




DATE: July 27, 2009

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1232396

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 (rhuMAb VEGF).

The following must be completed by all investigators using bevacizumab under NCI IND 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 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 this IND and/or NSC, and the total number of patients enrolled in trials under this IND and/or NSC.

A 51-year-old female with adenocarcinoma of the colon experienced a grade 4 CNS hemorrhage while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with oxaliplatin, 5-fluorouracil, and leucovorin.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 4: CNS hemorrhage
AE: 1232396	Protocol: E5202

The patient is a 51-year-old female with adenocarcinoma of the colon, who experienced a grade 4 CNS hemorrhage while on a phase 3 study utilizing the investigational agent bevacizumab in combination with oxaliplatin, 5-fluorouracil, and leucovorin. She began her first course of treatment on March 18, 2009, receiving bevacizumab 5 mg/kg IV over 30-90 minutes on Day 1, oxaliplatin 85 mg/m² IV over 2 hours on Day 1, leucovorin 400 mg/m² IV over 2 hours on Day 1 and 5-fluorouracil (5-FU) 400 mg/m² IV bolus on Day 1 followed by 5-FU 2.4 gm/m² CIV over 46 hours starting on Day 1, every 2 weeks. After the completion of 12 cycles, she was to receive bevacizumab 5 mg/kg IV over 30-90 minutes on Day 1, every 2 weeks for twelve additional cycles. The patient received her last doses of bevacizumab, oxaliplatin, 5-fluorouracil, and leucovorin on April 15, 2009 (Cycle 3, Day 1).

The subject was diagnosed with a stage II (T3N0M0) adenocarcinoma of the transverse colon. She is status post transverse colon resection done on January 23, 2009.

On April 16, 2009 (Cycle 3, Day 2), an acute change in the patient's mental status was noted and she was taken to a hospital where a CT scan of the head showed a large intraparenchymal hematoma in the left frontal lobe causing significant mass effect with a midline shift towards the right. She underwent an emergency left craniotomy with evacuation of the hematoma. She was extubated postoperatively and was able to move all her extremities spontaneously. She was alert with global aphasia. On April 17, 2009, a post-operative CT scan of the head showed pockets of pneumocephalus with a small area of residual hemorrhage. The midline shift had improved significantly and a mild subarachnoid hemorrhage was noticed. She was unable to eat or drink orally during the course of the hospitalization and a feeding tube was placed to initiate tube feeding. Her neurological condition gradually improved throughout the course of her hospitalization. She began to speak words intermittently. At the time of her discharge to acute rehabilitation on April 23, 2009, she was alert and oriented. The patient was to follow-up with her neurosurgeon after 4 weeks with a head MRI. During her rehabilitation, a peripheral venous ultrasound scan showed deep venous thrombosis of the right leg involving the posterior tibial through the popliteal vein for which she underwent an inferior vena cava filter placement on May 11, 2009.

The patient's family and social history is significant for lung cancer in her father, colon cancer in her mother and ovarian cancer in her paternal grandmother. The patient smoked half a pack of cigarettes per day for 35 years.

The patient's past medical and surgical history is significant for arthritis, iron deficiency anemia, hypertension, cervical dysplasia, menstrual disorder, joint pain in the lower leg, colonic polyp, constipation, neutropenia and morbid obesity. Medications taken at the time of the event included loperamide, prochlorperazine, polyethylene glycol and desonide.


CNS hemorrhage is an expected adverse event for bevacizumab. There have been 10 other cases of mental status change (Grade 3: 3 unrelated, 2 unlikely, 3 possible and Grade 2: 1 unrelated, 1 unlikely) previously reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND.

There have been 22615 patients enrolled in NCI-sponsored clinical trials under this NSC.

In this case, a possible causal relationship between bevacizumab and events exists.

	CNS hemorrhage
Bevacizumab	Possible
5-Fluorouracil	Unrelated
Leucovorin calcium	Unlikely
Oxaliplatin	Possible
Adenocarcinoma of the colon	Unlikely

Date: 28 July 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, Inc.