



DATE: MAR 09 2011

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1383388

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 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 these INDs and/or NSC, and the total number of patients enrolled in trials under these INDs and/or NSC.

A 58-year-old female with invasive breast carcinoma experienced grade 5 left ventricular systolic dysfunction while on a phase 3 study utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, paclitaxel, and filgrastim/pegfilgrastim.

ADVERSE EVENTS ASSESSMENT

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| IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF) | ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 5: Left ventricular systolic dysfunction |
| AE: 1383388 | Protocol: E5103 |

The patient was a 58-year-old female with invasive breast carcinoma who expired due to left ventricular systolic dysfunction while on a phase 3 study utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, paclitaxel, and filgrastim/pegfilgrastim. She began her first course of treatment on May 26, 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, filgrastim 5 mcg/kg SQ on Days 2-11 or pegfilgrastim 6 mg SQ on Day 2, every 14 days during Cycles 1-4. She then received 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 during Cycles 5-8. She received her last doses of bevacizumab/placebo and paclitaxel on September 29, 2010 (Cycle 8, Day 1), her last doses of doxorubicin and cyclophosphamide on July 7, 2010 (Cycle 4, Day 1), her last and only dose of filgrastim on September 2, 2010 (Cycle 7, day 16), and her last dose of pegfilgrastim on July 8, 2010 (Cycle 4, Day 2).

The patient was diagnosed with invasive breast carcinoma in March 2010, and was status post left partial mastectomy with initial sentinel node biopsy, complete axillary node dissection and mastopexy in March 2010, and left breast re-excisional biopsy in April 2010. She began the investigational therapy on May 26, 2010.

On May 12, 2010, the patient's baseline echocardiogram (Echo) revealed a calculated ejection fraction of 55%, which was within normal limits. There was no evidence of regional wall dyskinesia. On July 21, 2010 (Cycle 4, Day 15), a repeat Echo showed no change from the previous study in May 2010.

On October 6, 2010 (Cycle 8, Day 8), the patient presented to the clinic with a severe headache of several days, blurred vision, dyspnea, decreased oral intake, weakness, and was walking with a cane. Her blood pressure was 160/110 mmHg and heart rate 139 bpm. No obvious orthopnea, PND, or pedal edema was noted. The patient reported an occasional nonproductive cough. Her investigational treatment was held, and she was sent to the ER and admitted. The patient was started on IV fluids and oxygen, and a head CT scan was negative. A chest X-ray showed mild cardiomegaly with congestive changes and small pleural effusions. A CT scan also revealed similar findings with no obvious pulmonary embolism. At consultation with the pulmonologist, it was noted that the patient had more dyspnea when lying down, and it was felt that the dyspnea and small pleural effusions were mostly likely due to congestive heart failure. IV fluids were held.

On October 9, 2010, the patient underwent an echocardiogram which revealed severely depressed LV systolic function with an estimated LV ejection fraction of 10-15% and LV wall thickness; the LV chamber size was normal. There was also moderate mitral regurgitation, mild tricuspid regurgitation, and mild pulmonary hypertension (estimated right ventricular systolic pressure: 46 mmHg). The patient was started on spironolactone, digoxin and Coreg as well as lisinopril. According to discharge summary, the patient condition improved and she was discharged under stable condition on October 12, 2010. Discharge medications included digoxin, lisinopril and spironolactone.

On October 27, 2010, the patient was admitted again for severe shortness of breath, nausea and her blood pressure was low. She was sent to the ER, where the vital signs revealed a BP of 80/53 mmHg, pulse of 100/minute, temperature of 94 ° F and pulse ox of 99% on room air. Her BP improved to 130/80 mmHg

with hydration. She was admitted to the hospital and further work up revealed a markedly elevated digoxin level and a creatinine level of 3.5 mg/dL. She received cautious hydration and digoxin was held. The patient gradually improved clinically and the creatinine level improved to 2.5mg/dL. On November 1, 2010, she was discharged under stable condition. Her hypertensive and cardiac medications were adjusted upon discharge: digoxin was discontinued, and spironolactone and lisinopril were continued at reduced doses.

The patient was to be followed up at the clinic in two weeks after the last discharge from hospital on November 1. However, on November 12, 2010, the patient again presented to the ER with severe hypotension, lethargy, weakness, and was unresponsive. Her blood pressure was 40 by Doppler; pulse 122/minute (sinus); temperature approximately 93°F; and pulse ox 94% on 15L non-rebreather. Her skin was mottled and there were crackles bilaterally. Her creatinine was 4.7 mg/dL and hematocrit 36.8%. She was given IV fluids, oxygen, and started on Levophed®. The patient subsequently went into cardiac arrest with ventricular tachycardia. Resuscitation was attempted but not successful, and the patient expired in the ER. An echocardiogram was ordered but was not evaluable due to technical issues.

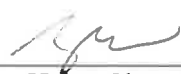
The patient's past medical and surgical history was significant for hypertension, hyperlipidemia, possible transient ischemic accident (TIA) (more than ten years ago), generalized anxiety disorder, partial tubal ligation, and hysterectomy.

There have been 31,449 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, the most likely cause of death is severe cardiomyopathy and decompensation. A possible relationship exists between the event and the investigational therapy bevacizumab.

| | Grade 5 Left ventricular systolic dysfunction |
|----------------------------------|--|
| Bevacizumab/placebo | Possible |
| Doxorubicin | Probable |
| Cyclophosphamide | Unlikely |
| Paclitaxel | Possible |
| Invasive breast carcinoma | Unrelated |
| Hypertension | Likely |

Date: 3/8/11

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

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

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