



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: July 11, 2008

To: NCCTG Primary Clinical Research Associates

From: Alicia Elsing

Re: N0626, Phase II Randomized Study Pemetrexed With Sorafenib versus Pemetrexed Alone as Second-line Therapy in Patients With Advanced Non-Small Cell Lung Cancer

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_1633079_F1

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 Alicia Elsing at elsing.alicia@mayo.edu or call 507/538-3893.

AE/df
enclosure



DATE: July 15, 2008

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# 1633079

TO: Investigators Using BAY 43-9006 Tosylate (NSC 724772)

JW
7/23/08

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 BAY 43-9006 tosylate, there does not appear to be a change in the risk-benefit ratio for BAY 43-9006 tosylate 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.

An 83-year-old male with melanoma metastatic to the lungs experienced grade 4 cardiac ischemia/infarction while 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. 31 |
| NSC 724772 | IND Safety Report: #1 |
| BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate) | Event: Gr. 4: Cardiac ischemia/infarction |
| AE: 1633079 | Protocol: E2603 |

The patient was an 83-year-old male with melanoma metastatic to the lung who experienced a myocardial infarction while 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 October 5, 2007, receiving BAY 43-9006 tosylate 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 December 26, 2007 (Cycle 4, Day 20), and the last doses of paclitaxel and carboplatin (stopped early due to toxicity) on October 26, 2007 (Cycle 2, Day 1).

The patient was initially diagnosed with malignant melanoma in March 2006 and is status post surgical excision of a right neck lesion. He began the investigational therapy on October 5, 2007, initially with a good response although he did not tolerate the treatment well.

On December 27, 2007 (Cycle 4, Day 21), the patient was transported to the emergency room with a 3-day history of increasing shortness of breath, intermittent confusion, and a dry cough. En route to the hospital his heart rate was 120 bpm and regular, his blood pressure was 182/87 mmHg, and he had decreased breath sounds bilaterally. While in the emergency room, his troponin level indicated a mild myocardial infarction, and his chest X-ray showed bilateral patchy infiltrates and cardiomegaly. He also had increased brain natriuretic peptide (BNP), creatinine, and BUN levels. Significant lab values are listed in the table below. His oxygen saturation was 88% on room air, and he was tachycardic. His ECG showed atrial fibrillation with a rapid ventricular response. A CT scan of the brain showed the possibility of an old CVA versus brain metastasis with calcification. He was admitted to the telemetry unit for a myocardial infarction, congestive heart failure, bilateral pneumonia with respiratory failure, and renal insufficiency. He was treated with slowly infused IV fluids, Lasix[®], Lovenox[®], Plavix[®], aspirin, Zosyn[®], Levaquin[®], and oxygen via a non-rebreather mask. It was felt that with evidence of disease progression and his poor performance status, the patient would not tolerate invasive procedures such as a thoracentesis or cardiac catheterization and would benefit most from palliative measures. He was removed from the protocol that day.

On December 28, 2007, an echocardiogram was significant for a left ventricular ejection fraction of 55%, mild concentric left ventricular hypertrophy, diastolic dysfunction, a mildly dilated right atrium, calcified restricted aortic valve leaflets, mild to moderate aortic stenosis, moderate to severe mitral valve regurgitation, mild tricuspid regurgitation, and a left pleural effusion. His respiratory status improved some and he was changed to oxygen via nasal cannula. He was discharged from the hospital on January 1, 2008 and transferred to hospice care where he expired on January 6, 2008.

The patient's past medical/surgical history is significant for mild hypertension, benign prostatic hypertrophy, and an appendectomy. Medications taken at the time of the event included his investigational therapy only.

Pertinent laboratory values are as follows:

| | 10/2007 Baseline | 12/27/08 C4, D1 | 12/28/08 C4, D22 | 12/31/08 |
|--|---------------------|--------------------|---------------------|-----------------|
| White blood cell count, K/mcL (reference range: 4.3-11.1 K/mcL) | 8.9 | 19.7 | 14.1 | 9.7 |
| Hemoglobin, g/dL (reference range: 12.9-16.9 g/dL) | 10.9 | 10.1 | 9.0 | 8.8 |
| Platelet Count, K/mcL (reference range: 140-400 K/mcL) | 298 | 148 | 102 | 107 |
| Creatinine, mg/dL (reference range: 0.8-1.5 mg/dL) | 1.1 | 1.6 | 1.6 | 1.7 12/29/08 |
| Blood urea nitrogen, mg/dL (reference range: 9-20 mg/dL) | 16 | 37 | 43 | 45 12/29/08 |
| Troponin-1, ng/mL (reference range: 0-0.19 ng/mL) | <0.04 | 4.9 | * | * |
| BNP, pg/mL (reference range: 0-100 pg/mL) | * | 2470 | * | * |

There have been 16 other cases of cardiac ischemia/infarction 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 |
|------------------------------------|-------------|---|
| Cardiac ischemia/infarction (n=16) | 5 4 3 | 1 Possible 7 Possible, 1 Unlikely 4 Possible, 2 Unlikely, 1 Unrelated |

A total of 4,121 patients have been enrolled in NCI-sponsored clinical trials under the BAY 43-9006 tosylate NSC.

In this case, it is felt that a possible causal relationship between the event and BAY 43-9006 tosylate or placebo exists.

| | Cardiac ischemia/infarction |
|--|--------------------------------|
| BAY 43-9006 tosylate or placebo | Possible |
| Carboplatin | Possible |
| Paclitaxel | Possible |
| Melanoma | Unlikely |
| Pleural effusion on prior CT-possible CHF | Probable |

Date: 7/23/08

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, MD
Diane M. Plateis, PharmD
Bayer Pharmaceuticals Corporation

Todd J. Yancey, MD
Onyx Pharmaceuticals, Inc.