



**DATE:** DEC 22 2010  
**FROM:** Kevin Conlon, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
**SUBJECT:** Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1226745  
**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 NSC, and the total number of patients enrolled in trials under these INDs and/or NSC.

A 47-year-old female with glioblastoma multiforme suffered a seizure and subsequently died of encephalopathy while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with temozolomide and radiation therapy.

## ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 <b>Bevacizumab (rhuMAb VEGF)</b>  AE: 1226745	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: <b>Gr. 5: Encephalopathy</b> <b>Gr. 3: Seizure</b> Protocol: <b>RTOG-0825</b>
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The patient was a 47-year-old female with glioblastoma multiforme (GBM) who suffered a seizure and subsequently died of encephalopathy while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with temozolomide and concurrent radiation. She began her first course of treatment on June 2, 2010, receiving bevacizumab/placebo 10 mg/kg of actual body weight IV over 30-90 minutes on Day 1 of Weeks 4 and 6, radiation therapy 60 Gy over 6 weeks (delivered in 2 Gy fractions on Days 1-5 every week), and temozolomide 75 mg/m<sup>2</sup> PO daily (Concurrent treatment course = 6 weeks); bevacizumab/placebo 10 mg/kg of actual body weight IV over 30-90 minutes at beginning of week 2 (Cycle = 4 weeks); and bevacizumab/placebo 10 mg/kg of actual body weight IV over 30-90 minutes on Days 1 and 15 and temozolomide 150-200 mg/m<sup>2</sup> PO on Days 1-5 for a maximum of 12 cycles (Cycle = 4 weeks). The patient received the last dose of bevacizumab/placebo on July 27, 2010 (Cycle 2, Day 9 of Concurrent treatment course), and the last doses of temozolomide and radiation therapy on July 14, 2010 (Cycle 1, Day 43 of Concurrent treatment course)

The patient was diagnosed with right frontal lobe GBM in April 2010. She was status post right fronto-parietal craniotomy with tumor resection on April 29, 2010, and chemotherapy with radiation. The patient began the investigational therapy on June 2, 2010.

On August 2, 2010 (Cycle 2, Day 15), the patient suffered a seizure at home. She was transported to the local emergency room where she experienced another seizure associated with an altered mental status. The patient was ill-appearing and afebrile with a heart rate 114 bpm, blood pressure 152/81 mmHg, and respiration 32 breaths per minute. Her sodium was 125 mEq/L (reference range: 136-145 mEq/L) from the previous day's value of 118 mEq/L. The patient was given IV hypertonic saline and Keppra<sup>®</sup>, which improved her mental status. She was later switched to oral sodium tablets, placed on fluid restriction, and admitted to the MICU with neuro-checks every 4 hours. Her intake and output was monitored. She was continued on Decadron<sup>®</sup>, and given Haldol<sup>®</sup> and Ativan<sup>®</sup>. The neurologist felt her encephalopathy was most likely related to hyponatremia and recommended increasing the dose of Keppra<sup>®</sup>.

On August 3, 2010 (Cycle 2, Day 16), the patient was lethargic and had a temperature of 101.2° F for which she received Tylenol<sup>®</sup>. Repeat laboratory results showed her sodium at 119 mEq/L and her urine was positive for *Enterococcus*. She was started on 3% saline IV fluid, and her antibiotics were adjusted. An MRI of the brain showed a new small area of restricted diffusion in the right insular cortex without associated contrast enhancement or hemorrhage, which was thought to be representative of seizure-related changes versus an area of infarction. On August 5, 2010, the patient was removed from the protocol.

On August 7, 2010, the findings of a CT scan of the head included a generalized lucent appearance to the right temporal lobe which appeared new as compared to the examination of August 3, 2010. Based on the recent MRI, an evolving acute infarct was of concern. A repeat MRI of the brain the next day showed evolving postsurgical changes in the frontal lobe with a cavity in the surgical bed containing blood breakdown products and developing hemosiderin ring. There was a significant interval increase in the area of parenchymal hyperintensity and restricted diffusion involving the right insular cortex, both medial temporal lobes, the cingulate gyri, and the left insular cortex. These changes were felt to be highly representative of encephalitis, especially herpes encephalitis. The patient was started on acyclovir.

On August 10, 2010, the patient was unresponsive and becoming progressively worse, though her sodium had improved to 134 mEq/L. She was transferred to another facility for continuous EEG monitoring. The neurologist thought her condition was probably related to progressive disease or possibly to seizures. Her antiepileptics were adjusted. The patient's husband declined further investigative treatments or escalation of care, following a discussion about her grim prognosis. She was made do not resuscitate (DNR). On August 13, 2010, the patient was discharged to inpatient hospice where she died 2 days later.

The patient's past medical/surgical history was significant for Lasik eye surgery, facial surgery, and deep venous thrombosis. Medications taken at the time of the events included Keppra<sup>®</sup>, tetracycline, Loestrin<sup>®</sup>, Wellbutrin<sup>®</sup>, dexamethasone, Protonix<sup>®</sup>, fluconazole, vitamin D, Zofran<sup>®</sup>, Peri-Colace<sup>®</sup>, Lovenox<sup>®</sup>, and potassium.

There have been 27 other cases of encephalopathy, 9 other cases of leukoencephalopathy, and 90 other cases of seizure reported to NCI as serious adverse events through ADEERS under the bevacizumab NSC and/or IND. Reversible posterior leukoencephalopathy syndrome (RPLS/PRES) is an expected event for bevacizumab.


Adverse Event	Grade	Attribution
Encephalopathy (n=27)	5	1 Unlikely
	4	1 Definite, 4 Possible, 3 Unlikely
	3	1 Definite, 1 Probable, 9 Possible, 3 Unlikely, 3 Unrelated
	2	1 Unlikely
Leukoencephalopathy (n=9)	3	1 Possible
	2	2 Probable, 4 Possible
	1	2 Probable
Seizure (n = 90)	4	5 Possible, 4 Unlikely, 3 Unrelated
	3	3 Probable, 20 Possible, 16 Unlikely, 14 Unrelated
	2	2 Probable, 3 Possible, 7 Unlikely, 13 Unrelated

There have been 30,180 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, a possible relationship exists between the events and the investigational agent bevacizumab.

	Encephalopathy	Seizure
Bevacizumab/placebo	Possible	Possible
Temozolomide	Possible	Unlikely
Glioblastoma multiforme	Possible	Probable
CNS hemorrhage	Possible	Possible
Herpes encephalitis	Possible	Possible
SIADH	Unlikely	Possible
Keppra <sup>®</sup>	Unrelated	Possible
Haldol <sup>®</sup>	Unrelated	Possible

Date: 15 December 2010

Signature:   
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(IDB Monitor for bevacizumab)

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

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Genentech, Inc.