DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

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FROM: John Wright, M.D., Ph.D., Investigational Drug Branch, CTEP, DCTD, NCI
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SUBJECT: BAY 43-9006 Tosylate (BAY 54-9085; Sorafenib Tosylate) and Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# **1475911**

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 69-year-old female with metastatic renal cell carcinoma experienced a **grade 5 intracerebral hemorrhage** while on a phase 2 trial using the investigational agent sorafenib in combination with bevacizumab.

ADVERSE EVENTS ASSESSMENT

IND **69896** **7921** NSC **724772** **704865** **BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate)** **Bevacizumab (rhuMAb VEGF)** AE: **1475911**	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: **# 1** Event: **Gr. 5: Hemorrhage, CNS** Protocol: **E2804**

The patient was a 69-year-old female with renal cell carcinoma metastatic to the periaortic and retroperitoneal lymph nodes who experienced an acute intracerebral hemorrhage and subsequently died while on a phase 2 trial utilizing sorafenib and bevacizumab. She began her first course of treatment on June 18, 2008, and received sorafenib 200 mg PO twice daily on Days 1-5, 8-12, 15-19, and 22-26 and bevacizumab 5 mg/kg IV over 30-90 minutes on Days 1 and 15, every 28 days. She received the last dose of sorafenib on November 10, 2008 (Cycle 6, Day 5), and the last dose of bevacizumab on November 6, 2008 (Cycle 6, Day 1).

The patient was initially diagnosed with clear cell adenocarcinoma in May 2008, and is status post left nephrectomy with periaortic and retroperitoneal lymph node dissection. On June 4, 2008, her baseline blood pressure was 150/82 mmHg. She began the investigational treatment on June 18, 2008, after which she reported mild on and off diarrhea or constipation, but otherwise tolerated the treatment well. Her CT scans from October 6, 2008, showed improving retroperitoneal adenopathy. On November 6, 2008, the patient was status post a surgical repair of a perirectal infection/fissure and reported mild, resolving sinus drainage and mild nosebleeds after blowing her nose; her physical exam revealed a resolving open wound on her right buttock and no other significant findings.

On November 12, 2008 (Cycle 6, Day 7), the patient developed a severe headache, and her systolic blood pressure was over 220 mmHg. She was driven to the hospital by her husband and, while en route, she became nauseated and lost consciousness. Upon arrival at the hospital, she was emergently intubated. A head CT scan revealed 2 large areas of intracerebral hemorrhage: an acute 5 × 4 cm hemorrhage in the left posterior temporoparietooccipital junction, an acute left frontal subdural hematoma 15 mm thick, and a significant midline shift of 13 mm. Upon examination, the patient was comatose, had a temperature of 95.7°F, a blood pressure of 191/66 mmHg, a pulse of 45 bpm, and a respiratory rate of 12 breaths per minute on the ventilator. Her left pupil was 4 mm and nonreactive, her right pupil was 2 mm and nonreactive, her lungs were clear bilaterally, and she had no spontaneous movements of her extremities. The patient's family discussed the case with neurosurgery, and as the patient's prognosis was very poor even with surgical intervention, she was made DNR in the event of a cardiac arrest but kept intubated for the current time. She was treated with mannitol, Dilantin®, and nicardipine. Later that day, as her condition deteriorated, the patient's care was changed to comfort measures only, and she died later that evening.

The patient's past medical/surgical history is significant for cholecystectomy, diabetes, hypertension, dysplipidemia, and gastroesophageal reflux disease. Medications taken at the time of the event included amlodipine, clonidine, lisinopril, glipizide, hydrochlorothiazide, and clindamycin.

CNS hemorrhage is known to occur with bevacizumab. There have been 18 other cases of CNS hemorrhage reported to the NCI as serious adverse events through AdEERS under the sorafenib NSC and/or IND which are summarized in the following table:

Sorafenib (NSC 724772)		
Adverse Event	**Grade**	**Attribution**
CNS hemorrhage (n = 18)	5 4 3 2	2 Possible, 1 Unlikely, 1 Unrelated 6 Possible, 3 Unlikely, 2 Unrelated 1 Possible 2 Possible

A total of 4,660 patients have been enrolled in NCI-sponsored clinical trials under the sorafenib NSC, and a total of 18,565 patients have been enrolled under the bevacizumab NSC.

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

	Hemorrhage, CNS
Sorafenib	Possible
Bevacizumab	Probable
Renal cell carcinoma	Possible
Diabetes	Possible
Hypertension	Definite

Date: 2/15/09 Signature: John Wright

John Wright, M.D., Ph.D.
(IDB Monitor for Sorafenib)

Date: 4/2/09 Signature:

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

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

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