



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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_1273968

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 or 507/284-4852.

JW/df
enclosure



DATE: May 25, 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# 1273968
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 64-year-old male with stage 4 metastatic melanoma experienced grade 3 sigmoid colon perforation while receiving treatment on a phase 3 trial utilizing the investigational agent BAY 43-9006 tosylate or placebo in combination with paclitaxel and carboplatin.

ADVERSE EVENTS ASSESSMENT

IND 69896	ADVERSE EXPERIENCE REPORT NO. 18
NSC 724772	IND Safety Report: Initial
BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate)	Event: Gr. 3: Perforation, GI: Colon
AE: 1273968	Protocol: E2603

The patient is a 64-year-old male with stage IV malignant melanoma metastatic to the axilla bilaterally and liver who experienced sigmoid colon perforation while receiving treatment on a phase 3 trial utilizing the investigational agent BAY 43-9006 tosylate (or placebo) in combination with paclitaxel and carboplatin. He began his first course of treatment on January 30, 2007, receiving BAY 43-9006 400 mg PO twice daily or placebo 2 tablets twice daily on Days 2-19, paclitaxel 225 mg/m² IV over 3 hours on Day 1, and carboplatin AUC 6 IV over 30 minutes on Day 1, every 21 days for Cycles 1-4. He received the last dose of BAY 43-9006 tosylate (or placebo) on February 17, 2007 (Cycle 1, Day 19), and his only doses of paclitaxel and carboplatin on January 30, 2007.

The patient was initially diagnosed with malignant melanoma of the shoulder in September 2006 and is status post excision of left shoulder melanoma and left axillary nodal dissection. He began BAY 43-9006 or placebo, paclitaxel and carboplatin therapy on January 30, 2007. On February 19, 2007 (Cycle 1, Day 21), the patient presented to the clinic with a 2-to-3 day history of abdominal pain, constipation, nausea, vomiting, and decreased oral intake. He was admitted to the hospital for dehydration and possible bowel obstruction. Upon physical examination, the patient was found to have a distended abdomen with pain on palpation, and decreased bowel sounds. His admission chest X-ray revealed a bowel perforation. The investigational therapy was placed on hold. He was treated with IV fluids and taken to surgery where he underwent an emergency exploratory laparotomy and was found to have a perforated sigmoid diverticulitis with pericolonic abscess and multiple 1-2 mm melanoma nodules on the liver requiring a segmental sigmoid colon resection, end colostomy, Hartman's pouch, and a wedge biopsy of the left lobe of the liver. Pathology findings from the surgical biopsies included metastatic melanoma in the left lobe liver wedge section and diverticulosis with focal areas of acute serositis and adhesion formation in the segment of sigmoid colon.

Following surgery he was taken to the intensive care unit where he developed a fever, leukocytosis, respiratory failure, and atrial fibrillation with rapid ventricular response. His chest X-ray showed a left lower lobe infiltrate, and sputum cultures were positive for gram negative rods. Pelvic abscess cultures were positive for *Bacteroides fragilis* and *Escherichia coli*, and blood cultures were negative. He was initially treated with steroids, which were tapered and discontinued. He was also treated with IV antibiotics and Flagyl[®]. On February 22, 2007, an echo cardiogram revealed a left ventricular ejection fraction of 65% with no focal wall motion abnormalities, the right ventricle with normal size and function, the left and right atrial chamber sizes in the upper limits of normal, and the mitral and aortic valves with some sclerosis but normal motion. There was no pericardial effusion or evidence of metastasis to the heart chambers seen. His troponin level on February 23, 2007 was elevated to 2.53 ng/mL (reference range: 0.0-0.4 ng/mL), suggestive of possible myocardial damage. The atrial fibrillation was treated with Rythmol[®]. His condition improved; he was able to be weaned from ventilator support; and his atrial fibrillation reverted to a normal sinus rhythm. On March 3, 2007, the patient was discharged home with abdominal binders. He was removed from the protocol on March 6, 2007 secondary to bowel perforation.

The patient's past medical history is significant for hypertension, hyperlipidemia, chronic obstructive pulmonary disease, osteoarthritis, sleep disorder, tobacco use (>40-pack-years, still smoking approximately two packs of cigarettes per day, and alcohol use (three to four drinks per day). Medications taken at the time of the event included atenolol, Lipitor[®], aspirin, Xanax[®], Vicodin[®], Lunesta[®], ibuprofen, and glucosamine.

There have been 13 other cases of GI perforation, including AE #1989015, reported to the NCI as serious adverse events through AdEERS under the BAY 43-9006 tosylate NSC, as shown in the table below:

Adverse Event	Grade	Attribution
GI Perforation: (n=13)	4 3	2 Possible 10 Possible, 1 Unlikely

A total of 2,394 patients have been enrolled in NCI-sponsored clinical trials under the BAY 43-9006 tosylate NSC.

In this case, it is felt that the colon perforation is probably related to BAY 43-9006 tosylate or placebo administration.

	Colon perforation
BAY 43-9006 tosylate or placebo	Probable
Carboplatin	Possible
Paclitaxel	Possible
Melanoma	Possible
Other – diverticulitis	Possible

Date: 5/25/07

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, Inc.