



DATE: July 13, 2009

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

SUBJECT: Bevacizumab (rhuMab VEGF) NCI IND Safety Report, AE# **1314985**

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

A 51-year-old female with invasive breast carcinoma **died suddenly** while on a double-blinded phase 3 trial using the investigational agent bevacizumab/placebo in combination with paclitaxel, doxorubicin, and cyclophosphamide.

ADVERSE EVENTS ASSESSMENT

| | |
|----------------------------------|-----------------------------------|
| IND 7921 | ADVERSE EXPERIENCE REPORT NO. |
| NSC 704865 | IND Safety Report: #1 |
| Bevacizumab (rhuMAb VEGF) | Event: Gr. 5: Sudden death |
| AE: 1314985 | Protocol: E5103 |

The patient was a 51-year-old female with invasive breast carcinoma who died suddenly while on a double-blinded phase 3 trial using the investigational agent bevacizumab/placebo in combination with paclitaxel, doxorubicin, and cyclophosphamide. The patient began her first course of treatment on November 20, 2008, 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 pegfilgrastim 6 SQ on Day 2, every 14 days (Cycles 1-4); and bevacizumab/placebo 15 mg/kg IV over 30-90 minutes on Day 1 and paclitaxel 80 mg/m² IV over 60 minutes on Days 1, 8, and 15, every 21 days (Cycles 5-8). The patient received her last doses of bevacizumab/placebo and paclitaxel on February 5, 2009 (Cycle 6, Day 1), her last doses of doxorubicin and cyclophosphamide on January 2, 2009 (Cycle 4, Day 1), and her last dose of pegfilgrastim on January 3, 2009 (Cycle 4, Day 2).

The patient was diagnosed with infiltrating ductal carcinoma, ER+/PR+, in October 2008 and is status post bilateral mastectomy. On November 11, 2008, the patient weighed 205 pounds, had a performance status of 0, a blood pressure of 158/84 mmHg, a left ventricular ejection fraction of 61%, and a mild aspartate aminotransferase (AST) elevation; she consented to participate in 2 clinical trials. On November 17, 2008, the patient was registered to the S0307 study, randomized to receive ibandronate. She began the E5103 investigational therapy on November 20, 2008.

During Cycle 1, the patient experienced nausea and vomiting after her course of bevacizumab and chemotherapy, and developed profound facial flushing and fluid accumulation as a result of dexamethasone. On December 4, 2008 (Cycle 2, Day 1), the patient had stable weight and hemoglobin. During Cycle 2, in addition to having nausea and vomiting, the patient experienced intermittent diarrhea, significant fatigue, and confusion. On December 18, 2008 (Cycle 3, Day 1), the patient had a heart rate of 113 beats per minute, but there were no other remarkable findings; blood pressure was 126/78 mmHg. Throughout Cycle 3, the patient experienced nausea, some memory loss, and fatigue. On January 2, 2009 (Cycle 4, Day 1), the patient weighed 194 pounds; command vital signs were reported normal. During Cycle 4, the patient experienced nausea, a weight loss of 9 pounds, and fatigue. On January 15, 2009 (Cycle 5, Day 1), the patient weighed 185 pounds, had a performance status of 1, alopecia, and a small fluid collection at the right mastectomy site. Laboratory results were significant for: hemoglobin 10.8 g/dL, potassium 3.4 mEq/L (reference range: 3.6-5.1 mmol/L) despite taking potassium supplements, and phosphorus 1.9 mg/dL (reference range: 2.5-4.5 mg/dL).

It was noted that the patient also had trace right ankle pitting edema. At her next appointment on February 5, 2009 (Cycle 6, Day 1), the patient cited a better energy level than it had been previously. Her weight was 180.4 pounds and her performance status was 0. Examination revealed normal vital signs, trace right ankle pitting edema, and was otherwise unremarkable. She was still taking ibandronate, and received bevacizumab that day.

On February 7, 2009 (Cycle 6, Day 3), the patient developed sudden-onset difficulty breathing and midline chest pain. She became quickly unresponsive and CPR was initiated by the patient's spouse. When EMS arrived, a combitube and left external jugular line were placed. The patient's initial cardiac rhythm was bradycardia with a heart rate in the 20s followed by ventricular fibrillation. After defibrillation, the patient's rhythm converted to asystole. Upon arrival to the ED, the patient's rhythm had converted back to ventricular fibrillation. During an initial exam, the patient was unresponsive. Her skin was cyanotic, cool, and mottled, pupils were unreactive, and lung sounds (while being ventilated via the combitube) were course and wet bilaterally. Resuscitation efforts were unsuccessful, and the patient expired. An autopsy was not performed. The treatment code was unblinded, and it was found that the patient was randomized to bevacizumab.

The patient's past medical/surgical history is significant for asthma, allergic rhinitis, previous tobacco abuse, and recent symptoms suggestive of a sinus infection with bronchitis on February 3, 2009. Medications taken at the time of the event included phenylephrine, guaifenesin, loratadine, albuterol, montelukast sodium, acetaminophen, Levaquin®, potassium chloride, and ibandronate.

There have been 35 other cases of sudden death and 55 cases of death NOS previously reported to the NCI as serious adverse events through ADEERS under the bevacizumab NSC and/or IND as shown in the table below:

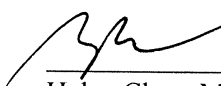
| Adverse Event | Grade | Attribution |
|---------------------|-------|--|
| Sudden Death (n=35) | 5 | 2 Unrelated, 3 Unlikely, 28 Possible, 2 Probable |
| Death NOS (n=55) | 5 | 11 Unrelated, 28 Unlikely, 16 Possible |

There have been 21,442 patients enrolled in NCI-sponsored clinical trials under this IND and/or NSC.

In this case, the etiology of the sudden pulmonary and cardiac arrest is uncertain but a possible causal relationship to the treatment regimen (bevacizumab and chemotherapy) cannot be ruled out.

| | Sudden death |
|----------------------------------|--------------|
| Bevacizumab | Possible |
| Cyclophosphamide | Unlikely |
| Paclitaxel | Possible |
| Doxorubicin hydrochloride | Possible |
| Pegfilgrastim | Unlikely |
| Invasive breast carcinoma | Unrelated |

Date: 7/14/09

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

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

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