

# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** June 9, 2006

**To:** NCCTG Primary Clinical Research Associates

**From:** Lori Bratvold  
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 Sorafenib (BAY43-9006) 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\_1108237

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 Lori Bratvold at 507/266-3549.

LB/dg  
enclosure



National Institutes of Health  
National Cancer Institute  
Bethesda, Maryland 20892

**DATE:** May 22, 2006

**FROM:** John Wright, M.D., Ph.D., Investigational Drug Branch, CTEP, DCTD, NCI (JW)  
Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI

**SUBJECT:** BAY 43-9006 Tosylate (BAY 54-9085, Sorafenib Tosylate) and  
Bevacizumab (rhuMAb VEGF) IND Safety Report, AE# 1108237

**TO:** Investigators Using BAY 43-9006 Tosylate (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 agent BAY 43-9006 tosylate (NSC 724772) and bevacizumab (NSC 704865).

The following must be completed by all investigators using BAY 43-9006 tosylate under NCI IND 69896 and bevacizumab under NCI BB-INDs 7921, 9877, and 11460:

- 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.

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

CTEP's evaluation of this IND Safety Report in light of previous experience with BAY 43-9006 tosylate and bevacizumab does not require a change in the clinical protocols for this agent at this time.

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

The Adverse Events Assessment that describes the following adverse events, previous experience under this IND, and the total number of patients enrolled in trials under this IND is attached:

A 54-year-old male with malignant fibrous histiocytoma metastatic to the lungs and liver experienced bronchopulmonary hemorrhage and died while on a phase 1 trial utilizing the investigational agents BAY 43-9006 tosylate and bevacizumab.

**ADVERSE EVENTS ASSESSMENT**

IND 69896		ADVERSE EXPERIENCE REPORT NO. 9
NSC 724772	704865	IND Safety Report: Initial
BAY 43-9006 Tosylate (BAY 54-9085, Sorafenib Tosylate)	Bevacizumab (rhuMab VEGF)	Event: Gr. 5: Hemorrhage, pulmonary/upper respiratory: Bronchopulmonary
AE: 1108237		Protocol: 6750

The patient was a 54-year-old male with malignant fibrous histiocytoma metastatic to the lungs and liver who experienced a bronchopulmonary hemorrhage and died while on a phase 1 trial utilizing the investigational agents BAY 43-9006 tosylate and bevacizumab. He began his first course of treatment on January 11, 2006, receiving only bevacizumab 5 mg/kg IV over 30-90 minutes on days 1 and 15 for Cycle 1 and bevacizumab 5 mg/kg IV over 30-90 minutes on days 1 and 15 in combination with BAY 43-9006 tosylate 200 mg PO twice daily for Cycles 2+, every 28 days. He received the last dose of bevacizumab on April 17, 2006 (Cycle 4, Day 15) and the last dose of Bay 43-9006 tosylate on April 30, 2006 (Cycle 4, Day 28).

The patient was initially diagnosed with malignant fibrous histiocytoma in January 2000 and was status post two surgical resections and radiation therapy. His baseline scans showed bulky right hilar lymph nodes that enveloped the main stem bronchus as well as multiple pulmonary nodules; other findings included a large right axillary mass, a left adrenal mass, liver cysts, and low density lesion within the periphery of the spleen. He began the investigational therapy on January 11, 2006 and completed four cycles of therapy. Restaging CT scans on March 6, 2006 (upon completion of cycle 2) showed decreased right hilar mass and increased axillary mass. On May 1, 2006 (upon completion of Cycle 4), the patient returned to the clinic for assessment with ongoing complaints of cough, anorexia, weight loss, hoarse voice and fatigue. A CT scan revealed stable bilateral pulmonary nodules, but the right hilar mass had enlarged, cavitated, and was communicating with the right upper lobe bronchus and the peripheral bronchi. There was no history of hemoptysis and dyspnea. The patient was removed from the study on May 1, 2006, due to concern about the risk of further erosion into the bronchus. On May 8, 2006, the patient's wife reported that the patient coughed up blood and died within minutes at home. No autopsy was performed.

The patient's past medical history is not significant for any other pulmonary problems. Medications taken at the time of the event included morphine, hydrochlorothiazide, Dolusate<sup>®</sup>, Lisinopril<sup>®</sup>, and Maxzide<sup>®</sup>.

There have been five other incidences of Grade 3-5 pulmonary/upper respiratory hemorrhage reported to the NCI as serious adverse events under IND 69896 (sorafenib) and other incidences of bronchopulmonary hemorrhage reported to the NCI as serious adverse events under BB-INDs 7921, 9877, and 11460 (bevacizumab). These and other incidences of hemorrhage are summarized in the tables below.

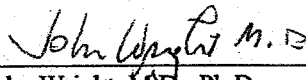
Investigational Agent	Hemorrhage	Grade	Attribution
BAY 43-9006 tosylate (IND 69896)	Pulmonary/Upper Respiratory: Bronchus (n=1)	3	1 Unlikely
	Pulmonary/Upper Respiratory: Lung (n=2)	4	1 Unlikely
		3	1 Possible
	Pulmonary/Upper Respiratory: Respiratory Tract NOS (n=1)	3	1 Possible


Investigational Agent	Hemorrhage	Grade	Attribution
Bevacizumab (NSC 704865)	Pulmonary/Upper Respiratory: bronchopulmonary (n=1)	3	1 Possible
		5	1 Probable, 5 Possible
	Hemoptysis (n=9) (all Grade 4-5 events occurred in patients with non-small cell lung cancer)	4	1 Possible
		3	1 Possible, 1 Unlikely

In this case, it is felt that a possible causal relationship between the investigational agents (BAY 43-9006 tosylate and bevacizumab) and the hemorrhage cannot be excluded. There have been 1,002 patients enrolled in NCI-sponsored clinical trials under IND 69896 and 8,219 patients enrolled in NCI-sponsored clinical trials under BB-INDs 7921, 9877, and 11460.

	<b>Bronchopulmonary hemorrhage</b>
<b>Bay 43-9006 tosylate</b>	Possible
<b>Bevacizumab</b>	Possible
<b>Malignant fibrous histiocyoma</b>	Probable

Date: 5/28/06

Signature:   
John Wright, M.D., Ph.D.  
(IDB Monitor for BAY 43-9006 Tosylate)

  
Helen Chen, M.D.  
(IDB Monitor for Bevacizumab)

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

cc: Brian Schwartz, M.D.  
Karen Wilson, M.D.  
Bayer Pharmaceuticals Corporation

Fabio Benedetti, M.D.  
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