



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** June 08, 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 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\_1989015**

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:** May 27, 2007 *John Wright*  
**FROM:** John Wright, M.D., Ph.D., Investigational Drug Branch, CTEP, DCTD, NCI  
**SUBJECT:** BAY 43-9006 Tosylate (BAY 54-9085; Sorafenib Tosylate) NCI IND Safety Report,  
AE# 1989015  
**TO:** Investigators Using 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.

Based on CTEP's assessment of the current information in light of previous experience with *AZD2171*, there does not appear to be a change in the risk-benefit ratio for *AZD2171* 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 this IND and/or NSC, and the total number of patients enrolled in trials under this IND and/or NSC.

A 38-year-old male with islet cell tumors of the pancreas developed grade 4 abdominal pain and grade 3 perforated duodenum while receiving treatment 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: 1989015	ADVERSE EXPERIENCE REPORT NO. 19 IND Safety Report: Initial Event: Gr. 4: Pain, Abdomen NOS Gr. 3: Perforation, GI: Duodenum  Protocol: 7046
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The patient is a 39-year-old male with islet cell tumor of the pancreas metastatic to the liver who developed abdominal pain and a perforated duodenum while receiving treatment on a phase 2 trial utilizing the investigational agent BAY 43-9006 tosylate. He began his first course of treatment on July 25, 2006, receiving BAY 43-9006 tosylate 400 mg PO twice daily on Days 1-28, every 28 days. On August 8, 2006 (Cycle 1, Day 15), the BAY 43-9006 tosylate dose was reduced to 200 mg twice daily secondary to hoarseness of his voice along with mouth sores. He received his last dose of BAY 43-9006 tosylate on January 19, 2007 (Cycle 7, Day 11).

The patient was initially diagnosed with islet cell tumor of the pancreas in March 2003 and is status post: exploratory laparotomy with pancreatectomy, cholecystectomy, omentectomy, portal vein resection, and splenectomy; radiation therapy (2003); and two chemoembolizations (February and April 2005). The patient started the investigational therapy on July 25, 2006, completing six cycles, which he tolerated reasonably well. He began Cycle 7 on January 9, 2007. On January 19, 2007 (Cycle 7, Day 11) while attending a conference, the patient developed severe left lower quadrant abdominal pain and presented to the local emergency room. He had a CT scan of the abdomen that showed free air anterior to the liver on both the left and right sides of the abdomen, consistent with a bowel perforation. The patient was taken to the operating room where he underwent an emergency exploratory laparotomy and was found to have an anastomotic ulcer perforation. He subsequently underwent a partial antrectomy and resection of gastrojejunostomy, jejunostomy, a revision of gastrojejunostomy, and vagotomy. The pathology report of the anastomotic site tissue was consistent with a perforated duodenal ulcer and a second sample with a nonperforated duodenal ulcer. There was no evidence of metastasis found in the proximal or distal margins. The investigational therapy was placed on hold at that time. After surgery, he was first admitted to the surgical intensive care unit and later transferred to a medical surgical floor. His postoperative recovery was without complications, and he was discharged to home on January 25, 2007 (Cycle 7, Day 17), in satisfactory condition. The patient was seen in the clinic for follow-up on January 30, 2007 at which time he was removed from the protocol therapy secondary to the duodenal perforation.

On the morning of February 1, 2007, the patient experienced sudden severe left lower quadrant abdominal pain significant enough that he was unable to ambulate. He was admitted to the hospital for evaluation. A CT scan of the abdomen showed numerous nodular peripheral enhancing liver metastases and small mesenteric and periaortic lymph nodes, which were minimally increased since his prior scan of January 9, 2007. The bowel was unremarkable except for some minimal colonic diverticulosis, and there was no free fluid in the pelvis. He reported a 2-day history of diarrhea prior to admission, but denied rectal bleeding or melanotic stools. Stool cultures were negative for *Clostridium difficile*. He was treated with morphine and IV fluids, with significant relief. After admission, he was able to tolerate oral intake. He had another onset of acute pain on the night of February 1, 2007, which resolved after oxycodone administration. He had no other episodes of pain or diarrhea and was discharged to home on February 2, 2007.

The patient's past medical/surgical history is significant for diabetes, pancreatitis, seasonal allergies and anterior cruciate ligament repair. Medications taken at the time of the initial event included Pancrease<sup>®</sup>, Aciphex<sup>®</sup>, Zoloft<sup>®</sup>, oxycodone, Carafate<sup>®</sup>, and Humalog<sup>®</sup>, as well as over-the-counter multivitamin, calcium, magnesium, and zinc supplements.

There have been 12 other cases of GI perforation and 73 other cases of abdominal pain in patients treated with BAY 43-9006 tosylate reported to the NCI as serious adverse events through AdEERS under the BAY 43-9006 NSC, which are summarized in the following table:

Adverse Event	Grade	Attribution
GI perforation (n=12)	4 3	2 Possible 9 Possible, 1 Unlikely
Abdomen pain (n=73)	4 3 2	2 Possible, 2 Unlikely 2 Probable, 18 Possible, 21 Unlikely, 11 Unrelated 10 Possible, 4 Unlikely, 3 Unrelated

A total of 2,394 patients have been enrolled in NCI-sponsored clinical trials under NSC 724772.

In this case, a possible relationship between the events and the investigational agent cannot be excluded.

	Abdomen pain	GI perforation: Duodenum
BAY 43-9006 tosylate	Possible	Possible
Islet cell tumors of the pancreas	Possible	Possible
Ulcer	Possible	Probable

Date:

5/27/07

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