



DATE: MAY 11 2011

FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1751032

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 this letter to your Institutional Review Board (IRB) of record according to your 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 female with invasive breast carcinoma experienced a grade 4 wound complication while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, paclitaxel and filgrastim/pegfilgrastim.

ADVERSE EVENTS ASSESSMENT

IND 7921	ADVERSE EXPERIENCE REPORT NO.
NSC 704865	IND Safety Report: # 1
Bevacizumab (rhuMAb VEGF)	Event: Gr. 4: Wound complication
AE: 1751032	Protocol: E5103

The patient is a 57-year-old female with invasive breast carcinoma who experienced a wound complication while on a phase 3 study utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, paclitaxel, and filgrastim/pegfilgrastim. She began her first course of treatment on December 29, 2010, receiving bevacizumab/placebo 10 mg/kg IV over 30-90 minutes on Day 1, doxorubicin 60 mg/m² IVP on Day 1, cyclophosphamide 600 mg/m² IV over 20-30 minutes on Day 1, filgrastim 5 mcg/kg SC on Days 2-11 or pegfilgrastim 6 mg SC on Day 2, every 14 days during Cycles 1-4. She was to receive bevacizumab/placebo 15 mg/kg IV over 30-90 minutes on Day 1 and paclitaxel 80 mg/m² IV over 1 hour on Days 1, 8, and 15, every 21 days during Cycles 5-8. She received her last and only doses of bevacizumab/placebo, doxorubicin, and cyclophosphamide on December 29, 2010 (Cycle 1, Day 1), and her last and only dose of pegfilgrastim on December 30, 2010 (Cycle 1, Day 2).

The patient was diagnosed with invasive breast carcinoma in October 2010, and is status post right breast lumpectomy and lymph node dissection. Of note, the patient had a history of a lower midline ventral hernia which originally occurred at the site of her C-section incision. She underwent surgical reduction and repair of that incarcerated/strangulated incisional hernia in October 2006 (no mesh was placed due to contamination), but the hernia recurred less than 1 year later. A CT scan on December 14, 2010, revealed a large abdominal hernia, diverticulosis, and a left adrenal adenoma. She began the investigational therapy on December 29, 2010.

On January 8, 2011 (Cycle 1, Day 11), the patient started to experience abdominal pain, nausea, and vomiting. The following day, she presented to the emergency department with continued pain and abdominal bulging from her baseline hernia. She had an elevated white blood count of 16.21 K/ μ L (reference range: 4.00-12.00 K/ μ L). She was given normal saline as well as IV Zofran[®] and Dilaudid[®]. An abdominal and pelvic CT scan revealed an incarcerated ventral hernia. The patient was admitted, and continued monitoring along with serial abdominal exams were performed. The patient was unblinded on January 10, 2011, pending surgical intervention. It was determined that the patient had received bevacizumab. A repeat CT scan of the abdomen and pelvis on January 11, 2011, revealed a fairly large anterior abdominal wall hernia containing multiple loops of the small bowel which were slightly increased from the previous exam. This was concerning for a partial obstruction. It also confirmed a left adrenal adenoma.

On January 12, 2011, a ventral hernia repair with biological mesh was performed. Postoperatively, the patient had a slow return of GI function and strength. She was able to ambulate without difficulty, her pain was controlled with oral medications, and she was discharged to home on January 20, 2011.

On January 26, 2011, the patient was re-admitted for an enteric leak status post the ventral hernia repair. An exploratory laparotomy with removal of the infected mesh and oversewing of the enterotomy was performed. The leak persisted and there were several other surgeries for additional repair. The patient subsequently developed an enterocutaneous fistula in the middle of the open wound which required further surgery on February 25, 2011. An exploratory laparotomy, lysis of the adhesions, an appendectomy and resection of the small bowel containing the fistula were performed. During the course of this hospitalization, the patient also developed a left upper extremity deep vein thrombosis and was heparinized. After the final surgical procedure, the patient's course was unremarkable and she was

discharged to home on March 8, 2011.

The patient's past medical and surgical history is significant for morbid obesity, right wrist ganglion, right shoulder synovitis, valgus deformity of the right ankle, hypertension, chronic fatigue syndrome, joint pain, pyelonephritis, urinary tract infection, cervical disc displacement, neuropathy, visual disturbances, depression, allergic rhinitis, irritable bowel syndrome, asthma, dermatophytosis, cesarean sections, laparoscopic gastric band surgery, tonsillectomy, omentectomy, and adenoidectomy. Medications taken at the time of the event included aprepitant, lorazepam, omeprazole, ondansetron, prochlorperazine, citalopram, spironolactone, vitamin D3, Vicodin[®], fluoxetine, fexofenadine, hyoscyamine, ProAir[®] HFA, Proventil[®] HFA, lisinopril-hydrochlorothiazide, hydrocodone-acetaminophen, Aleve[®], and gabapentin.


Wound complication is an expected event for bevacizumab.

There have been 32,044 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, it is felt that a possible causal relationship exists between the event and the investigational agent bevacizumab.

	Wound complication
Bevacizumab/placebo	Possible
Cyclophosphamide	Unlikely
Doxorubicin	Unlikely
Pegfilgrastim	Unrelated
Invasive breast carcinoma	Unrelated
Prior history of ventral hernia	Possible

Date: 5/6/11

Signature: 
Helen Chen, M.D.
(IDB Monitor for bevacizumab)

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

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Genentech, Inc.