



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** October 3, 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\_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 Sara Braun at [braun.sara@mayo.edu](mailto:braun.sara@mayo.edu) or 507-538-8226.

SB/kjm  
enclosure



**DATE:** September 9, 2008  
**FROM:** Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
**SUBJECT:** Bevacizumab (rhuMAb VEGF) IND Safety Report, AE# 1466045  
**TO:** Investigators Using Bevacizumab (rhuMAb VEGF), 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 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 IND 7921 or 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.

CTEP's evaluation of this IND Safety Report in light of previous experience with bevacizumab does not require a change in the clinical protocols for this agent at this time. The risk benefit ratio has not been altered based on CTEP's assessment.

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 NSC, and the total number of patients enrolled in trials under these INDs and/or NSC.

A 63-year-old male with adenocarcinoma of the colon experienced a **grade 2 non-infectious external otitis with tympanic membrane perforation** while on a phase 2 trial utilizing the investigational agent bevacizumab.

## ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 <b>Bevacizumab (rhuMab VEGF)</b>  AE: 1466045	ADVERSE EXPERIENCE REPORT NO. 32 IND Safety Report: #1 Event: Gr. 2: <b>Otitis, external ear (non-infectious) with tympanic membrane perforation</b>  Protocol: NSABP-C-08
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The patient is a 64-year-old male with advanced adenocarcinoma of the colon, who experienced non-infectious external otitis with tympanic membrane perforation while on a phase 3 trial using the investigational agent bevacizumab in combination with 5-fluorouracil (5-FU), leucovorin, and oxaliplatin (mFOLFOX6). The patient began his first course of treatment on September 22, 2005, receiving bevacizumab 5 mg/kg IV every 2 weeks X 1 year, after which he was to receive oxaliplatin 85 mg/m<sup>2</sup> IV on Day 1, leucovorin 400 mg/m<sup>2</sup> IV on Day 1, 5-FU 400 mg/m<sup>2</sup> IV bolus on Day 1, and 5-FU 400 mg/m<sup>2</sup> CIV over 46 hours on Days 1 and 2, every 14 days for 12 cycles. The patient received his last dose of bevacizumab on August 31, 2006 (Cycle 26, Day 1).

The patient was diagnosed with adenocarcinoma of the colon in August 2005 and is status post surgical resection with partial colectomy. He began the investigational therapy on September 22, 2005.

On September 5, 2006, the patient presented to the clinic with a 3-week history of left ear otalgia with discharge and hearing loss. The ear was lavaged of debris and topical antibiotics were administered 3 weeks ago, but the otalgia persisted. At this current visit, the left ear was full of soft debris that was consistent with a fungal external otitis. Upon microscopic examination of the left ear, an area of bare exposed bone was seen in the external auditory canal with surrounding inflammatory soft tissue changes, and two perforations of the tympanic membrane were also seen. Black hyphae material, thought to be mycotic debris, was observed in the external auditory canal at the junction of the tympanic membrane. Cultures were obtained but failed to show any fungal growth. The patient's left ear was cleaned with peroxide and an antifungal agent was applied with a cotton swab topically to the patient's ear canal. The tympanic membrane rupture precluded the use of any antifungal drops due to their potential ototoxic effect to the middle ear. Suctioning for removal of debris was performed, and the patient was placed on topical antibiotic drops, Ciprodex<sup>®</sup> otic suspension, and oral Diflucan<sup>®</sup>.

On November 27, 2006, the patient underwent a tympanoplasty with fascia graft to the left ear, and tissue samples were submitted for routine pathology. Pathology report showed portions of left tympanic membrane and keratinous debris. On January 2, 2007, the patient was seen for a follow-up postoperative visit, and it was discovered that the tympanoplasty graft was not completely successful. It was thought there were two perforations present in the overlying graft in the same position as the original perforation preoperatively. Edema was observed in the grafted area; the perforations margins showed evidence of graft tissue sloughing. There was a 1 mm area of the ear canal soft tissue showing dehiscence with exposure of the bone, which was thought to be postauricular wound cellulitis. The ear canal was cleaned with peroxide solution and blood crusting debris was removed. He had 3 Vicryl sutures that were removed at that time. The wound was coated with antibiotic ointment, and he was treated with systemic ciprofloxacin 500 mg PO BID for 7 days and topical ciprofloxacin otic solution 5 drops BID.

On January 16, 2007, the patient was seen for follow-up and there were no signs of local infection. Microscopic examination demonstrated that the previous tympanic membrane perforations no longer present. There was delayed healing of the underlying fascia graft with tissue granulation in the area. The patient was instructed to continue with the Ciprofloxacin otic solution 3 drops TID for 14 days. Microscopic examination on January 30, 2007, revealed that he had a fully intact tympanic membrane and complete resolution of the inflammatory changes of the graft site. He stated his hearing had improved. At his 1-year post-operative follow-up on January 22, 2008, the patient had a fully intact tympanic membrane.

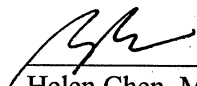
The patient's past medical history is significant for hypertension, hyperlipidemia, benign prostatic hypertrophy, and alcohol dependence with abstinence for approximately 30 years. Medications taken at the time of the event included atenolol, HCTZ, trazodone, and multivitamins.

There have been no other cases of non-infectious external otitis, and 1 case of grade 2 middle ear otitis (non-infectious) (unlikely related) previously reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC. There have been 17,047 patients enrolled in NCI-sponsored clinical trials under this NSC.

In this case, it is felt that a possible causal relationship between bevacizumab and non-infectious external otitis cannot be excluded.

<b>External Otitis (non-infectious) with tympanic membrane perforation</b>	
<b>Bevacizumab</b>	Possible
<b>Adenocarcinoma of the colon</b>	Unrelated

Date: 9/9/08

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

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

cc: Murielle Mueller  
Drug Safety: [onc\\_drug.safety@gene.com](mailto:onc_drug.safety@gene.com)  
Genentech, Incorporated