



DATE: JUL 15 2011
FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1675188
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 this letter 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 56-year-old female with invasive breast carcinoma experienced grade 3 pneumonitis/pulmonary infiltrates while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, filgrastim or pegfilgrastim, and paclitaxel.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF) AE: 1675188	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 3: Pneumonitis/pulmonary infiltrates Protocol: E5103
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The patient is a 56-year-old female with invasive breast carcinoma who experienced pneumonitis/pulmonary infiltrates while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, filgrastim or pegfilgrastim, and paclitaxel. The planned protocol therapy the patient was assigned to is as follows:

Cycle = 14 days (Cycles 1-4)
 Bevacizumab/Placebo: 10 mg/kg IV over 30-90 minutes on Day 1
 Doxorubicin: 60 mg/m² IVP on Day 1
 Cyclophosphamide: 600 mg/m² IV over 20-30 minutes on Day 1
 Filgrastim: 5 mcg/kg SQ on Days 2-11; or pegfilgrastim: 6 mg SQ on Day 2

Cycle = 21 days (Cycles 5-8)
 Bevacizumab/Placebo: 15 mg/kg IV over 30-90 minutes on Day 1
 Paclitaxel: 80 mg/m² IV over 1 hour on Days 1, 8, and 15

The patient was diagnosed with invasive breast carcinoma in December 2010, and is status post left lumpectomy with axillary node dissection in December 2010. The patient began the investigational agent on February 3, 2011, and received the last dose of bevacizumab/placebo on May 12, 2011 (Cycle 7, Day 1), the last doses of doxorubicin and cyclophosphamide on March 17, 2011 (Cycle 4, Day 1), the last dose of pegfilgrastim on March 18, 2011 (Cycle 4, Day 2), and the last dose of paclitaxel on May 26, 2011 (Cycle 7, Day 15).

On June 2, 2011, the patient presented to the clinic with a low-grade fever, neuropathy of her fingers and toes, a burning sensation in both feet when weight bearing, weakness, and fatigue. Her lung examination was negative. The study agents were held, and urine culture/urinalysis was ordered. The patient was unblinded, and it was determined that she received bevacizumab. The patient was advised to go to the ER if her symptoms persisted.

On June 5, 2011, the patient presented to the ER with a sore throat and a 3-day history of fever which she had been treating with Tylenol[®], and peaked at 102.9 °F. Upon examination, her temperature was 101 °F, blood pressure was 124/76 mmHg, pulse rate was 137 bpm, and respiratory rate was 22 breaths per minute. Her oxygen saturation was 96% on room air. She was started on IV fluids with IV vancomycin and Maxipime[®]. On the morning of June 6, 2011, the patient was admitted for a fever of unknown origin (atypical infection vs. drug induced pneumonia). She was continued on antibiotics and started on oxygen 2 L/min via nasal cannula. A chest X-ray showed clear lungs without consolidation, mass, or infiltrate. There was no radiographic evidence for pneumonia or other acute cardiopulmonary disease. However, on June 7, 2011, a chest/thorax CT scan (April 13, 2011, comparison) revealed new significant airspace disease demonstrated by bilateral diffuse increased interstitial markings more prominent in the upper lobes. There were diffuse areas of ground glass and frank opacity; small nodular densities were also present. In addition, a small right pleural effusion was present. These findings were most concerning for an infectious or inflammatory process. Pulmonary edema and hemorrhage were less likely, and a drug reaction was also considered. She remained febrile with a temperature reaching 103° F. The patient's blood, urine, and portacath cultures were negative. On June 8, 2011, the patient underwent a

bronchoscopy with bronchial lavage of the right middle lobe, which showed no malignancy and was negative for *Pneumocystis* or fungus. A transbronchial biopsy of the right lung revealed alveolated tissue with focally necrotizing granulomatous inflammation; it was negative for fungal, *Pneumocystis*, and acid-fast organisms. The patient was started on 3-day course of high dose steroids of Solu-Medrol[®], followed by a 10-day course of prednisone 60 mg, followed by a 4-week course of prednisone 40 mg, while continuing on prophylactic antibiotics. On June 10, 2011, a chest X-ray showed a moderate amount of improvement in the diffuse bilateral pulmonary opacification, and a small left pleural effusion. On June 14, 2011, the patient's fevers and her condition had improved with the use of steroids, and she was discharged with a final diagnosis of interstitial pneumonitis on antibiotics and prednisone.

At a follow-up visit on June 21, 2011, the patient reported that although oxygen was used at night, she felt she had improved. She was continued on a tapering dosage of prednisone and antibiotics. On July 5, 2011, a chest CT scan revealed minimal ground glass nodular opacities in the left upper lobe, which may represent residual infection or inflammation versus scarring. There was near-complete resolution of the previously visualized lung findings.

The patient's past medical/surgical history is significant for hypertension, diverticulitis, osteoporosis, lumbar disc disease, degenerative joint disease of the left knee, chronic lower back pain, radiculopathy, peripheral neuropathy, supraventricular tachycardia (SVT), interstitial necrotizing granulomatous pneumonia, ectopic pregnancy, left salpingectomy, 2 Cesarean sections, uterine ablation (2005) appendectomy, and discectomy of L3, L4, L5, and S1 (June 2010). Medications taken at the time of the event included Neurontin[®], Lopressor[®], Dyazide[®], Calcium Plus, vitamin D, Flexeril[®], Aleve[®], and Ativan[®].

There have been 199 other cases of pneumonitis/pulmonary infiltrates reported to the NCI through AdEERS as serious adverse events for bevacizumab as summarized in the table below:

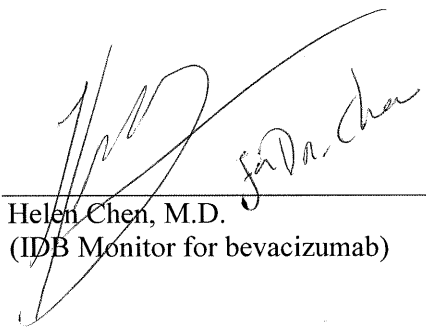
Adverse Event	Grade	Attribution
Pneumonitis/pulmonary infiltrates (n=199)	5	11 Unlikely, 3 Possible
	4	2 Unrelated, 14 Unlikely, 12 Possible, 3 Probable
	3	19 Unrelated, 45 Unlikely, 57 Possible, 8 Probable, 1 Definite
	2	7 Unrelated, 7 Unlikely, 5 Possible, 3 Probable
	1	1 Unrelated, 1 Possible

There have been 33,172 patients 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 the investigational agent.

	Pneumonitis/pulmonary infiltrates
Bevacizumab	Possible
Cyclophosphamide	Unrelated
Doxorubicin hydrochloride	Unrelated
Paclitaxel	Probable
Pegfilgrastim	Unrelated
Invasive breast carcinoma	Unrelated

Date: 7/13/11

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.