr. 5: Death: Sudden death Protocol: 6750
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The patient was a 55-year-old female with recurrent metastatic uterine cancer who died suddenly while on a phase 1 trial utilizing sorafenib in combination with bevacizumab. She began her first course of treatment on June 9, 2008, and was to receive sorafenib 400 mg PO twice daily on Days 1-5 each week and bevacizumab 5 mg/kg IV over 30-90 minutes on Days 1 or 2 and 15 or 16. Due to a misunderstanding, the patient received sorafenib 200 mg PO twice daily from June 9, 2008, to June 23, 2008. On June 23, 2008, sorafenib was held for 1 week due to severe mucositis and was restarted on July 3, 2008, at the dose of 100 mg daily. The bevacizumab Cycle 1, Day 15 or 16 dose was held due to hypertension and poor oral intake. She received the last dose of sorafenib on July 17, 2008 (Cycle 2, Day 4), and the last dose of bevacizumab on July 14, 2008 (Cycle 2, Day 1).

The patient was initially diagnosed with uterine cancer in March 2002 and is status post radical hysterectomy followed by cisplatin and ifosfamide from April to August 2002. She was disease free until late 2005 when she was found to have tumor confined to the L3 spine for which she underwent CyberKnife® and radiation. From June 2006 to April 2008, the patient developed multiple disease recurrences in the lung, liver and pelvis for which she underwent chemotherapy, radiofrequency ablation and surgical intervention. In April 2008, new liver lesions were again found by CT scan, and she began the investigational treatment on June 9, 2008. Since reduction of the doses after the first course, the patient had tolerated therapy well. At the routine clinical visit on July 14, 2008, the patient had normal blood pressure (105/96 mmHg), O2 saturation, and CBC. Besides 10-pound weight loss compared to baseline, there was no complaint of bleeding or shortness of breath.

On July 18, 2008 (Cycle 2, Day 5), the patient was admitted to the hospital with a left leg DVT and was treated with Lovenox® and Coumadin®. The investigational treatment was put on hold. On July 21, 2008, she was discharged home with instructions to continue anticoagulation with Coumadin® to be managed by her local physician. On July 23, 2008 (Cycle 2, Day 10), her protime was 22.0 seconds (reference range: 11.9-15.2 seconds), and her INR was 2.50 (reference range: 0.90-1.20). On July 24, 2008, the patient was informed that if she wished to restart sorafenib she would need to discontinue Coumadin® and restart Lovenox®. Bevacizumab was discontinued. On July 25, 2008, after consulting with her local physician, she called the clinic and indicated that she wanted to restart sorafenib. She was given instructions, and on July 26, 2008, she was to stop Coumadin®, begin Lovenox®, and return to the clinic for evaluation on July 28, 2008. On July 28, 2008, the patient did not return to the clinic for her appointment. On July 29, 2008, after being unable to contact the patient at home, the investigational site contacted her local physician and was informed that the patient had died on the previous day. The patient's emergency contact confirmed that the patient had expired on July 28, 2008 (Cycle 2, Day 15), and stated that no autopsy was planned.

The patient's past medical/surgical history is significant for radical hysterectomy, hernia, hepatic resection, cholecystectomy, benign essential tremor since age 5, and seasonal rhinitis. Family history is significant for one brother with prostate cancer and multiple family members who are status post myocardial infarctions. Medications taken at the time of the event included propranolol, losartan, vitamin B6, and ibuprofen.

There have been 19 other cases of sudden death reported to the NCI as serious adverse events through AdEERS under the sorafenib NSC, and 40 other cases of sudden death reported to the NCI as serious

adverse events through AdEERS under the bevacizumab NSC, which are summarized in the following table:

Adverse Event	Grade	Attribution
Sorafenib (NSC 724772)		
Death: Sudden (n = 19)	5	1 Probable, 4 Possible, 13 Unlikely, 1 Unrelated
Bevacizumab (NSC 704865)		
Death: Sudden (n = 40)	5	1 Probable, 25 Possible, 12 Unlikely, 2 Unrelated

A total of 4,326 patients have been enrolled in NCI-sponsored clinical trials under the sorafenib NSC, and a total of 17,055 patients have been enrolled under the bevacizumab NSC.

In this case, it is felt that a possible causal relationship between the event and sorafenib or bevacizumab therapy cannot be excluded.

	Death: Sudden
Sorafenib	Possible
Bevacizumab	Possible
Uterine Cancer	Unlikely
Thrombosis	Possible

Date: 9/10/08

Signature: R. Austin Doyle MD (for Dr Wright)
 John Wright, M.D., Ph.D.
 (IDB Monitor Sorafenib)

Date: 9/8/08

Signature: [Signature]
 Helen Chen, M.D.
 (IDB Monitor for Bevacizumab)

If this assessment is changed, we will notify your office.

cc: Diane M. Plateis, Pharm D.
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