



DATE: MAR 21 2011

FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI *cc for HE*

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1852653

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 44-year-old female with invasive breast carcinoma experienced a grade 5 skin infection (necrotizing fasciitis) while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, and paclitaxel.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF) AE: 1852653	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 5: Infection: Skin: Necrotizing fasciitis Protocol: E5103
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The patient was a 44-year-old female with invasive breast carcinoma who expired from a skin infection (necrotizing fasciitis) while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, and paclitaxel. She did not receive paclitaxel. The patient began her first course of treatment on March 16, 2010, receiving bevacizumab/placebo 15 mg/kg IV over 30-90 minutes on Day 1, doxorubicin 60 mg/m² IVP on Day 1, and cyclophosphamide 600 mg/m² IV over 20-30 minutes on Day 1, every 21 days. She received her last doses of bevacizumab/placebo, doxorubicin, and cyclophosphamide on June 9, 2010 (Cycle 4, Day 1).

The patient was diagnosed with invasive breast carcinoma which was estrogen receptor positive in December 2009, and was status post partial mastectomy with sentinel node biopsy. She began the investigational agent on March 16, 2010.

On June 15, 2010 (Cycle 4, Day 7), the patient presented to the clinic with a 2 to 4-day history of fever, and left groin swelling and pain. She had a temperature of 103.1°F, a tender left groin region, and a small white head deep inside the folds of her left groin. There was no obvious exudate or expressible discharge. The patient's white blood cell (WBC) count was 0.7 × 10⁹/L (reference range: 5.0-10.0 × 10⁹/L), and her ANC was 0 (reference range: 2500-8000/mm³). The patient was treated with vancomycin and IV fluids and sent to the hospital for urgent admission. Her WBC at the hospital was 0.3 × 10⁹/L. A CT scan of the pelvis was suspicious for subcutaneous edema and emphysema without a clear abscess. The patient was found to have necrotizing fasciitis. She was started on clindamycin, daptomycin, and Azactam®. On June 17, 2010 (Cycle 4, Day 9), the patient underwent wound exploration and debridement with Versajet®, which was well tolerated.

On July 15, 2010 (Cycle 4, Day 37), the patient, who had been improving, developed a fever of 103°F, diarrhea, and leukocytosis. Her WBC count was 16.1 × 10⁹/L, with 9% banded neutrophils, and 83% segmented neutrophils. The patient's urinalysis showed a large amount of leukocyte esterase with 0 to 2 white blood cells, positive nitrites, and 4+ bacteria. It was recommended that she continue on Zosyn® and vancomycin, and that stool for *Clostridium difficile* toxin be obtained. The next day, her blood cultures were positive for *Pseudomonas*, and she was started on tobramycin.

On July 19, 2010 (Cycle 4, Day 41), the patient underwent another wound debridement, irrigation, and skin grafting. She also developed a skin rash with desquamation and underlying erythema around her neck, arms, chest, upper abdomen, and thighs. On July 20, 2010 (Cycle 4, Day 42), she was removed from the protocol. On July 23, 2010, the patient was evaluated by a dermatologist, who considered the possibilities of acute generalized exanthematous pustulosis, miliaria, and/or disseminated candidiasis. A shave skin biopsy revealed subcorneal collections of neutrophils, and sparse superficial mononuclear cells, and rare eosinophils in the dermis. Periodic Acid Schiff (PAS) and gram stains were negative for fungus and bacteria. The overall picture was suggestive of subcorneal pustular dermatitis.

On August 9, 2010, the patient went into septic shock in the ICU. She remained hemodynamically unstable despite increasing fluid and pressors. The following day, the patient went into asystole and expired. An autopsy was not performed.

The patient's past medical and surgical history was significant for hypertension, obstructive sleep apnea, morbid obesity, problems with visual acuity thought to be related to hypertensive retinopathy, mild chronic kidney disease, type 2 diabetes, and port placement. Medications taken at the time of the event were insulin, Diovan[®], carvedilol, furosemide, hydralazine, metformin, metolazone, simvastatin, Colace[®], multivitamins, potassium chloride, and vitamin D.

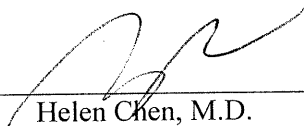
Infections are known events for bevacizumab.

There have been 31,362 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, a causal relationship between the event and bevacizumab/placebo cannot be excluded. The treatment assignment is unknown.

	Necrotizing fasciitis
Bevacizumab/placebo	Possible
Doxorubicin	Possible
Cyclophosphamide	Possible
Pegfilgrastim	Unrelated
Invasive breast cancer	Unrelated

Date: 3/18/11

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.