



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: October 3, 2008

To: NCCTG Primary Clinical Research Associates

From: Janis Wobschall

Re: N0776, Phase II Trial of Avastin® in Combination with Sorafenib in Recurrent Glioblastoma Multiforme

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with bevacizumab 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_1285866

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/kjm
enclosure



DATE: September 3, 2008
FROM: Igor Espinoza-Delgado, M.D., Senior Investigator, Investigational Drug Branch, CTEP, DCTD, NCI
Helen Chen, M.D., Senior Investigator, Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: Vorinostat NCI IND and Bevacizumab NCI IND Safety Report: **Initial Written Report, AE# 1285866**
TO: Investigators Using CTEP-supplied Investigational Vorinostat (NSC 701852) 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 agent Vorinostat and Bevacizumab.

The following must be completed by all investigators using Vorinostat and Bevacizumab under NCI IND 71976 and 7921 respectively:

- 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 71976 and IND 7921, 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 Vorinostat and Bevacizumab, there does not appear to be a change in the risk-benefit ratio for Vorinostat 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 Initial Written Report, which has been submitted to the FDA, 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 58-year-old female with invasive breast carcinoma experienced sudden death while on a phase 1/2 study utilizing the investigational agents Vorinostat and Bevacizumab.

IF UPON FURTHER INVESTIGATION THIS EVENT IS CONSIDERED POSSIBLY RELATED TO THE INVESTIGATIONAL AGENT/THERAPY, WE WILL SUBMIT A FOLLOW-UP WRITTEN REPORT WITH ASSESSMENT AS SOON AS THE RELEVANT INFORMATION IS AVAILABLE IN ACCORDANCE WITH 21CFR312.32(d)(2).

Attachment: Initial Written Report

IND SAFETY REPORT: INITIAL WRITTEN REPORT

No. 30

TO: *Division of Drug Oncology Products, Center for Drug Evaluation and Research, FDA*
Division of Biologic Oncology Products, Center for Drug Evaluation and Research, FDA

FAX: 301-796-9845

FAX: 301-796-9849

1. IND NUMBER 71976 7921	2. AGENT NAME Vorinostat (suberoylanilide hydroxamic acid; SAHA) Bevacizumab (rhuMAb VEGF)	3. DATE September 3, 2008
4. SPONSOR Division of Cancer Treatment and Diagnosis, National Cancer Institute		
5. REPORTER'S NAME, TITLE, AND INSTITUTION Igor Espinoza-Delgado, MD-Senior Investigator for Biologics Evaluation, Investigational Drug Branch, CTEP, DCTD, NCI Helen Chen, MD-Senior Investigator for Biologics Evaluation, Investigational Drug Branch, CTEP, DCTD, NCI		6. PHONE NUMBER 301-496-1196
		7. FAX NUMBER 301-402-0428
8. PROTOCOL NUMBER (AE #) 7703 (AE # 1285866)		
9. PATIENT IDENTIFICATION MMCOL-041	10. AGE 58	11. SEX Female
12. DESCRIPTION OF ADVERSE EVENT The patient was 58 year-old female with invasive breast carcinoma who experienced a sudden death while on a phase 1/2 study using the investigational agent vorinostat in combination with bevacizumab and paclitaxel. She began her first course of treatment on June 17, 2008, and received the last dose of bevacizumab, and paclitaxel on July 30, 2008 (Cycle 2, Day 16), and the last administered dose of vorinostat was on July 31, 2008 (Cycle 2, Day 17). On August 13, 2008 it was reported that the patient did not show up for her Cycle 3, Day 2 appointment. It was reported that the patient expired on August 15, 2008 (Cycle 3, Day 4) and the cause was sudden death. Additional information has been requested from the site.		
13. DOSE, ROUTE, AND SCHEDULE (Cycle = 28 days) Vorinostat 300 mg PO BID on Days 1-3, 8-10 and 15-17, and Bevacizumab 10 mg/kg IV over 30 to 90 minutes on Days 2 and 16.		
14. DATES OF TREATMENT The patient began her first course of treatment on June 17, 2008, and received the last dose of vorinostat on July 31, 2008 (Cycle 2, Day 17) and bevacizumab on July 30, 2008 (Cycle 2, Day 16).		
15. ACCRUAL AND IND EXPERIENCE Number of patients enrolled in NCI-sponsored clinical trials using vorinostat = 1,202; bevacizumab = 17,055. There have been 5 other cases of sudden death and 6 other cases of death nos reported to the NCI through AdEERS as serious adverse events for vorinostat; there have been 40 other cases of sudden death and 52 other cases of death nos reported to the NCI through AdEERS as serious adverse events for bevacizumab.		
16. COMMENTS Also administered on this protocol: Paclitaxel 90 mg/m ² IV over 60 minutes on Days 2, 9 and 16. It is unknown if the patient took the last scheduled dose of vorinostat.		
AT THIS TIME, NO OTHER INFORMATION IS AVAILABLE. IF UPON FURTHER INVESTIGATION RELEVANT INFORMATION BECOMES AVAILABLE, THEN A FOLLOW-UP REPORT WILL BE SUBMITTED IN ACCORDANCE WITH 21 CFR312.32(d)(2).		
DISCLAIMER per 21 CFR 312.32(e): THIS SAFETY REPORT DOES NOT NECESSARILY REFLECT A CONCLUSION OR ADMISSION BY THE CTEP IDB SENIOR INVESTIGATOR/SPONSOR THAT THE INVESTIGATIONAL AGENT/THERAPY CAUSED OR CONTRIBUTED TO THE ADVERSE EXPERIENCE BEING REPORTED.		