



DATE: DEC 15 2010

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report #2, AE# 1295253

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 63-year-old female with invasive breast carcinoma died of colitis while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, paclitaxel, and pegfilgrastim.

The attached report has been amended to reflect a change in attribution. 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.

ADVERSE EVENTS ASSESSMENT

IND 7921	ADVERSE EXPERIENCE REPORT NO.
NSC 704865	IND Safety Report: #2
Bevacizumab (rhuMab VEGF)	Event: Gr. 5: Colitis
AE: 1295253	Protocol: E5103

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The patient was a 63-year-old female with invasive breast cancer who died of colitis while on a phase 3 study using the investigational agent bevacizumab in combination with doxorubicin, cyclophosphamide, paclitaxel, and pegfilgrastim. She began her first course of treatment on September 18, 2009. She received bevacizumab/placebo 10 mg/kg IV over 30-90 minutes on Day 1, doxorubicin 60 mg/m² IV over 20-30 minutes on Day 1, cyclophosphamide 600 mg/m² IV over 20-30 minutes on Day 1, and pegfilgrastim 6 mg SQ on Day 2, every 14 days, for Cycles 1-4. She was to have received 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, for Cycles 5-8. She received her last doses of bevacizumab, doxorubicin, and cyclophosphamide on November 6, 2009 (Cycle 4, Day 1), and her last dose of pegfilgrastim on November 7, 2009 (Cycle 4, Day 2). She never received paclitaxel.

The patient was diagnosed with invasive breast carcinoma in June 2009, and was status post bilateral mastectomy in August 2009. She began the investigational agent on September 18, 2009.

On November 13, 2009 (Cycle 4, Day 8), the patient presented to the emergency room after sustaining a fall at home. On physical examination, she was severely dehydrated, and had a temperature of 100.7 F. Her blood pressure was 90/70 mmHg, and her pulse rate was 120 bpm. She was pancytopenic with a white blood cell count of $0.2 \times 10^9/L$ (reference range: $5.0-10.0 \times 10^9/L$), an absolute neutrophil count of $0.0 \times 10^9/L$ (reference range: $2.0-9.0 \times 10^9/L$), platelet count of 17 K/cumm (reference range: 150-450 K/cumm), and hemoglobin of 8.1 gm/dL (reference range: 12.0-16.0 gm/dL). The patient was admitted, pan-cultured, and started on Fortaz[®] and IV vancomycin. On November 14, 2009 (Cycle 4, Day 9), her stool culture was positive for *Clostridium difficile*, and she was started on IV Flagyl[®], fluconazole, and acyclovir. Over the course of the hospitalization, she was transfused PRBCs and platelets.

On November 15, 2009 (Cycle 4, Day 10), the patient complained of persistent nausea, weakness, and non-bloody diarrhea. Her physical examination was significant for tachycardia. On November 17, 2009 (Cycle 4, Day 12), she was started on total parenteral nutrition. Her examination during an infectious disease consult on November 18, 2009 (Cycle 4, Day 13), revealed a soft, distended abdomen with mild generalized tenderness, and a pre-existing severe mucositis which was unchanged. The IV vancomycin, and Fortaz[®] were discontinued, and the IV Flagyl[®], oral vancomycin, fluconazole, and acyclovir were continued. The patient continued to have diarrhea and a distended abdomen.

On November 20, 2009 (Cycle 4, Day 15), the patient's condition deteriorated as she became restless and confused. She was given Ativan[®], and she later became difficult to arouse. A CT scan of the abdomen and the pelvis showed diffuse wall thickening throughout the colon consistent with colitis. On November 21, 2009 (Cycle 4, Day 16), the patient was made Do Not Resuscitate (DNR)/supportive care. She became less and less responsive and on November 22, 2009 (Cycle 4, Day 17), died with her family at her bedside. It was felt that the event was a treatment-related death, that the patient's condition involved more than the *C. difficile* colitis, and that she suffered some type of irreversible bowel complication such as ischemia, necrosis or a typhlitis type of process. The patient's family did not want an autopsy.

The patient's past medical and surgical history was significant for hypertension, a total abdominal hysterectomy and bilateral salpingo-oophorectomy in 2004, and port placement. Her family history is positive for a history of breast cancer in her mother. Medications taken at the time of the event were Toprol[®], Xanax[®], Lomotil[®] and Zofran[®].

Colitis is a known event for bevacizumab.


There have been 27,798 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

~~In this case, there is a probable relationship between the event and bevacizumab. The patient was unblinded and found to have received placebo.~~

	Colitis
Bevacizumab (rhUMAb VEGF)	Probable Unrelated
Doxorubicin	Possible
Cyclophosphamide	Possible
Pegfilgrastim	Unrelated
Invasive breast cancer	Unlikely
Perforation	Probable

Date: 13 Dec 2006

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.