



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** March 13, 2009

**To:** NCCTG Primary Clinical Research Associates

**From:** Lynn Flickinger  
Protocol Development Coordinator

**Re:** N0735, Phase II Trial of Albumin-Bound Paclitaxel in Combination with Gemcitabine and Bevacizumab in Patients with Metastatic Breast Cancer

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\_1477246\_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 Lynn Flickinger at [Flickinger.lynn@mayo.edu](mailto:Flickinger.lynn@mayo.edu) or 507-538-7034.

LF/kjm  
enclosure



**DATE:** December 16, 2008

**FROM:** Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI 

**SUBJECT:** Bevacizumab (rhuMab VEGF) NCI IND Safety Report, AE# 1477246

**TO:** Investigators Using 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 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 INDs 7921 and 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.

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 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 female with primary peritoneal carcinoma experience **sudden death** while on a phase 3 trial utilizing the investigational agent bevacizumab.

## ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 <b>Bevacizumab (rhuMAb VEGF)</b>	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: <b>Gr. 5: Death not associated with CTCAE term: Sudden death</b>
AE: 1477246	Protocol: <b>GOG-0218</b>

The patient was a 58-year-old female with primary peritoneal carcinoma who died suddenly while on a randomized, double-blind, phase III study utilizing the investigational agent bevacizumab or placebo in combination with paclitaxel and carboplatin. The patient began her first course of treatment on March 31, 2008, receiving paclitaxel 175 mg/m<sup>2</sup> IV over 3 hours on Day 1 for 6 cycles, carboplatin AUC 6 IV over 30 minutes on Day 1, for 6 cycles, and bevacizumab or placebo 15 mg/kg IV on Day 1 starting with Cycle 2, for 5 cycles, every 21 days. She received the last dose of bevacizumab or placebo on July 28, 2008 (Cycle 6, Day 9).

The patient was initially diagnosed with stage IIIC primary peritoneal carcinoma in March 2008 and was status post exploratory laparotomy, bilateral salpingo-oophorectomy, and optimal radical tumor debulking and total omentectomy. She had a CA-125 of 1049 U/mL (reference range: 0-35 U/mL) at the time. She began the investigational therapy on March 31, 2008, and completed Cycle 1 without incident. On April 31, 2008, she began Cycle 2 which was delayed for uncontrolled hypertension. On June 18, 2008, the patient received Cycle 3 in which bevacizumab/placebo was again held secondary to the patient's hypertension. Cycle 4 and Cycle 5 were completed without any difficulty.

On July 28, 2008, the patient presented to the clinic for Cycle 6 with complaints of minimal fatigue and very mild neuropathy with noted tingling in the tips of her finger. She denies any pain, nausea or vomiting, abdominal pain, myalgias, fever, or chills. Her physical examination was unremarkable with a blood pressure of 106/78 mmHg, oxygen saturation of 97% on room air, temperature of 37.6°C, a pulse of 118 bpm, respirations of 18 breaths/minute, and a normal cardiac and lung examination. Laboratory studies revealed normal hemoglobin and hematocrit; total T4 was elevated but TSH was normal. A CT scan of the chest, abdomen and pelvis performed on June 2, 2008, was compared with the previous scan from March 28, 2008, and showed resolution of the bilateral pleural effusions; resolution of a peritoneal nodule along the right hemi-diaphragm; a large amount of multiloculated ascites that was similar in volume to the previous scan, with resolution of the serosal enhancement; and persistent nodular-appearing infiltration of the anterior mesenteric fat, although this was an improvement from the previous examination.

On August 5, 2008 (Cycle 6, Day 9), the patient's son called the clinic to say that his mother would not be keeping her appointment for follow-up blood work because she had diarrhea and weakness. On August 6, 2008, the family notified the clinic that the patient had died suddenly shortly after the initial phone cancelling the appointment on August 5, 2008. EMS attempted resuscitation at her home, and continued efforts were unsuccessful in the ambulance and the emergency room. An autopsy was not performed.

The patient's past medical history was significant for hypertension, hypothyroidism and hypercholesterolemia. The patient had 5 pregnancies with 5 life births. She received birth control pills but never took hormone replacement therapy. Medication taken at the time of the event included Levothyroxine<sup>®</sup>, Avalide<sup>®</sup>, amlodipine, Compazine<sup>®</sup>, dexamethasone, Percocet<sup>®</sup>, Zofran<sup>®</sup>, lorazepam, Colace<sup>®</sup>, and atorvastatin.

There have been 43 other cases of sudden death, 60 cases of death NOS, previously reported to the NCI

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as serious adverse events through AdEERS under the bevacizumab NSC, as shown in the table below:

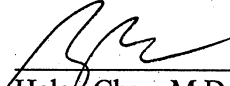
Adverse Event	Attribution
Sudden Death (n = 43)	1 Probable, 29 Possible, 11 Unlikely, 2 Unrelated
Death NOS (n=60)	15 Possible, 34 Unlikely, 11 Unrelated

To date, there have been 18,179 patients enrolled in NCI-sponsored clinical trials under this NSC.

In this case, the cause of sudden death is unknown. However, a probable causal relationship cannot be ruled out between the protocol therapy and the sudden death. Although electrolyte imbalance was suspected given the history of diarrhea before death, it has not been documented.

	Sudden death
Bevacizumab/placebo	Probable
Carboplatin	Probable
Paclitaxel	Probable
Primary peritoneal carcinoma	Unlikely
Amlodipine	Possible
Avalide®	Possible

Date: 12/16/08

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](mailto:onc_drug.safety@gene.com)  
Genentech, Incorporated