



**DATE:** APR 01 2011  
**FROM:** Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
**SUBJECT:** Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1523186  
**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 73-year-old female with stage III-C serous adenocarcinoma of the fallopian tube developed grade 4 necrotic skin infection and died of sepsis while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with paclitaxel and carboplatin.

## ADVERSE EVENTS ASSESSMENT

IND <b>7921</b> NSC <b>704865</b> <b>Bevacizumab</b> <b>(rhuMab VEGF)</b>  AE: <b>1523186</b>	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # <b>1</b> Event: <b>Gr. 5: Infection with unknown</b> <b>ANC: Blood</b> <b>Gr. 4: Infection – Other: Necrotic</b> <b>skin infection</b>  Protocol: <b>GOG-0252</b>
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The patient was a 73-year-old female with stage III-C serous adenocarcinoma of the fallopian tube who developed a necrotic skin infection and sepsis and subsequently died while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with paclitaxel and carboplatin. She began her first course of treatment on October 18, 2010, receiving paclitaxel 80 mg/m<sup>2</sup> IV over 1 hour on Days 1, 8, and 15, carboplatin AUC 6 IV on Day 1, and bevacizumab 15 mg/kg IV over 30-90 minutes on Day 1, beginning with Cycle 2, every 21 days for Cycles 1 to 6 during Phase A. The patient was to receive bevacizumab 15 mg/kg IV over 30-90 minutes on Day 1 of Cycles 7-22 during Phase B. She received her last doses of bevacizumab, paclitaxel, and carboplatin on January 12, 2011 (Cycle 5, Day 1).

The patient was diagnosed with stage III-C serous adenocarcinoma of the fallopian tube in August 2010, and was status post total abdominal hysterectomy with bilateral salpingo-oophorectomy and multiple-agent systemic chemotherapy. She began the investigational treatment on October 18, 2010.

On October 22, 2010 (Cycle 1, Day 5), the patient was admitted and treated for multiple health problems including worsened right lower quadrant abdominal pain, pneumonia, pleural effusion, respiratory distress, anemia, ascites, peritonitis, and atrial fibrillation. She was discharged home on November 15, 2010 (Cycle 2, Day 8) after which she developed sacral decubitus ulcers which had progressively worsened.

On January 12, 2011 (Cycle 5, Day 1), the patient returned to the clinic for treatment and complained of multiple areas of progressive skin breakdown, left-sided abdominal pain around her gastrostomy-jejunostomy tube site, persistent diarrhea, progressive weakness, decreased appetite, and failure to thrive. The patient received the investigational treatment as scheduled and she was admitted to the hospital for failure to thrive and anemia. She was started on IV fluids and Lomotil<sup>®</sup>. Per site, the patient's stool was not tested for *Clostridium difficile*. The patient was transfused with 3 units of packed red blood cells (PRBC).

On January 13, 2011, her WBC was 1.7 ×10<sup>9</sup>/L (reference range: 4.5-11.0 ×10<sup>9</sup>/L) and her hemoglobin increased to 12.4 g/dL. The following day, she had a WBC of 0.3 ×10<sup>9</sup>/L, lactic acid of 3.4 mg/dL (reference range: 0.5-2.2 mg/dL), and a potassium of 2.9 mEq/L (reference range: 3.4-5.0 mEq/L). The patient had a temperature of a 102.2°F. The chest X-ray later that day revealed bibasilar atelectasis or infiltrate and trace bilateral effusions. An ECG showed atrial fibrillation with rapid ventricular response. The patient was transferred to the ICU and started on 2 liters of oxygen. Her systolic blood pressure was in the 100s. She developed dyspnea and lower back pain. The patient was started on morphine, IV Levophed<sup>®</sup>, Diflucan<sup>®</sup>, vancomycin, Invanz<sup>®</sup>, and potassium replacement.

On January 15, 2011, the patient again developed a fever with a temperature of 102.9°F. She had anasarca, bilateral lower extremity rash and skin denudation, and necrotic skin in the area of her posterior right thigh and sacral area. A repeat chest X-ray showed pulmonary congestion with perihilar edema. The patient was diagnosed with neutropenic sepsis, necrotic ulcers on her posterior right thigh and sacral area, nonhealing percutaneous endoscopic gastrostomy tube site, and ascites. The peritoneal fluid was aspirated. Per site, no surgical procedures were done for the necrotic skin infection and the peritoneal cavity fluid was not cultured. Her blood cultures were positive for *Escherichia coli*. The patient's

prognosis was graved, and she opted to stop further treatment. She was made do not resuscitate, and placed on comfort care. Her condition continued to deteriorate and she died later that day.


The patient's past medical and surgical history was remarkable for hypertension, diverticulitis, depression, anxiety, thyroid disease, arthritis, alopecia, and lumbar laminectomy. Medications taken at the time of the event included Celexa<sup>®</sup>, Lotensin<sup>®</sup>, PLH cream, triple mix swish, Nystop<sup>®</sup> powder, Imodium<sup>®</sup>, Nucynta<sup>®</sup>, clonidine, diltiazem, Synthroid<sup>®</sup>, Zocor<sup>®</sup>, Fragmin<sup>®</sup>, multivitamin, famotidine, and Dulcolax<sup>®</sup> suppository.

There have been 31,564 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, a causal relationship between the sepsis, necrotic skin infection, and bevacizumab cannot be excluded. Infections are known events for bevacizumab.

	<b>Infection with unknown ANC: Blood</b>	<b>Necrotic skin infection</b>
<b>Bevacizumab</b>	Possible	Possible
<b>Carboplatin</b>	Probable	Possible
<b>Paclitaxel</b>	Probable	Possible
<b>Fallopian tube carcinoma</b>	Unrelated	Unrelated
<b><i>Escherichia coli</i></b>	Definite	Unrelated
<b>Necrotic thigh/sacral infection</b>	Probable	Definite

Date: 3/30/11

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

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

cc: Arthur Cannon  
Gilbert Jirau-Lucca, M.S.  
Safety Contact: onc\_drug.safety@gene.com  
Genentech, Inc.