



DATE: DEC 15 2010

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Report #2, AE# 1366672

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 57-year-old male with glioblastoma multiforme *developed grade 4 encephalopathy and* expired while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with temozolomide and radiation therapy.

This report has been amended to reflect new information. Changes to the attached report are indicated by bold and italics (new information) and/or strikethrough (deleted information). If this assessment is changed further, we will notify your office. Please note that this modified report will be distributed to investigators.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #2 Event: Gr. 5: Death not associated with CTCAE term: Death NOS Gr. 4: Encephalopathy Protocol: RTOG-0825
AE: 1366672	

This report has been amended to reflect new information. Changes to the original summary are indicated by bold and italics (new information) and/or strikethrough (deleted information). If this assessment is changed further, we will notify your office. Please note that this modified report will be distributed to investigators.

The patient was a 57-year-old male with glioblastoma multiforme who *developed encephalopathy and* expired while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with temozolomide and radiation therapy (RT). He began the first course of the investigational therapy on September 28, 2009, receiving bevacizumab/placebo 10 mg/kg of actual body weight IV over 30-90 minutes on Day 1 of Weeks 4 and 6, temozolomide 75 mg/m² PO daily, and RT 60 Gy over 6 weeks (delivered in 2 Gy fractions on Days 1-5 of every week), for Cycle 1 (cycle = 6 weeks). During Cycle 2, he received bevacizumab/placebo 10 mg/kg of actual body weight IV over 30-90 minutes at the beginning of Week 2 (cycle = 4 weeks). He then received bevacizumab/placebo 10 mg/kg of actual body weight IV over 30-90 minutes on Days 1 and 15, and temozolomide 150-200 mg/m² PO on Days 1-5, starting on Cycle 3, for a maximum of 12 cycles (cycle = 4 weeks). The patient received his last dose of bevacizumab/placebo on January 20, 2010 (Cycle 3, Day 16), the last dose of temozolomide on January 10, 2010 (Cycle 3, Day 6), and the last dose of RT on October 15, 2009 (Cycle 1, Day 18).

The patient was initially diagnosed with glioblastoma multiforme in July 2009, and is status post total surgical resection. He began the investigational therapy on September 28, 2009.

On October 27, 2009 (Cycle 1, Day 30), the investigational treatment was held for a platelet count of 20 × 10⁹/L (reference range: 150-450 × 10⁹/L) and resumed on November 10, 2009, when the platelet count recovered to 131 × 10⁹/L. On November 10, 2009, an MRI of the brain showed a smaller left temporal lobe resection cavity than on the previous study done in September 2009, two peripheral lesions which were unchanged, no significant mass effect, and evidence of possible radiation-associated microangiopathy.

On December 8, 2009, the investigational treatment was again held for 2 weeks due to the patient's confusion and listlessness, which did not improve with Decadron®. He was started on Ativan®, which was later changed to Haldol®, and showed much improvement. On December 14, 2009, a repeat MRI of the brain showed a slightly larger left lobe resection cavity with stable peripheral enhancement, no significant mass effect, and stable radiation-associated microangiopathy. On December 22, 2009, after his evaluation, the investigational treatment remained held due to the patient's continued confusion. A repeat CT scan of the head showed no acute hemorrhage or mass effect, and was similar to the previous scan of December 14, 2009. By January 5, 2010 (Cycle 3, Day 1), it was apparent that the patient's problem with cognition and instability was not resolving, and he patient had sustained some falls. It was recommended that the Haldol® dose be held at this time. The protocol officer was queried about the patient's eligibility for continued treatment.

On February 1, 2010, during a clinic visit, the patient was very confused and clinically deteriorating. He was removed from the protocol and referred to hospice care. The patient had a fall the next day resulting in a laceration on his forehead. He was admitted to hospice and was started on phenobarbital, then Restoril®. On February 5, 2010, the patient's blood pressure was 200/110 mmHg, pulse 72 bpm, respiration 18 breaths per minute, and oxygen saturation 94% on room air. He had a facial laceration with sutures, bruising around the eyes, dried mucus membranes, decreased distal pulses, marked gait disturbance, intermittent agitation, restlessness, impaired communication, and bowel and bladder

incontinence. He was continued on his antihypertensive medications. After discussions with his wife, the patient was placed on do not resuscitate (DNR) status. The patient died peacefully at home on February 10, 2010.

The patient's past medical/surgical history is significant for uncontrolled hypertension, peripheral vascular disease, hyponatremia, right-sided visual field loss post surgical resection of tumor, and left femoral stent placement. Medications taken at the time of the event included Keppra[®], phenobarbital, hydrocodone, Restoril[®], Zofran[®], Phenergan[®], lisinopril, Toprol[®] XL, and Catapres[®].

There have been 50 other cases of sudden death, 68 cases of death NOS, *and 27 other cases of encephalopathy* previously reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND as shown in the table below:

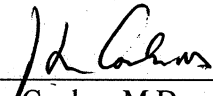
Adverse Event	Grade	Attribution
Sudden Death (n=50)	5	4 Unrelated, 12 Unlikely, 31 Possible, 3 Probable
Death NOS (n=68)	5	12 Unrelated, 36 Unlikely, 20 Possible
<i>Encephalopathy (n=27)</i>	<i>4</i> <i>3</i> <i>2</i> <i>1</i>	<i>1 Definite, 2 Possible, 2 Unlikely</i> <i>9 Possible, 3 Unlikely, 3 Unrelated</i> <i>1 Unlikely</i> <i>1 Unlikely</i>

There have been ~~25,908~~ **30,180** patients enrolled in NCI-sponsored clinical trials under this IND and/or NSC.

In this case, it is thought that a possible causal relationship between bevacizumab and the patient's death exists, *and a possible causal relationship between bevacizumab and encephalopathy exists.*

	Death NOS	Encephalopathy
Bevacizumab	Possible	<i>Possible</i>
Temozolomide	Unlikely	<i>Unrelated</i>
Radiation	Unlikely	<i>Possible</i>
Glioblastoma multiforme	Probable	<i>Possible</i>

Date: 13 December 2010

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

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

cc: Arthur Cannon
 Drug Safety: onc_drug_safety@gene.com
 Genentech, Inc.