



DATE: August 11, 2009

FROM: Kevin Conlon, M.D., Senior Investigator, IDB, CTEP, DCTD, NCI *Kevin Conlon*

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE # **1833568**

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 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.

The patient is a 60-year-old female with invasive breast carcinoma who experienced grade 3 seizures while on a double-blind phase 3 study utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, paclitaxel, and pegfilgrastim.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMab VEGF) AE: 1833568	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 3: Seizure Protocol: E5103
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The patient is a 60-year-old female with invasive breast carcinoma who experienced seizures while on a double-blind phase 3 study utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, paclitaxel, and pegfilgrastim. She began her first course of treatment on September 8, 2008, receiving bevacizumab/placebo 10 mg/kg IV over 30-90 minutes on Day 1, doxorubicin 60 mg/m² IVP on Day 1, cyclophosphamide 600 mg/m² IV over 20-30 minutes on Day 1 and pegfilgrastim 6 mg SQ on Day 2, every 14 days for Cycles 1-4. After 4 cycles, she received bevacizumab 15 mg/kg IV over 30-90 minutes on Day 1, and paclitaxel 80 mg/m² IV over 1 hour on Days 1, 8, and 15, every 21 days for Cycles 5-8. Following Cycle 8, she received bevacizumab/placebo 15 mg/kg IV over 30-90 minutes on Day 1, every 21 days for Cycles 9-18 concurrent with hormonal therapy. The patient received her last dose of bevacizumab/placebo on February 4, 2009 (Cycle 9, Day 1). She received her last dose of paclitaxel on January 27, 2009 (Cycle 8, Day 1), cyclophosphamide and doxorubicin on October 21, 2008 (Cycle 4, Day 1), and pegfilgrastim on October 22, 2008 (Cycle 4, Day 2).

The patient was diagnosed with invasive ductal carcinoma (high grade, T2, N0, triple negative, node-negative) of the right breast in July 2008, and is status post lumpectomy and chemotherapy. She began the investigational therapy on September 8, 2008.

On February 18, 2009 (Cycle 9, Day 15), the patient presented to the emergency room (ER) via ambulance after her husband found her unresponsive that morning with drooling of bloody drainage from the mouth. Emergency medical services also found that the patient had urinary incontinence, and that she had bitten her tongue; these were attributed to an unwitnessed seizure. While on the way to the ER, the patient was observed to have a tonic-clonic seizure. In the ER, she had a temperature of 100.5° F, blood pressure of 236/104 mmHg, heart rate of 154 bpm, respiration rate of 28 breaths per minute, and a Glasgow Coma Scale score of 8. The patient exhibited incoherent speech, confusion, disorientation, and combativeness. She was placed on oxygen via a non-rebreather mask and given Ativan®, Narcan®, and Valium®, and Dilantin®. Due to a concern for possible bacterial meningitis and herpes (HSV) encephalitis, she was started on empirical IV antibiotics, IV fluids, and acyclovir. Her blood pressure improved somewhat to 188/90 mmHg. A CT scan of the brain showed some low density changes on the posterior right with questionable white matter changes. An attempt at a lumbar puncture in the ER was unsuccessful. The patient was admitted to the intensive care unit where she underwent a successful (although traumatic) lumbar puncture.

On February 19, 2009, an MRI of the head with and without contrast revealed extensive subcortical white matter abnormalities likely caused by reversible posterior leukoencephalopathy syndrome (RPLS); this was thought to be related to bevacizumab and uncontrolled hypertension. A repeat CT scan of the brain showed diffused hypodensity in the white matter bilaterally as described on the MRI report. Cerebral spinal fluid cultures grew no organisms. HSV PCR was negative. The patient was continued on the antibiotic therapy, her hypertension was managed with hydralazine and Norvasc®, and her tachycardia was controlled with a beta blocker.

The patient gradually improved, suffering no further seizures, and on February 23, 2009 (Cycle 9, Day 22), she was afebrile, alert and oriented × 3, and coherent. Her blood pressure was lower than it had been with systolic readings in the 140's to 170's and the diastolic blood pressure readings in 60's to 70's mmHg. The seizures and mental status changes were attributed to RPLS. The patient developed acute

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renal failure secondary to the medications given during this hospitalization (creatinine gradually rose from a baseline value of 0.9 mg/dL [reference range: 0.5-1.0 mg/dL] to 1.9 mg/dL on February 25, 2009). The antibiotic therapy was discontinued. She was discharged home in stable condition on February 26, 2009. A follow up MRI of the head with and without contrast on March 16, 2009, showed the white matter abnormalities previously demonstrated had completely resolved.

The patient's past medical and surgical history is significant for hypertension, obesity, depression, hyperlipidemia, herpes zoster in September 2008, C-section, and back surgery. Medications taken at the time of the event included simvastatin, Lexapro[®], trazodone, trimethobenzamide, possible hydrochlorothiazide, folic acid, vitamin B12, Glucosamine, and Estrin[®].

There have been 51 other cases of seizure previously reported to the NCI as serious adverse events through ADEERS under the bevacizumab NSC and/or IND.

Event	Grade	Attribution
Seizure (n=51)	4	1 Unrelated, 3 Unlikely, 2 Possible
	3	6 Unrelated, 10 Unlikely, 15 Possible, 2 Probable
	2	6 Unrelated; 4 Unlikely; 2 Possible

There have been 22,954 patients enrolled in NCI-sponsored clinical trials under this IND and/or NSC.

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

Seizure	
Bevacizumab	Probable
Cyclophosphamide	Unrelated
Doxorubicin	Unrelated
Paclitaxel	Unrelated
Pegfilgrastim	Unrelated
Invasive breast carcinoma	Unrelated

Date: March 7 2009

Signature: 
 Kevin Conlon, M.D.
 (IDB Monitor for bevacizumab)

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

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 Genentech, Incorporated

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