



**DATE:** July 30, 2009

**FROM:** Kevin Conlon, M.D., Senior Investigator, Investigational Drug Branch, CTEP, DCTD, NCI

**SUBJECT:** Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE # **1293580**

**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 IND 7921 or 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 75-year-old female with ovarian epithelial carcinoma died from an opportunistic infection while on a phase 3 study utilizing the investigational agent bevacizumab/placebo in combination with carboplatin and paclitaxel.

## ADVERSE EVENTS ASSESSMENT

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|--|--|
| IND <b>7921</b><br>NSC <b>704865</b><br><b>Bevacizumab (rhuMab VEGF)</b> | ADVERSE EXPERIENCE REPORT NO.<br>IND Safety Report: <b>#1</b><br>Event: <b>Gr. 5: Opportunistic infection associated with &gt;=Grade 2 Lymphopenia</b> |
| AE: <b>1293580</b>   | Protocol: <b>GOG-0218</b>  |

The patient was a 75-year-old female with stage IIIC ovarian epithelial carcinoma who died of an opportunistic infection while on a phase 3 study utilizing the investigational agent bevacizumab/placebo in combination with carboplatin and paclitaxel. She began the first course of treatment on January 13, 2009, receiving carboplatin AUC 6 IV over 30 minutes on Day 1 and paclitaxel 175 mg/m<sup>2</sup> IV over 3 hours on Day 1, every 21 days for 6 cycles. She received bevacizumab/placebo 15 mg/kg on Day 1, every 21 days, starting with Cycle 2 for a total of 5 cycles. The patient received her last dose of bevacizumab/placebo on April 21, 2009 (Cycle 5, Day 1). She received her last doses of carboplatin and paclitaxel on April 21, 2009 (Cycle 5, Day 1).

The patient was diagnosed with mucinous adenocarcinoma in December 2008 and was status post total abdominal hysterectomy, bilateral salpingo-oophorectomy, tumor debulking and staging, and omentectomy. She began the investigational therapy on January 13, 2009.

On April 23, 2009 (Cycle 5, Day 3), the patient presented to the emergency room (ER) with multiple complaints including nausea and vomiting since her last treatment, the inability to maintain any oral intake, and a 2-week history of cough which had worsened over the past 2-days. She also reported dyspnea with episodes of emesis and coughing, extreme fatigue with the inability to ambulate independently over the past 2-days, increased abdominal distension from her baseline over the past 2-4 days, abdominal and severe back pain, and urinary incontinence. The patient described the emesis as dark brown to black but denied a coffee ground character or blood in the emesis. Physical examination in the ER and during admission revealed the following remarkable findings: 92% oxygen saturation on room air (97% on 2 liters of oxygen), bibasilar coarse and decreased breath sounds in the lungs, and a soft, moderately distended, nontender abdomen with a fluid wave suggesting ascites, hypoactive bowel sounds, tympany in all 4 quadrants, no clear organomegaly, no rebound or guarding, and a midline surgical incision that appeared to be healing well. She had 2+ pitting edema of the lower extremities up to the knees which was unchanged from the past 4-6 weeks. Laboratory results showed a WBC of  $7.9 \times 10^9/L$  (reference range:  $3.8-9.8 \times 10^9/L$ ), hemoglobin of 11.6 g/dL (reference range: 12.1-15.3 g/dL), and a platelet count of  $136 \times 10^9/L$  ( $150-450 \times 10^9/L$ ). Note that the patient received 2 units of PRBCs in the clinic the previous day. A CT scan of the abdomen and pelvis showed massive ascites in the abdomen and pelvis, significant gastroesophageal reflux, and a cirrhotic liver. The patient was given Zofran<sup>®</sup>, morphine for pain, had a nasogastric tube inserted, and kept NPO ("nothing by mouth").

On April 24, 2009 (Cycle 5, Day 4), a chest X-ray revealed poor inspiration, small bilateral pleural effusions, and no infiltrate. The nasogastric tube drained 860 cc of fluid overnight. Laboratory reports showed pancytopenia, and the patient was given 2 units of fresh frozen plasma. A CT-guided paracentesis drained 20 cc of yellow-tinged clear fluid; the peritoneal drain placed after the procedure yielded 11 liters of clear yellowish fluid in approximately 24 hours. The patient's vital signs remained stable, and she reported improvement of the nausea, vomiting, and abdominal pain. The pathology report of the abdominal fluid showed rare chronic inflammatory cells in a background of amorphous proteinaceous material and no diagnostic malignant cells, while the gram stain and culture showed few WBCs and no organisms. On April 25, 2009, the patient developed mental status changes and a temperature of 102° F with chills, dyspnea, hypotension (blood pressure 70/30 mmHg), a pulse of 110 bpm, varying oxygen saturations ranging from 60-80%, and bilateral lung crackles. She continued to

deteriorate clinically, and it was suspected that her symptoms were secondary to sepsis. After consulting with the patient's family, she was made DNR ("do not resuscitate") and provided with comfort measures. The patient expired at 3:33 am on April 26, 2009 (Cycle 1, Day 6). An autopsy was not performed.

The patient's past medical and surgical history was significant for hypertension, diabetes, seizure disorder, bilateral knee replacements, appendectomy, and bilateral tubal ligation. Medications taken at the time of the event included Coumadin®, Dilantin®, carvedilol, lovastatin, phenobarbital, docusate sodium, and Compazine®.

There have been 18 other cases of opportunistic infection as serious adverse events through AdEERS under the bevacizumab NSC and/or IND.

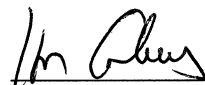
| Adverse Event                  | Grade  | Attribution   |
|--------------------------------|--------|---|
| Opportunistic infection (n=18) | 3<br>2 | 1 Probable, 2 Possible, 7 Unlikely; 3 Unrelated<br>1 Possible, 1 Unlikely |

There have been 21,541 patients enrolled in NCI-sponsored clinical trials under this IND and/or NSC.

In this case, it is thought that a causal relationship between bevacizumab and the event could not be excluded.

|                           | Opportunistic infection |
|---------------------------|-------------------------|
| Bevacizumab               | Probable                |
| Carboplatin               | Probable                |
| Paclitaxel (Taxol)        | Probable                |
| Ovarian epithelial cancer | Unrelated               |

Date: 30 July 2009

Signature:   
 Kevin Conlon, M.D.  
 (IDB Monitor for bevacizumab)

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

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 Genentech, Inc.