



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: September 5, 2008

To: NCCTG Primary Clinical Research Associates

From: Sara Braun

Re: N0775, A Randomized Phase II Trial of Temozolomide (TMZ) and Avastin® or ABI-007/Carboplatin (CBDCA) and Avastin® in Patients with Unresectable Stage IV Malignant Melanoma

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_1466045

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 Sara Braun at braun.sara@mayo.edu or 507-538-8226.

SB/kjm
enclosure



DATE: August 25, 2008

FROM: Helen Chen, M.D., Senior Investigator for Biologics Evaluation, Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: Bevacizumab NCI IND Safety Report: **Initial Written Report**, AE# 1466045

TO: Investigators Using CTEP-supplied Investigational 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 bevacizumab.

The following must be completed by all investigators using bevacizumab under NCI IND 7921:

- 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 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 bevacizumab, there does not appear to be a change in the risk-benefit ratio for 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 63-year-old male with adenocarcinoma of the colon experienced a grade 2 non-infectious external otitis while participating in a phase 3 trial of 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

CONFIDENTIAL
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IND SAFETY REPORT: INITIAL WRITTEN REPORT

No. 62

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

FAX: 301-796-9849

1. IND NUMBER
79212. AGENT NAME
Bevacizumab (rhuMAb VEGF)3. DATE
August 25, 20084. SPONSOR
Division of Cancer Treatment and Diagnosis, National Cancer Institute5. REPORTER'S NAME, TITLE, AND INSTITUTION
Helen Chen, MD-Senior Investigator for Biologics Evaluation, Investigational
Drug Branch, CTEP, DCTD, NCI6. PHONE NUMBER
301-496-11967. FAX NUMBER
301-402-04288. PROTOCOL NUMBER (AE #)
NSABP-C-08 (AE # 1466045)9. PATIENT IDENTIFICATION
28105493610. AGE
6311. SEX
Male

12. DESCRIPTION OF ADVERSE EVENT
The patient is a 63-year-old male with adenocarcinoma of the colon who experienced a grade 2 non-infectious external otitis with tympanic perforation while on a phase 3 study using the investigational agent bevacizumab in combination with 5-fluorouracil, leucovorin, and oxaliplatin. He began his first course of treatment on September 22, 2005, and received the last dose of bevacizumab on August 31, 2006 (Cycle 26, Day 1). On September 5, 2006 (Cycle 26, Day 6), the patient was seen by an ENT specialist due to left ear pain. External otitis was diagnosed that was originally thought to be fungal in nature but all cultures came back negative. Upon examination he was found to have two tympanic membrane perforations and an area of exposed bone in the external auditory canal with inflammatory changes to the surrounding soft tissue. There was evidence of black hyphae material in the canal which was thought to be mycotic debris. He was treated with topical antibiotic drops and oral anti-fungal medication. The patient underwent successful tympanoplasty with fascia graft on November 27, 2006. Additional information has been requested.

13. DOSE, ROUTE, AND SCHEDULE
Bevacizumab 5 mg/kg every 2 weeks x 1 year (Cycle = 14 days)

14. DATES OF TREATMENT
The patient began his first course of treatment on September 22, 2005, and received the last dose of bevacizumab on August 31, 2006 (Cycle 26, Day 1).

15. ACCRUAL AND IND EXPERIENCE
Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 17,047.
There have been no other cases of non-infectious external otitis reported to the NCI through AdEERS as serious adverse events for bevacizumab.

16. COMMENTS
Also administered on this protocol: oxaliplatin 85 mg/m² IV Day 1, leucovorin 400 mg/m² Day 1, 5-fluorouracil 400 mg/m² IV bolus Day 1, and 5-fluorouracil 2400 mg/m² CIV over 46 hours on Days 1 and 2, every 14 Days X 12 cycles.

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 CFR 312.32(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.

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