



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: December 12, 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_1506455_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/kjm
enclosure



DATE: October 16, 2008
FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: Bevacizumab (rhuMAb VEGF) IND Safety Report, AE# **1506455**
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 68-year-old male with adenocarcinoma of the prostate with metastases to the bone and lymph nodes died suddenly while on a phase 3 trial utilizing the investigational agent bevacizumab.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF)	ADVERSE EXPERIENCE REPORT NO. 64 IND Safety Report: #1 Event: Gr. 5: Sudden death
AE: 1506455	Protocol: CALGB-90401

The patient is a 68-year-old male with adenocarcinoma of the prostate with metastases to the bone and lymph nodes, who died suddenly while on a phase 3 trial using the investigational agent bevacizumab/placebo in combination with dexamethasone, docetaxel, and prednisone. The patient began his first course of treatment on November 15, 2007, receiving bevacizumab/placebo 15 mg/kg IV over 30-90 minutes on Day 1, dexamethasone 8 mg PO 12 hours, 3 hours, and 1 hour prior to docetaxel on Day 1, docetaxel 75 mg/m² IV over 1 hour on Day 1, and prednisone 5 mg PO twice daily, every 21 days. The patient received his last doses of bevacizumab/placebo, dexamethasone, docetaxel, and prednisone on September 4, 2008 (Cycle 15, Day 1).

The patient was diagnosed with adenocarcinoma of the prostate in June 2004 and is status post radiation therapy in December 2004 and January 2005. After a steady increase and doubling of his PSA in September 2007, metastases to the bone and lymph nodes were diagnosed in November 2007, and he began the investigational therapy on November 15, 2007. Complications included myelosuppression after Cycle 3 and a perianal fistula noted during Cycle 12 (not infected and not requiring surgical intervention).

On September 4, 2008, the patient came to the clinic for a routine visit. His vital signs, including blood pressure, were normal. He complained of fatigue, mild lower extremity edema, parasthesias of his hands and feet, and pain at the site of his pre-existing perianal fistula. Of note, the patient had a history of obstructive sleep apnea, for which he had not been evaluated in the recent past. The oncologist felt that his fatigue was most likely related to his sleep apnea. The patient was advised to see his primary care provider for a sleep study and reassessment of his CPAP pressure settings, as he had clear worsening of his sleep apnea. Physical examination revealed a perianal fistula at the 2:00 position with mild oozing of stool in the area, but it was unclear whether it was emanating from the fistula. There was no evidence of infection. He was given wound care instructions for the perianal fistula.

On September 13, 2008 (Cycle 15, Day 10), the patient's wife found the patient dead in his bed, having died in his sleep. Per her report, his body was cold and already beginning to stiffen upon discovery. The patient's wife called 911. A deputy sheriff and an ambulance responded to the home, and they attempted to resuscitate the patient but were unsuccessful. The deputy coroner was called, pronounced him dead, and his body was transported directly to the mortuary. No autopsy was performed. The oncologist felt that his obstructive sleep apnea was the cause of his death.

The patient's past medical/surgical history is significant for obstructive sleep apnea, osteoarthritis of both knees and the right shoulder, degenerative disease of the spine, open reduction internal fixation of a fracture in 1954, and an abdominal wall hernia repair in 1990. The patient's family history is significant for death due to heart disease of his father at age 87 and his sister at age 26. Medications taken at the time of the event included gabapentin, lidocaine 2% gel, Magic Mouthwash[®], nystatin, oxycodone, prochlorperazine maleate, senna, and Xenaderm[®].

There have been 41 other cases of sudden death, and 57 other cases of death NOS previously reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC.


There have been 17,245 patients enrolled in NCI-sponsored clinical trials under the bevacizumab NSC.

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In this case, it is felt that a possible causal relationship between the protocol therapy and sudden death cannot be excluded.

Sudden death	
Bevacizumab/placebo	Possible
Dexamethasone	Unlikely
Docetaxel	Possible
Prednisone	Unlikely
Adenocarcinoma of the prostate	Unrelated
Obstructive sleep apnea	Probable

Date: 10/16/08

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
Genentech, Inc.

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