



DATE: APR 14 2011

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# **1483749**

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 66-year-old female with invasive breast carcinoma experienced grade 4 pneumonitis/pulmonary infiltrates while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, filgrastim/pegfilgrastim and paclitaxel.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF) AE: 1483749	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 4: Pneumonitis/pulmonary infiltrates Protocol: E5103
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The patient is a 66-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. She began her first course of treatment on August 18, 2010, receiving 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, and filgrastim 5 mcg/kg SQ on Days 2-11 or pegfilgrastim 6 mg SQ on Day 2, every 14 days for Cycles 1-4. During Cycles 5-8, she was to receive bevacizumab/placebo 15 mg/kg IV over 30-90 minutes on Day 1 and paclitaxel 80 mg/m² IV over 1 hour on Days 1, 8, and 15, every 21 days. She received the last dose of bevacizumab/placebo on December 3, 2010 (Cycle 6, Day 3), the last doses of doxorubicin, pegfilgrastim, and cyclophosphamide on October 20, 2010 (Cycle 4, Day 7), and the last dose of paclitaxel on December 8, 2010 (Cycle 6, Day 8).

The patient was diagnosed with invasive breast carcinoma in April 2010, and is status post right mastectomy with lymph node dissection. She began the investigational agent on August 18, 2010.

On December 14, 2010 (Cycle 6, Day 14), the patient presented to the emergency room with a 2-3 day history of shortness of breath, fever, dry cough, and sore throat and was admitted to the hospital. A chest x-ray revealed interval development of vague bibasilar opacities which may represent developing pneumonia.

On December 15, 2010, a chest CT scan revealed fibrotic changes of the upper lungs bilaterally, patchy areas of both ground glass and more consolidative opacities, which could represent multifocal pneumonia, cryptogenic organizing pneumonia, and/or sarcoidosis, as well as bilateral diffuse interstitial infiltration mostly in upper lobes which could represent intestinal pneumonitis secondary to current chemotherapy regimen. Despite antibiotics, the patient worsened and was transferred to the intensive care unit (ICU) with acute respiratory failure which required intubation. The patient underwent a bronchoscopy, and all cultures were negative. She was started on high-dose steroids and continued broad spectrum antibiotics, with quick improvement in her respiratory status. She was extubated 2 days after starting the steroids. The patient had a slow recovery in the ICU and was transferred to the respiratory unit, where she required a few days on BiPAP, CPAP, and face mask oxygen. The patient developed bilateral pleural effusions while in the ICU. Bronchoscopic cytology showed some atypical cells suggestive of adenocarcinoma, but ultimately, it was difficult to judge these cells in the setting of acute respiratory failure and intubation. The patient did not have an echocardiogram performed or a cardiology consultation. The patient gradually improved, and she was discharged on January 6, 2011, to a rehabilitation facility.

The patient's past medical and surgical history is significant for internal hemorrhoids, pancreatitis, hyperlipidemia, hypothyroidism, hypertension, osteopenia, uterine carcinoma, sarcoidosis, depression, vagal syncope, hysterectomy, thyroidectomy, deviated septum repair, and left axillary portacath. Medications taken at the time of the event included ondansetron and promethazine.

There have been 195 other cases of pneumonitis/pulmonary infiltrates reported to the NCI through AdEERS as serious adverse events under the bevacizumab NSC and/or IND as shown in the table below:


Adverse Event	Grade	Attribution
Pneumonitis/pulmonary infiltrates (n=195)	5	11 Unlikely, 3 Possible
	4	1 Unrelated, 14 Unlikely, 12 Possible, 3 Probable
	3	18 Unrelated, 45 Unlikely, 56 Possible, 7 Probable, 1 Definite
	2	6 Unrelated, 7 Unlikely, 5 Possible, 4 Probable
	1	1 Unrelated, 1 Possible

There have been 31,563 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 cannot be excluded.

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

Date: 4/6/11

Signature: 
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(IDB Monitor for bevacizumab)

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

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Genentech, Inc.