



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** March 6, 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 industry report of an adverse event that has occurred in association with Bevacizumab, at a non-NCCTG institution. You may have also received this communication directly from the drug manufacturer.

**AE\_1636469\_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 8, 2008  
**FROM:** Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
**SUBJECT:** Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE # 1636469  
**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 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.

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 this NSC, and the total number of patients enrolled in trials under this NSC:

A 53-year-old female with stage IV serous adenocarcinoma of the ovaries experienced **grade 3 fat necrosis** in the abdominal wall while on a phase 3 trial utilizing the investigational agent bevacizumab or placebo in combination with paclitaxel and carboplatin.

**ADVERSE EVENTS ASSESSMENT**

IND 7921 NSC 704865 <b>Bevacizumab (rhuMAb VEGF)</b>	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 3: <b>Fat necrosis (abdominal wall)</b>
AE: 1636469	Protocol: <b>GOG-0218</b>

The patient is a 53-year-old female with stage IV ovarian serous adenocarcinoma who experienced fat necrosis in the abdominal wall while on a phase 3 trial utilizing the investigational agent bevacizumab or placebo in combination with paclitaxel and carboplatin. She began the first course of treatment with Phase A on December 13, 2007, receiving paclitaxel 175 mg/m<sup>2</sup> IV over 3 hours on Day 1, and carboplatin AUC 6 IV over 30 minutes on Day 1, for 6 cycles, and bevacizumab or placebo 15 mg/kg IV over 30 minutes on Day 1 starting with Cycle 2 for 5 cycles, every 21 days. Phase B consisted of bevacizumab or placebo 15 mg/kg IV on Day 1 starting with Cycle 7 for 16 cycles (maximum 22 cycles total), every 21 days. She received the last dose of bevacizumab or placebo on September 9, 2008 (Cycle 12, Day 1).

The patient was initially diagnosed with serous adenocarcinoma of the ovaries in November, 2007, and is status post total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic lymph node dissection, omentectomy, and multiple tumor resections. She began the investigational treatment on December 13, 2007. Restaging in March, 2008, showed decrease in the peritoneal thickening and enhancement.

On June 18, 2008 (Cycle 9, Day 1), the patient complained of abdominal discomfort after receiving treatment. Physical examination revealed a palpable mass on the left upper quadrant of the abdomen. On June 19, 2008, a CT scan of the abdomen showed a new 2.9 × 1.4 cm irregular soft tissue infiltrative lesion in the left abdomen subcutaneous fat layer. She underwent a lower left quadrant excisional biopsy on June 21, 2008, which revealed a whitish mass covered with soft tissue measuring 3 × 1.5 cm. Histological analysis of the soft tissue was consistent with fat necrosis (no other descriptions were given). The patient was discharged home in a stable condition. On July 8, 2008, when she was due for Cycle 10 protocol therapy, an abdominal examination revealed another palpable mass measuring 0.5-1.0 cm in the epigastric region at the midline. An ultrasound-guided needle biopsy revealed some clusters of atypical cells and scattered giant cells. On July 17, 2008, another excisional biopsy was done, and histology again revealed fat necrosis.

The patient's past medical/surgical history is significant for hypertension, an appendectomy, and a para-aortic lymph node biopsy. Her family history is significant for a sister with rectal cancer. Medications taken at the time of the event included ascorbic acid and Gasmotin®.

There have been no other cases of fat necrosis reported to the NCI as a serious adverse event through AdEERS under the bevacizumab NSC.


To date, there have been 18,136 patients enrolled in NCI-sponsored clinical trials under this NSC.

In this case, it is felt that a causal relationship between the events and bevacizumab could not be excluded.

	<b>Fat necrosis</b>
<b>Bevacizumab</b>	Possible
<b>Ovarian adenocarcinoma</b>	Unrelated

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Date: 12/8/08

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