



National Institutes of Health  
National Cancer Institute  
Bethesda, Maryland 20892

**DATE:** June 29, 2009

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

**SUBJECT:** Bevacizumab (rhuMab VEGF) NCI IND Safety Report, AE# 1809441

**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 IND 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 this IND and/or NSC, and the total number of patients enrolled in trials under this IND and/or NSC.

A 45-year-old female with invasive breast carcinoma developed a **grade 2 pneumothorax** (spontaneous) while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, and paclitaxel.

## ADVERSE EVENTS ASSESSMENT

IND <b>7921</b> NSC <b>704865</b> <b>Bevacizumab (rhuMAb VEGF)</b> AE: <b>1809441</b>	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: <b>#1</b> <b>Gr. 2: Pneumothorax (spontaneous)</b> Protocol: <b>E5103</b>
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The patient is a 45-year-old female with invasive breast carcinoma who developed a pneumothorax while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, and paclitaxel. She began her first course of treatment on October 27, 2008, receiving bevacizumab/placebo 10 mg/kg IV over 30-90 minutes on Day 1, doxorubicin 60 mg/m<sup>2</sup> IVP on Day 1, cyclophosphamide 600 mg/m<sup>2</sup> IV over 20-30 minutes on Day 1, and pegfilgrastim 6 mg SQ on Day 2, every 14 days for Cycles 1-4. For Cycles 5-8, she received bevacizumab/placebo 15 mg/kg IV over 30-90 minutes on Day 1 and paclitaxel 80 mg/m<sup>2</sup> IV over 1 hour on Days 1, 8, and 15, every 21 days. She received the last dose of bevacizumab/placebo on February 24, 2009 (Cycle 8, Day 1).

The patient was initially diagnosed with stage II invasive breast carcinoma (T1, N1, M0) in June 2008 and is status post left lumpectomy and chemotherapy. She began the investigational therapy on October 27, 2008.

On February 27, 2009 (Cycle 8, Day 4), the patient presented to the ER after being awakened at approximately 2 AM by left-sided radiating chest pain which worsened throughout the night. A chest X-ray revealed a large left-sided pneumothorax (approximately 80%) and a questionable partially-healed left 10<sup>th</sup> rib fracture; a chest tube was placed by thoracic surgery. Her admission examination revealed an oxygen saturation of 96% on room air, blood pressure of 112/80 mm/Hg, respiratory rate of 20 per minute, pulse of 114 bpm, and temperature of 97.6° F. The patient's lung sounds were decreased in the left base, and the chest tube was in place. A repeat chest X-ray on February 28, 2009, revealed that the pneumothorax was stable, as was a small pneumomediastinum and left basilar atelectasis. A non-contrast chest CT scan showed moderate-sized left pneumothorax with left lower lobe atelectasis and posterior apical atelectasis.

Serial chest X-rays tracked the progress of the pneumothorax. On March 2, 2009 (Cycle 8, Day 7), a chest X-ray showed a slightly improved small left pneumothorax, small bilateral pleural effusions in the posterior costophrenic angles, and a small amount of left subcutaneous emphysema surrounding the insertion site of the left chest tube. On March 5, 2009 (Cycle 8, Day 10), a portable chest X-ray was performed which revealed minimal basal atelectasis and no evidence of a pneumothorax, and the patient's chest tube was removed. No clear etiology for the pneumothorax could be determined, although there was a concern that the patient's smoking history and/or the investigational therapy may have been factors. During her hospitalization, the patient was also diagnosed with and treated for left herpes zoster ophthalmicus with IV acyclovir. She was discharged on March 8, 2009 (Cycle 8, Day 13).

The patient's past medical/surgical history is significant for tobacco abuse, occasional marijuana, and a hernia repair. Her maternal grandmother had breast cancer in her 40s, her paternal grandmother had breast cancer in her 60s, her paternal aunt had possible uterine cancer, and her mother died of lung cancer at age 62. Medications taken at the time of the event included Ambien<sup>®</sup>, lorazepam, Klonopin<sup>®</sup>, Zofran<sup>®</sup>, Compazine<sup>®</sup>, Colace<sup>®</sup>, senna, Percocet<sup>®</sup>, Alcar<sup>®</sup>, and Preparation H<sup>®</sup>.

There have been 22 other cases of pneumothorax reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND as shown in the table below:


Adverse Event	Grade	Attribution
Pneumothorax (n = 22)	4 3 2	1 Possible, 1 Unlikely 1 Unlikely, 5 Unrelated 1 Possible, 8 Unlikely, 5 Unrelated

To date, a total of 21,442 patients have been 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 bevacizumab.

	<b>Spontaneous Pneumothorax</b>
<b>Bevacizumab (rhuMAb VEGF)</b>	Possible
<b>Cyclophosphamide</b>	Possible
<b>Doxorubicin</b>	Possible
<b>Paclitaxel (Taxol)</b>	Possible
<b>Pegfilgrastim (Neulasta)</b>	Unlikely
<b>Invasive breast carcinoma</b>	Unlikely

Date: 6/29/09

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.