



DATE: AUG 31 2010

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1236502

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 61-year-old female with metastatic carcinoid tumor experienced a grade 5 small bowel obstruction while on a phase 3 study using the investigational agent bevacizumab in combination with octreotide.

ADVERSE EVENTS ASSESSMENT

IND 7921	ADVERSE EXPERIENCE REPORT NO.
NSC 704865	IND Safety Report: # 1
Bevacizumab (rhuMAb VEGF)	Event: Gr. 5: Obstruction, GI: Small bowel NOS
AE: 1236502	Protocol: S0518

The patient was a 61-year-old female with a metastatic carcinoid tumor who expired from a small bowel obstruction (SBO) while on a phase 3 study using the investigational agent bevacizumab in combination with octreotide. She began her first course of treatment on March 13, 2009, receiving bevacizumab 15 mg/kg IV over 30-90 minutes on Day 1, and an octreotide LAR depot 20 mg IM on Day 1, every 21 days. She also received an octreotide test dose of short-acting octreotide 100 mcg SQ, on Day 1 of Cycle 1 only. She received the last dose of bevacizumab on December 18, 2009 (Cycle 13, Day 1), and the last dose of octreotide on January 8, 2010 (Cycle 14, Day 1).

The patient was diagnosed with metastatic carcinoid tumor in September 2007 when an exploratory laparotomy revealed carcinoid tumor in the liver and retroperitoneum. She was status post multiple-agent systemic chemotherapy from April 2008 to February 2009. She began the investigational agent on March 13, 2009.

On January 8, 2010, the patient, who had a prior history of chronic partial small bowel obstruction noted on an October 2009 CT scan, was admitted to the hospital for severe abdominal pain with new onset of numbness and weakness in the lower extremities during a clinic visit. Bevacizumab was held. A CT scan of the abdomen and pelvis showed multiple dilated loops of small bowel with air-fluid levels and "fecalized" contents. These findings were felt to be consistent with either an early complete small bowel obstruction or exacerbation of partial small bowel obstruction and extensive metastatic disease. A bilateral lower extremity venous Doppler[®] ultrasound was negative for thrombosis. She was treated with Cipro[®], MS Contin[®], lactulose, MiraLax[®], and a clear liquid diet. The patient's condition improved and she was discharged home on January 12, 2010.

From January 28-30, 2010, the patient was re-hospitalized for a deep vein thrombosis of the right lower extremity. She was started on Lovenox[®] and discharged home.

On February 2, 2010, the patient presented to the local emergency room with lower extremity edema, a cold left lower extremity, generalized weakness, and weight loss of at least 10 pounds in the last 2 weeks. She was emaciated, mildly tachycardic, and had stage 2 decubitus ulcer on her back and her lower extremities. The patient was admitted for observation and supportive care, and a consult for hospice care was obtained.

On February 4, 2010, the patient became hypoglycemic, and appeared to have aspirated. She was emergently intubated for acute respiratory failure, placed on mechanical ventilation, and transferred to the ICU. The patient's abdomen was uniformly distended with absent bowel sounds, and no obvious masses or pulsatile masses felt. Her endotracheal tube drained copious foul smelling secretions, which appeared to be fecal material. It was felt that she probably aspirated this fecal material and was at a high risk of developing extensive pneumonia. The patient was removed from the study. After discussions with the patient's family regarding end-of-life issues and life support, the patient was made do not resuscitate (DNR), and she expired later that evening. An autopsy was not performed.

The patient's past medical and surgical history is significant for CVA in 2005, hypercholesterolemia, hypertension, hysterectomy and bilateral salpingo-oophorectomy for bleeding, laparotomy in 2007, port

CONFIDENTIAL

AE # 1236502

Page 1 of 2

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placement in September 2008, depression, and a 40 pack-year smoking history. Medications taken at the time of the event included Cartia[®], morphine, lactulose, Equate[®] stool softener, oxycodone, citalopram, Peri-Colace[®], Plavix, lisinopril[®], and megestrol.

There have been 133 other cases of small bowel obstruction reported to the NCI through AdEERS as serious adverse events under the bevacizumab NSC and/or IND as shown in the table below:

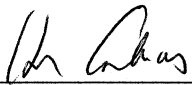
Adverse Event	Grade	Attribution
Small Bowel Obstruction (n=133)	4	4 Unrelated, 8 Unlikely, 3 Possible
	3	46 Unrelated, 40 Unlikely, 22 Possible, 1 Probable
	2	6 Unrelated, 3 Unlikely

There have been 28,649 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, a possible relationship between the event and bevacizumab cannot be excluded.

	Small bowel obstruction
Bevacizumab	Possible
Octreotide acetate	Unrelated
Carcinoid tumor	Probable

Date: 31 August 2010

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.