



**DATE:** August 17, 2010

**FROM:** Kevin Conlon, M.D., Investigational Drug Branch, CTEP, DCTD, NCI *Kevin Conlon*

**SUBJECT:** Bevacizumab (rhUMAb VEGF) NCI IND Safety Report, AE# 1138043

**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 67-year-old female with glioblastoma multiforme developed grade 4 cerebrovascular ischemia and grade 4 encephalopathy and died of cerebral edema while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with temozolomide and radiation.

## ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 <b>Bevacizumab (rhuMab VEGF)</b>	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: <b>Gr. 5: Cerebral edema</b> <b>Gr. 4: CNS cerebrovascular ischemia</b> <b>Gr. 4: Encephalopathy</b>
AE: 1138043	Protocol: <b>RTOG-0825</b>

The patient was a 67-year-old female with glioblastoma multiforme (GBM) who developed cerebrovascular ischemia and encephalopathy and died of cerebral edema while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with temozolomide and radiation. She began her first course of treatment on November 23, 2009, 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 February 3, 2010 (Cycle 1, Day 1), temozolomide on March 7, 2010 (Cycle 2, Day 5), and radiation therapy on January 6, 2010 (Concurrent treatment course).

The patient was diagnosed with left parietal glioblastoma multiforme in October 2009 and was status post left parietal craniotomy with tumor resection in October 2009. She began the investigational therapy on November 23, 2009.

On March 8, 2010 (Cycle 2, Day 6), the patient presented to the emergency room with poor appetite, constipation, and weakness. A brain CT scan revealed left sided edema with a possible ischemic infarction, and she was admitted with a diagnosis of left middle cerebral artery (MCA) ischemia and a cerebrovascular accident (CVA) with cerebral edema.

By March 11, 2010 (Cycle 2, Day 9), the patient had developed increasing somnolence as well as a fever of 101.7°F. She was transferred to the intensive care unit at another hospital with a diagnosis of encephalopathy likely secondary to GBM vs. acute stroke vs. underlying infection. A repeat CT scan of the brain was compared to a scan from February 2, 2010, and the results revealed a significant worsening of vasogenic edema in the left fronto-parieto-temporal region, 3 mm midline shift, and some compression of the ipsilateral ventricle. An MRI of the brain also revealed significant edema within the left temporoparietal lobe, extending into the left occipital lobe with mass effect on the left lateral ventricle. It was felt that the patient's encephalopathy was likely secondary to necrosis of the tumor bed. The patient continued to receive IV Decadron®, which was started at the initial facility. She was also given IV antibiotics, IV insulin for hyperglycemia, and continuous oxygen therapy.

On March 12, 2010, the patient went into cardiac arrest. She was successfully resuscitated and started on an amiodarone drip. On March 13, 2010, the patient was extubated and was able to receive adequate oxygen per nasal cannula. On March 16, 2010 (Cycle 2, Day 14), a repeat CT scan of the brain revealed no significant changes compared to the prior MRI. The patient continued to deteriorate. Following a meeting with the patient's oncologist on March 17, 2010, the family decided to withdraw care and discontinue all medications except morphine. She was removed from the protocol. On March 21, 2010, the patient expired.

The patient's past medical/surgical history was significant for diabetes mellitus type 2, hypertension, deep

vein thrombosis of lower left leg, Caesarean section, hysterectomy, surgery for right arm fracture, and right shoulder replacement. Medications taken at the time of the events included Diovan<sup>®</sup>/hydrochlorothiazide, Catapres<sup>®</sup>, Keppra<sup>®</sup>, Coumadin<sup>®</sup>, Protonix<sup>®</sup>, docusate, Zofran<sup>®</sup>, DuoNeb<sup>®</sup>, and insulin.

There have been 2 other cases of cerebral edema, reported to NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND. Cerebrovascular ischemia and RPLS are known events for bevacizumab.

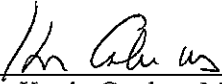
Adverse Event	Grade	Attribution
Cerebral edema (n=2)	5	None
	4	1 Unrelated
	3	1 Unlikely
Encephalopathy (n=23)	5	1 Unlikely
	4	1 Definite, 2 Possible, 2 Unlikely
	3	1 Probable, 9 Possible, 3 Unlikely, 3 Unrelated
	2	1 Unlikely
Leukoencephalopathy (n=7)	3	1 Possible
	2	1 Probable, 3 Possible
	1	2 Probable
RPLS (n=17)	4	4 Probable, 1 Unlikely
	3	2 Definite, 2 Probable, 2 Possible
	2	2 Definite, 1 Probable, 2 Possible
	1	1 Possible

There have been 28,605 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.

	Cerebral Edema	Cerebrovascular ischemia	Encephalopathy
Bevacizumab/placebo	Possible	Possible	Unlikely
Temozolomide	Unlikely	Unlikely	Possible
Radiation	Possible	Unlikely	Probable
Glioblastoma multiforme	Definite	Unrelated	Probable
Increased intracranial pressure	NA	Unrelated	Definite
Infection	Possible	Unrelated	Possible

Date: 17 August 2012

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

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

cc: Arthur Cannon  
Safety Contact: [onc\\_drug.safety@gene.com](mailto:onc_drug.safety@gene.com)  
Genentech, Inc.