

NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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_1900831

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



DATE: May 16, 2006

FROM: 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) IND Safety Report, AE# 1900831

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 47-year-old female with melanoma metastatic to the neck, lung, adrenal gland, spine, and abdomen experienced grade 3 perforation of the appendix 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. 8
NSC 724772	704865	IND Safety Report: Initial
BAY 43-9006 Tosylate	Bevacizumab	Event: Gr. 3: Perforation, GI: Appendix
(BAY 54-9085, Sorafenib Tosylate)	(rhuMAb VEGF)	
AE: 1900831		Protocol: 6750

The patient is a 47-year-old female with melanoma metastatic to the neck, lung, adrenal gland, spine, and abdomen who experienced perforation of the appendix while on a phase 1 trial utilizing the investigational agents BAY 43-9006 tosylate and bevacizumab. She began her first course of treatment on January 26, 2006, receiving BAY 43-9006 tosylate 200 mg PO twice daily on days 1-21 for Cycle 1 and twice daily on days 1-28 for subsequent cycles, as well as bevacizumab 5 mg/kg IV over 30-90 minutes on days 1 and 15, every 28 days. She received the last dose of BAY 43-9006 tosylate on April 23, 2006 (Cycle 4, Day 7) and the last dose of bevacizumab on April 17, 2006 (Cycle 4, Day 1).

The patient was initially diagnosed with stage III melanoma in October 1995, with metastatic disease to the lymph nodes diagnosed in February 2003. In May 2004, a left adrenal mass was detected on a restaging CT scan, and spinal lesions were diagnosed a year later. She is status post multiple systemic chemotherapy regimens, radiation therapies, and surgical treatments. A baseline CT scan on January 23, 2006 demonstrated a 2.6 cm centrally necrotic left cervical mass anterior to the left jugular vein, marked interval enlargement of a left infrahilar mass with associated bronchial compression, a lytic lesion in the left thoracic pedicle, irregular multilobulated bilateral adrenal masses, an increasing pelvic mass measuring at least 15 cm and extending out of the pelvis with possible areas of necrosis, as well as interval development of a 4.2 cm mass in the appendix with gas bubbles, which may have gotten through the intestinal tract, or may represent necrosis or infection. She tolerated the initial three cycles of therapy well and received her Cycle 4, Day 1 dose of bevacizumab on April 17, 2006; however, BAY 43-9006 tosylate was withheld due to nausea, but resumed on April 20, 2006 (Cycle 4, Day 4). On April 24, 2006 (Cycle 4, Day 8), she presented to the Emergency Room with abdominal pain, nausea, and vomiting. She was admitted to the hospital and diagnosed by CAT scan with appendicitis. Treatment with BAY 43-9006 tosylate was again withheld. On April 25, 2006, the patient underwent surgical removal of her appendix with findings of a large tumor mass involving the distal small bowel and its mesentery, as well as a ruptured appendix with a large retrocecal abscess. Both an infarcted appendix epiploica and appendix were leading to the abscess. The surgical pathology report confirmed the findings of acute inflammatory changes in the soft tissue surrounding the appendix and adjacent to tumor; the tumor involved the soft tissue outside the appendix and extended into the wall of the appendix. The patient was discharged in stable condition on May 4, 2006.

The patient's past medical history is significant for asthma and hypothyroidism. Medications taken at the time of the event included albuterol inhaler, Foradil[®] inhaler, Paxil[®], Synthroid[®], Cozaar[®], and multivitamin supplements.

There have been 2 other incidences of gastrointestinal perforations and 1 other incidence of appendicitis reported to the NCI as serious adverse events under IND 69896 (BAY 43-9006). The incidences and attributions are summarized in the following table:

Agent	Adverse Event	Grade	Attribution
BAY 43-9006 (IND 69896)	Perforation GI: Colon (n=2)	3	1 Possible, 1 Unlikely
	Appendicitis (n=1)	3	1 Unlikely

Gastrointestinal perforation is rare but serious side effect with known association with bevacizumab therapy.

CONFIDENTIAL

1 of 2

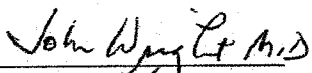
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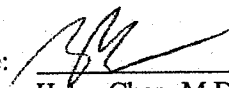
In this case, it is felt that a possible causal relationship between the perforated appendix and both investigational agents cannot be excluded. There have been 974 patients enrolled in NCI-sponsored clinical trials under IND 69896 (for sorafenib) and 8,206 patients enrolled in NCI-sponsored clinical trials using bevacizumab under CTEP INDs 7921, 9877, and 11460.

	Perforation: Appendix
BAY 43-9006	Possible
Bevacizumab	Possible
Melanoma	Possible

Date: 5/29/06

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

Date: 5/25/06

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

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

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