



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: June 27, 2008

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_1304683_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 Janis Wobschall at wobschall.janis@mayo.edu or 507/284-4852.

JW/df
enclosure



DATE: May 15, 2008

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

SUBJECT: BAY 43-9006 Tosylate (BAY 54-9085; Sorafenib Tosylate) and 17-Allylaminogeldanamycin (17-AAG) NCI IND Safety Report, AE# **1304683**

TO: Investigators Using Sorafenib (NSC 724772) and 17-AAG (NSC 330507)

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 sorafenib and 17-AAG.

The following must be completed by all investigators using sorafenib under NCI IND 69896 and 17-AAG under NCI IND 57966:

- 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 and 57966, 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 sorafenib and 17-AAG, there does not appear to be a change in the risk-benefit ratio for sorafenib and 17-AAG 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 these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 58-year-old male with renal papillary carcinoma metastatic to the omentum died suddenly while on a phase 1 trial utilizing the investigational agents sorafenib and 17-AAG.

ADVERSE EVENTS ASSESSMENT

IND	69896	57966	ADVERSE EXPERIENCE REPORT NO. 55
NSC	724772	330507	IND Safety Report: #1
BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate)		17-allylaminogeldanamycin (17-AAG)	Event: Gr. 5: Sudden death
AE:	1304683		Protocol: 6972

The patient was a 58-year-old male with renal papillary carcinoma metastatic to the omentum who died suddenly while on a phase 1 trial utilizing the investigational agents BAY 43-9006 tosylate (sorafenib) and 17-AAG. He began his first course of treatment on March 11, 2008 (Day -14), and was to receive sorafenib 400 mg PO twice daily for 14 days, continuing on Days 1-28, and 17-AAG 450 mg/m² IV over 3 hours on Days 1, 8, and 15. He received his last dose of sorafenib on March 26, 2008 (Cycle 1, Day 2) and his first and only dose of 17-AAG on March 25, 2008 (Cycle 1, Day 1).

The patient was initially diagnosed with renal papillary carcinoma in July 2006 and is status post left radical nephrectomy with removal of adjacent lymph nodes on August 25, 2006. He received single agent chemotherapy with XL880 from January 2006 to February 2008. The patient started the investigational therapy on March 11, 2008, receiving sorafenib 400 mg twice daily for 14 days as scheduled. On March 25, 2008, he presented to the clinic to begin Cycle 1, Day 1, therapy with 17-AAG (and continue sorafenib). He reported a mild cough and continued mild nausea, which was present at baseline. He was afebrile, his vital signs were stable, and there were no significant findings upon physical examination.

On March 27, 2008 (Cycle 1, Day 3), the patient experienced severe dyspnea at home and was transported to the emergency room by ambulance. While en route to the hospital, the patient arrested. He was intubated, and CPR was initiated. Asystole was noted on the monitor. CPR continued for 30 minutes without success. After arrival in the emergency room, the patient was pronounced dead. No autopsy was performed per the family's wishes.

The patient's past medical/surgical history is significant for hypertension, 20-pack-year tobacco use (quit 18 years ago), occasional alcohol use, and previous marijuana use. The patient's family history is significant for a mother who died of breast cancer at age 59 years and a father who died of a myocardial infarction at age 62 years. Medications taken at the time of the event included Aleve[®], Compazine[®], Lomotil[®], aspirin, vitamins, Norco[®], and Norvasc[®].

There have been 16 other occurrences of sudden death reported to the NCI as serious adverse events through AdEERS under the sorafenib NSC, and 3 other occurrences of sudden death reported to the NCI as serious adverse events through AdEERS under the 17-AAG NSC, which are summarized in the following table:

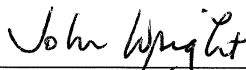
Adverse Event	Attribution
Sorafenib	
Sudden death (n=16)	4 Possible, 11 Unlikely, 1 Unrelated
17-AAG	
Sudden death (n=3)	2 Possible, 1 Unlikely

A total of 4087 patients have been enrolled in NCI-sponsored clinical trials under the sorafenib NSC and a total of 645 patients have been enrolled under the 17-AAG NSC.

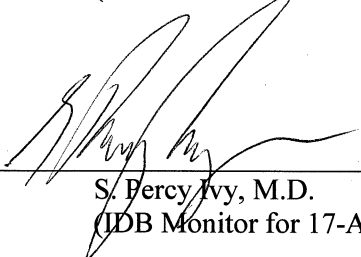
In this case, it is felt that a possible causal relationship between the event and the sorafenib/17-AAG therapy cannot be excluded.

	Sudden death
Sorafenib	Possible
17-AAG	Possible
Renal papillary carcinoma	Possible

Date: 6/12/08

Signature: 
John J. Wright, M.D., Ph.D.
(IDB Monitor Sorafenib)

Date: 05.15.08

Signature: 
S. Percy Ivy, M.D.
(IDB Monitor for 17-AAG)

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

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