



# 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\_1843518\_F2**


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 1, 2008  
**FROM:** Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
**SUBJECT:** Bevacizumab (rhuMAb VEGF) IND Safety Report, AE# 1843518   
**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.

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

A 43-year-old female with stage IV epithelial ovarian carcinoma experienced **grade 4 cerebellar syndrome** while on a phase 3 trial utilizing the investigational agent bevacizumab.

## ADVERSE EVENTS ASSESSMENT

IND 7921	ADVERSE EXPERIENCE REPORT NO.
NSC 704865	IND Safety Report: #2
Bevacizumab (rhuMAb VEGF)	Event: Gr. 4: Neurology: Cerebellar syndrome
AE: 1843518	Protocol: GOG-0218

The patient is a 43-year-old female with stage IV epithelial ovarian cancer who experienced cerebellar syndrome while on a phase 3 study utilizing the investigational agent bevacizumab or placebo in combination with paclitaxel and carboplatin. The patient began her first course of treatment on December 4, 2007, receiving Phase A of the protocol: 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, each for 6 cycles, and bevacizumab/placebo 15 mg/kg IV on Day 1 starting with Cycle 2 for 5 cycles, every 21 days, followed by Phase B. Phase B consisted of bevacizumab/placebo 15 mg/kg IV starting on Cycle 7 for 16 cycles, every 21 days. Paclitaxel was changed to docetaxel for cycle 3-6 due to peripheral neuropathy. She received the last dose of docetaxel and carboplatin on March 28, 2008 (Cycle 6, Day 1) and the last dose of bevacizumab/placebo on August 29, 2008 (Cycle 12, Day 1).

The patient was diagnosed with stage IV epithelial ovarian cancer with metastases to the supraclavicular lymph nodes in October 2007 and is status post lymph node dissection, total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, recto-sigmoid resection with anastomosis, and suboptimal ovarian tumor debulking. She began the protocol therapy on December 4, 2007.

During Cycle 11 (July 2008), the patient developed headache, dizziness, blurred vision with diplopia, right-sided neck pain, nausea and vomiting. Her blood pressure was stable in the range of 120-130/70-90 mmHg. Neurological examinations revealed coarse nystagmus, ataxia and disequilibrium. A brain MRI on July 17, 2008, showed no metastatic disease or abnormal T2 signals. She saw a neurologist on August 4, 2008, who made the diagnosis of cerebellar syndrome with a concern for paraneoplastic syndrome. Tests for Purkinje cell (Yo) antibodies were positive. Restaging scans in July 2008 showed a sustained partial response compared to scans at baseline and in April 2008. She was treated with IV steroids and Valium<sup>®</sup>, which was associated with resolution of nystagmus and dizziness. Of note, the patient also skipped two doses of bevacizumab during the time. Her CA-125 was 7 U/mL at the time (reference range: 1-35 U/mL). Given the suspicion of paraneoplastic syndrome as the cause of the neurological disturbance, decision was made to resume bevacizumab, and a dose (Cycle 12) was given on August 29, 2008. However, the patient experienced an immediate return of her previous symptoms later that day. She was again treated with Solu-Medrol<sup>®</sup>, but with no response this time; her symptoms were, in fact, worse. She developed a stutter, vertigo, and worsening ataxia. A brain MRI on September 29, 2008, was unremarkable. The decision was made to remove her from the protocol treatment.

On October 5, 2008, the patient presented to the emergency room for an increase in seizure-like activity described as jerky movements of the upper and lower extremities with upper extremity rigidity accompanied by blurring of vision, eyes rolling back, agitation, tremor and headache. These seizure-like events had been occurring for several weeks previously but had recently increased in severity and frequency. The symptoms would last for 5-15 seconds and would resolve spontaneously. There was no mention of loss of consciousness or bowel or bladder incontinence associated with these events. She was admitted to the hospital for evaluation and treatment. Blood work was normal and a CT scan of the brain was unremarkable. An EEG was done on October 7, 2008, which showed no organic seizure activity. During the hospitalization, it was noted that the patient remained conscious during subsequent episodes of this activity; it was possible to talk her down from at least one episode. Consequently, it was suggested that these seizure-like spells could be psychogenic in nature.

The patient was discharged from the hospital on October 8, 2008. Her overall neurologic condition was thought to be possibly due to the protocol therapy or paraneoplastic syndrome with cerebellar degeneration,

while the acute episodes of tremulousness were thought to be due to anxiety. There were no further plans for work-up or evaluation of her condition. Currently the patient is wheelchair-bound and unable to feed or care for herself, and plans are being made to place her in a nursing home facility for more assisted care. Repeat CT scans on October 16, 2008 showed no changes from the July 2008 studies, and CA-125 was 14 U/mL.

The patient's past medical history is significant for gastro-esophageal reflux disease, anemia, and prior tobacco use (quit 6 years ago). Her surgical history is significant for an exploratory laparotomy around the time of her cancer diagnosis and an appendectomy at age 4. Family medical history is significant for a mother with breast cancer and lymphoma who coincidentally experienced symptoms similar to the patient during chemotherapy. Medications taken at the time of the event included ascorbic acid, Colace<sup>®</sup>, ferrous sulfate, lorazepam, multi-vitamins, Prilosec<sup>®</sup>, prochlorperazine, Tramadol<sup>®</sup>, and Valium<sup>®</sup>.

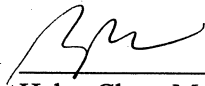
There has been no other case of cerebellar syndrome reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC.

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

In this case, the patient developed a constellation of neurological symptoms consistent with a cerebellar syndrome after 11 cycles of the protocol therapy, with symptoms initially responding to steroids but recurring after resumption of bevacizumab. Although the anti-O antibody was positive, suggestive of a paraneoplastic syndrome, the tumor had actually responded to the protocol therapy. It is felt that the cerebellar syndrome is probably related to the investigational agent although a possible attribution to paraneoplastic syndrome cannot be ruled out.

	<b>Cerebellar syndrome</b>
<b>Bevacizumab</b>	Probable
<b>Carboplatin</b>	Unlikely
<b>Docetaxel</b>	Unlikely
<b>Paclitaxel</b>	Unlikely
<b>Ovarian cancer</b>	Possible
<b>Possible paraneoplastic syndrome</b>	Possible

Date: 12/8 108

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

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

cc: Murielle Mueller  
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Genentech, Incorporated