



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: November 30, 2007

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_1896903

AE_1129949

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. (Do not use the following sentence if this involves a CTEP warning letter.) 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: November 6, 2007

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

SUBJECT: BAY 43-9006 Tosylate (BAY 54-9085; Sorafenib Tosylate) and Bevacizumab (rhuMab VEGF) NCI IND Safety Report, AE# 1896903 and AE# 1129949

TO: Investigators Using CTEP-supplied Investigational 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 agents BAY 43-9006 tosylate and bevacizumab.

The following must be completed by all investigators using BAY 43-9006 tosylate under NCI IND 69896 and bevacizumab under NCI INDs 7921 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.

If your study is not covered under INDs 69896, 7921, and 11460 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 and bevacizumab, there does not appear to be a change in the risk-benefit ratio for BAY 43-9006 tosylate and bevacizumab 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 Assessments describe the adverse event(s) (synopsis provided below), relevant previous experience under these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 57-year-old male with renal cell carcinoma metastatic to the lungs developed cardiac ischemia and subsequently died while on a phase 1/2 trial utilizing the investigational agents BAY 43-9006 tosylate in combination with bevacizumab.

A 71-year-old male with renal cell carcinoma metastatic to the lungs, retroperitoneum, and sinuses developed an acute anterolateral myocardial infarction while on a phase 1/2 trial utilizing the investigation agents BAY 43-9006 tosylate in combination with bevacizumab.

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Page 1 of 1

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ADVERSE EVENTS ASSESSMENT

IND 69896 NSC 724772 BAY 43-9006 tosylate (BAY 54-9085, sorafenib tosylate) AE: 1896903 and 1129949	7921 704865 Bevacizumab (rhuMab VEGF)	ADVERSE EXPERIENCE REPORT NO. 49 IND Safety Report: Initial Event: Gr. 5: Cardiac ischemia/infarction Gr. 4: Cardiac ischemia/infarction Protocol: 6555
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Two cases of cardiac ischemia have been reported to the NCI as serious adverse events under IND 69896 and IND 7921 on protocol 6555 a "Phase 1/2 Trial of BAY 43-9006 in Combination with Bevacizumab in Patients with Advanced Renal Cancer." Both patients received BAY 43-9006 200 mg PO BID on days 1-28 and bevacizumab 5 mg/kg IV over 30-90 minutes every 2 weeks (one cycle=28 days). Their cases are summarized below.

AE #1896903: The first patient was a 57-year-old male with renal cell carcinoma metastatic to the lungs and lymph node who experienced cardiac ischemia and subsequently expired while on protocol 6555. He began his first course of treatment on June 9, 2005. He received his last dose of BAY 43-9006 tosylate on August 5, 2007 (Cycle 28, Day 4) and the last dose of bevacizumab on August 2, 2007 (Cycle 28, Day 1).

The patient was initially diagnosed with renal cell carcinoma of the left kidney in 2000 and was status post multiple surgeries and one month of therapy with IL-2 and interferon in 2004. He began investigational therapy on June 9, 2005, tolerating treatment well with a partial response. On July 1, 2007, he had a CT scan of the chest, abdomen, and pelvis which showed no evidence of metastasis and was otherwise stable compared to a previous study from April 2007. He began Cycle 28 on August 2, 2007.

On August 5, 2007 (Cycle 28, Day 4) prior to 1:00 am, the patient presented to the local emergency room with complaints of back pain. He reported that he exercised at the gym and sustained a lot of pain in the thoracic area. He did not have a history of heart disease or hypertension. His vital signs on admission included a pulse of 84, blood pressure of 160/108 mmHg, temperature of 98°F, and oxygen saturation of 92% on room air. His EKG was significant for sinus tachycardia. His lungs were clear upon auscultation and his chest X-ray showed no active disease. Abnormal laboratory findings included a creatine kinase of 2928 U/L (reference range: 20-232 U/L), CK-MB of 13.4 ng/mL (reference range: 0.0-5.0 ng/mL), troponin-I level of 0.14 ng/mL (reference range: 0.01-0.06 ng/mL), and a potassium level of 3.4 mmol/L (reference range: 3.5-5.0 mmol/L). Although his pain resolved while he was in the emergency room, he was admitted for cardiac monitoring and observation. Upon admission, the patient was comfortable, did not require injectable pain medication, and slept well. Repeat laboratory tests done at 5:45 am were remarkable for increases in his CK-MB level to 14.3 ng/mL and his troponin-I level to 3.4 ng/mL. Later that morning, after breakfast, while talking to the nurse, he suddenly developed pain in his back that radiated to the front and went into cardiac arrest. Cardio-pulmonary resuscitation was immediately initiated at 9:45 am and after one hour, despite intubation with adequate ventilation and femoral pulses noted with compressions, the patient expired at 10:48 am. The autopsy report confirmed that the patient died of myocardial infarction.

The patient had no other significant past medical or surgical history. Medications taken at the time of the event included Zometa®, Aranesp®, Xanax®, Oxycontin®, and Imodium®.

In this case, a possible causal relationship between the cardiac ischemia and the investigational therapy with BAY 43-9006 tosylate and bevacizumab could not be excluded.

	Cardiac ischemia
BAY 43-9006 tosylate	Possible
Bevacizumab	Possible
Renal cell carcinoma	Unrelated

AE #1129949: The second patient is 71-year-old male with stage IV clear cell renal cell carcinoma metastatic to the lungs, retroperitoneum, and sinuses who experienced grade 4 cardiac ischemia while on protocol 6555. He began his first course of treatment on October 19, 2006, and received his last dose of BAY 43-9006 tosylate on July 25, 2007 (Cycle 10, Day 28), and his last dose of bevacizumab on May 17, 2007 (Cycle 8, Day 14).

The patient was initially diagnosed with renal cell carcinoma in March 1999 and is status post left nephrectomy, partial right nephrectomy, excision of a retroperitoneal metastasis involving the psoas muscle, multiple resections of sinus metastases, and biological therapy with interferon ending on May 16, 2006. He began his first course of BAY 43-9006 tosylate and bevacizumab on October 19, 2006. Bevacizumab was discontinued secondary to proteinuria and hypertension on May 17, 2007 (Cycle 8, Day 14), and Cycle 10 of BAY 43-9006 tosylate was completed on July 25, 2007. The patient was removed from the protocol on July 26, 2007, due to progression of disease.

On August 5, 2007, at 5:00 am, the patient awoke with mid sternal chest pain, took aspirin and went to the emergency room where an ECG showed a sinus rhythm with acute findings of anterolateral myocardial infarction. He reported having similar but milder symptoms of non radiating chest pain and nausea on the previous day. His oxygen saturation was 99% on room air, his blood pressure was 183/110 mmHg, and his pulse was 76 bpm. His troponin I level was 161.58 ng/mL (reference range: 0.0-0.08 ng/mL). He received oxygen, nitroglycerin, TNKase[®], Plavix[®], heparin, morphine, Lopressor[®], and aspirin and was transferred directly to the catheterization laboratory at another facility where he underwent an emergency left heart catheterization with COOL-MI catheter insertion from right common femoral vein into the inferior vena cava as part of a COOL-MI study protocol. He was found to have a mid left anterior descending artery occlusion with 95% stenosis. Intervention with PTCA stent placement resulted in improvement of stenosis to 0%. He tolerated the procedure well and was discharged to home on August 7, 2007.

The patient's past medical history included hypertension, benign prostatic hypertrophy, smoking (45-year history of less than 1 pack/day, quit in 2002), and wrist surgery. Medications taken at the time of the event included Nexium[®], Vasotec[®], Lomotil[®], Flonase[®], Phenergan[®], Imodium[®], nitroglycerin, Valium[®], Viagra[®], atenolol, Hyzaar[®], aspirin, Cozaar[®]. Of note, the patient had an episode of palpitations with supraventricular tachycardia leading to an emergency room visit in August 2006. The patient's ECG and Stestamibi stress test performed on November 11, 2006, showed a normal sinus rhythm, no myocardial ischemia, a normal hemodynamic response to adenosine plus exercise stress, and poor exercise capacity. The adenosine cardiac nuclear perfusion scan showed normal myocardial perfusion imaging, no ischemia or infarction, a calculated left ventricular ejection fraction of 57%, and no regional wall motion abnormalities.

In this case, a possible causal relationship between the cardiac ischemia and the investigational therapy with BAY 43-9006 tosylate and bevacizumab could not be excluded.

	Cardiac ischemia
BAY 43-9006 tosylate	Possible
Bevacizumab	Possible
Renal cell carcinoma	Unlikely
Supraventricular tachycardia	Unlikely
Structural cardiovascular disease (95% LAD occlusion)	Probable

There have been 13 other cases of cardiac ischemia reported to the NCI as serious adverse events through AdEERS under the BAY 43-9006 tosylate IND and/or NSC and 69 other cases of cardiac ischemia reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC, which are summarized in the following table:

Adverse Event	Grade	Attribution
BAY 43-9006 tosylate (NSC 724772)		
Cardiac ischemia (n=13)	4	6 Possible, 1 Unlikely
	3	3 Possible, 2 Unlikely, 1 Unrelated
Bevacizumab (NSC 704865)		
Cardiac ischemia (n=69)	5	5 Possible, 1 Unrelated
	4	4 Probable, 35 Possible, 4 Unlikely
	3	2 Probable, 9 Possible, 5 Unlikely, 2 Unrelated
	2	2 Possible

A total of 3206 patients have been enrolled in NCI-sponsored clinical trials under the BAY 43-9006 NSC, and a total of 13,100 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab NSC.

The NCI is currently sponsoring 2 trials evaluating the combination of BAY 43-9006 tosylate and bevacizumab. A total of 95 patients have been enrolled in these combination trials and no additional cases of cardiac ischemia have been reported.

Date: 11/7/07

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

Date: 11/2/07

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

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

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