

**IND SAFETY REPORT: FOLLOW-UP #1**TO: *Division of Biologic Oncology Products, Center for Drug Evaluation and Research, FDA*

FAX: 301-796-9849

1. IND NUMBER  
79212. AGENT NAME  
Bevacizumab (rhuMAb VEGF)3. DATE  
May 29, 20094. SPONSOR  
Division of Cancer Treatment and Diagnosis, National Cancer Institute5. REPORTER'S NAME, TITLE, AND INSTITUTION  
Kevin Conlon, MD – Senior Investigator, Investigational Therapeutics III,  
Investigational Drug Branch, CTEP, DCTD, NCI6. PHONE NUMBER  
301-496-11967. FAX NUMBER  
301-402-04288. PROTOCOL NUMBER (AE #)  
E5103 (1158823)9. PATIENT IDENTIFICATION  
5011810. AGE  
6811. SEX  
Female

## 12. DESCRIPTION OF ADVERSE EVENT

The patient is a 68-year-old female with invasive breast carcinoma who experienced grade 3 pulmonary hypertension and grade 2 pleural effusion while on a phase 3 study utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, filgrastim, and paclitaxel. She began her first course of the investigational therapy on March 11, 2008, and received the last doses of bevacizumab/placebo on July 22, 2008 (Cycle 8, Day 1), the last doses of doxorubicin and cyclophosphamide on April 22, 2008 (Cycle 4, Day 1), the last dose of filgrastim on May 1, 2008 (Cycle 4, Day 10), and the last dose of paclitaxel on August 5, 2008 (Cycle 8, Day 15). On May 8, 2009, the patient presented to the emergency room with complaints of a 4-day history of worsening dyspnea with exertion and a smothering sensation in the chest. She denied chest pain, nausea, vomiting, fever, or chills. Chest examination revealed decreased breath sounds with bilateral crackles. A chest X-ray revealed bilateral pulmonary edema with bibasilar atelectasis, and the EKG showed an incomplete left bundle-branch block. An echocardiogram showed an ejection fraction of 30-35%. The patient has a history of cardiomyopathy post chemotherapy with a previous exacerbation of CHF. She was started on oxygen, aspirin, and admitted to the hospital for further management of her symptoms. The patient responded well to treatment with IV diuretics, Coreg<sup>®</sup>, lisinopril and Aldactone<sup>®</sup>. She was discharged home on May 10, 2009, with instructions to follow-up with the cardiologist. Additional information has been requested from the investigational site. There is a reasonable possibility that the experience may have been caused by the drug.

## 13. DOSE, ROUTE, AND SCHEDULE

Cycles 1-4: Bevacizumab/Placebo 10 mg/kg IV over 30-90 minutes on Day 1 (Cycle = 14 days); Cycles 5-8: Bevacizumab/Placebo 15 mg/kg IV over 30-90 minutes on Day 1 (Cycles = 21 days)

## 14. DATES OF TREATMENT

The patient began the investigational therapy on March 11, 2008, and received the last dose of bevacizumab/placebo on July 22, 2008 (Cycle 8, Day 1).

## 15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 21,394. There have been 4 other incidences of pulmonary hypertension and 48 other incidences of pleural effusion reported to the NCI through ADeERS as serious adverse events for bevacizumab.

## 16. COMMENTS

The following was also administered: Cycles 1-4: Doxorubicin: 60 mg/m<sup>2</sup> IV on Day 1 and Cyclophosphamide: 600 mg/m<sup>2</sup> IV over 20-30 minutes on Day 1; Last administered on April 22, 2008 (Cycle 4, Day 1). Filgrastim: 5 mcg SQ on Day 2-11; Last administered on May 1, 2008 (Cycle 4, Day 10).  
Cycles 5-8: Paclitaxel: 80 mg/m<sup>2</sup> IV over 1 hour on Days 1, 8, and 15; Last administered on August 5, 2008 (Cycle 8, Day 15).

**FOLLOW-UP:**

**Based upon further investigation, the Senior Investigator at the Investigational Drug Branch has decided not to file this adverse event expeditiously.**

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