



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** March 2, 2007

**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\_1007443**

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](mailto:wobschall.janis@mayo.edu) or 507/284-4852.

JW/df  
enclosure



DATE: January 26, 2007

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

SUBJECT: BAY 43-9006 Tosylate (BAY 54-9085; Sorafenib Tosylate) IND Safety Report,  
AE #1007443

TO: Investigators Using CTEP-supplied Investigational BAY 43-9006 Tosylate, NSC 724772

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.

The following must be completed by all investigators using BAY 43-9006 tosylate under NCI IND 69896:

- 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 IND 69896, 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.

CTEP's evaluation of this IND Safety Report in light of previous experience with BAY 43-9006 tosylate 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/or NSC, and the total number of patients enrolled in trials under this IND and/or NSC is attached:

A 53-year-old male with bladder cancer metastatic to the retroperitoneal and iliac lymph nodes developed a grade 3 perforation of the jejunum while on a phase 2 trial utilizing the investigational agent BAY 43-9006 tosylate.

**ADVERSE EVENTS ASSESSMENT**

IND 69896 NSC 724772 BAY 43-9006 tosylate (Bay 54-9085; sorafenib tosylate) AE: 1007443	ADVERSE EXPERIENCE REPORT NO. 15 IND Safety Report: Initial Event: Gr. 3: Perforation, GI: Jejunum Protocol: 7062
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The patient is a 53-year-old male with bladder cancer metastatic to the retroperitoneal and iliac lymph nodes who developed a perforation in his jejunum while on a phase 2 trial utilizing the investigational agent BAY 43-9006 tosylate. He began his first course of treatment on September 8, 2006, receiving BAY 43-9006 tosylate 400 mg PO, twice daily, on Days 1-28, every 28 days. He received the last dose of BAY 43-9006 tosylate on November 13, 2006 (Cycle 3, Day 8).

The patient was initially diagnosed with node positive high grade bladder cancer in March 2004 and is status post radical cystectomy, prostatectomy, and creation of an ileoneobladder in June 2004. He began the investigational therapy on September 8, 2006 and completed 2 cycles, without any significant adverse events reported. The patient began his third cycle on November 6, 2006. On November 13, 2006 (Cycle 3, Day 8), he presented to the ER with a 15-hour history of severe abdominal pain and hypotension. His abdominal exam revealed distension, diffuse tenderness, and absence of bowel sounds. The patient reported that he had not had a bowel movement or flatus in the past 24 hours. An emergency CT scan of the abdomen showed pneumatosis intestinalis. He was immediately taken to the operating room where he underwent resection of the small bowel (10 cm of jejunum), primary side-to-side anastomosis, and lysis of adhesions without complications. The pathology report of the small bowel tissue excised was consistent with metastatic anaplastic infiltrative carcinoma. BAY 43-9006 tosylate was discontinued as of November 13, 2006, at which time the patient was removed from protocol treatment. He did well post-operatively and was released from the hospital in stable condition on November 19, 2006. At the time of discharge, the patient was tolerating solid foods, passing gas, and having bowel movements; his pain was controlled; and he was ambulatory.

The patient's past medical/surgical history is significant for elevated liver enzymes secondary to a hepatitis B infection, hypertension, acid reflux, hematuria, and eczema. Medications taken at the time of the event included Zantac®, Colace®, and Senokot®. Of note, the patient was taking Norvasc® (amlodipine) regularly until approximately 1 month prior to the event.

There have been 11 other cases of GI perforation reported to the NCI as serious adverse events through AdEERS under the BAY 43-9006 tosylate NSC, which are summarized in the following table:

Adverse Event	Grade	Attribution
GI Perforation (n=11)	4	2 Possible
	3	8 Possible, 1 Unlikely

A total of 1993 patients have been enrolled in NCI-sponsored clinical trials under NSC 724772.

In this case, it is felt that a possible causal relationship between the event and BAY 43-9006 tosylate administration cannot be excluded.

	GI Perforation: Jejunum
BAY 43-9006 tosylate	Possible
Bladder cancer	Possible
Amlodipine	Possible

Date: 2/18/07

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

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

cc: Jeffrey Humphrey, M.D.  
Karen Wilson  
Bayer Pharmaceuticals Corporation

Todd J. Yancey, M.D.  
Onyx Pharmaceuticals Incorporated