



DATE: MAR 29 2011

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1659292

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.

An 80-year-old female with invasive breast carcinoma experienced grade 5 Adult Respiratory Distress Syndrome (ARDS) while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with nab-paclitaxel.

ADVERSE EVENTS ASSESSMENT

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| IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF) AE: 1659292 | ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 5: Adult Respiratory Distress Syndrome Protocol: CALGB-40502 |
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The patient was an 80-year-old female with invasive breast carcinoma who expired due to Adult Respiratory Distress Syndrome (ARDS) while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with nab-paclitaxel. She began her first course of treatment on July 1, 2010, and was to receive bevacizumab 10 mg/kg IV over 30-90 minutes on Days 1 and 15, and nab-paclitaxel 150 mg/m² IV over 30 minutes on Days 1, 8, and 15, every 28 days. She received her last and only dose of bevacizumab on July 1, 2010 (Cycle 1, Day 1), and her last dose of nab-paclitaxel on July 8, 2010 (Cycle 1, Day 8).

The patient was initially diagnosed with invasive breast carcinoma in April 2003 and was status post left mastectomy and hormonal therapy. On June 10, 2010, a CT scan of the chest, abdomen, and pelvis showed extensive bony metastatic changes manifested by numerous sclerotic lesions in the thoracic spine, ribs, right scapula, and right humeral head which were compatible with widespread metastatic disease. Other findings included a presumed metastatic small effusion, extensive left lower lobe compressive atelectasis secondary to a combination of the mass and the pleural effusion, emphysema, and a recurrent soft tissue mass in the right chest wall presumably in the region of the right mastectomy. On June 21, 2011, a whole body PET and CT scan showed diffuse presumably metastatic disease from the patient's previous left breast cancer. She began the investigational therapy on July 1, 2010.

On July 12, 2010 (Cycle 1, Day 12), the patient presented to the ER with a 2 to 3 day history of worsening dyspnea, cough, and generalized weakness. She was hypoxic with decreased breath sounds in both lung bases and an oxygen saturation of 52% on room air. The patient was started on oxygen via 100% non-rebreather mask which increased her oxygen saturation to 88%. She was then placed on a BIPAP machine. A chest X-ray showed bilateral pleural effusions with atelectasis. The patient was admitted to the ICU and started on IV Levaquin[®], Avelox[®], and ceftriaxone, nebulizers, Lasix[®], and Lovenox[®]. The patient was made do not resuscitate/do not intubate (DNR/DNI). On July 13, 2010 (Cycle 1, Day 13), a CT scan of the chest confirmed large bilateral pleural effusions with associated atelectasis in both lung bases. There were also multiple sclerotic areas throughout all the visualized vertebrae in the lower cervical, thoracic and upper lumbar region, the rib cage, as well as the left scapula, which was consistent with metastatic disease. The patient was transfused with 2 units of leukocyte-poor packed red blood cells for a hemoglobin of 8.0 g/dL (reference range: 12.0-15.6 g/dL), which increased her hemoglobin to 9.2 g/dL the next day. On July 14, 2010, the patient underwent a right thoracentesis, which improved her breathing. The cytopathology findings were most consistent with macrophages and mesothelial cells, and were unremarkable for malignant cells. An echocardiogram showed a large right pleural effusion and no pericardial effusion. There is no baseline echocardiogram for comparison.

On July 15, 2010 (Cycle 1, Day 15), the patient developed bilateral pneumothoraces which was felt to be more related to her cancer. The left pleural effusion resolved and the right pleural effusion was smaller as compared to the previous study. There was still some atelectasis of the left lung. Bilateral chest tubes were placed and the chemotherapy was held. A repeat chest X-ray the next day showed left basilar consolidation and/or undrained fluid, and there was pulmonary vascular congestion with increased interstitial lung markings which were likely pulmonary edema. On July 19, 2010, a bronchoscopy with bronchoalveolar lavage showed patent bronchi without any endobronchial lesions. Mucus plugs were aspirated. A repeat thoracentesis that day removed 1200 cc of straw colored fluid. A chest X-ray status post the bronchoscopy showed no evidence of pneumothorax. On July 21, 2010, following a pleurodesis to stop drainage from the left chest tube, the patient became hypoxic requiring 24 hours of mechanical

ventilation after which her condition improved. On July 22, 2010, the patient had a brief episode of supraventricular tachycardia which resolved after treatment with IV Cardizem®. An CT scan of the chest on July 27, 2010, revealed new probable obstruction of the left main stem of the bronchus which was possibly due to mucus plugging, a probable pneumothorax and a probable hydropneumothorax on the left chest, an unchanged small right pleural effusion, and a near whiteout left hemithorax which was probably persistent atelectasis.

On July 30, 2010 (Cycle 1, Day 16), the chest X-ray findings were consistent with worsening consolidation/atelectasis/ infiltrate/postobstructive pneumonitis/pleural effusion on the left and worsening atelectasis/infiltrate in the right mid-lung, right middle lobe and lower lobe with a persistent moderate right pleural effusion.

A repeat bronchoscopy to remove mucus plugging was successfully performed on August 2, 2010. On August 3, 2010, the patient received and tolerated chemotherapy; however, she later developed respiratory distress. On August 4, 2010, the patient continued to receive comfort care and she was given morphine. She died later that day.

The patient's past medical and surgical history was significant for hypertension, coronary artery disease, osteopenia, myocardial infarction, tonsillectomy, cardiac catheterization, cholecystectomy, and hysterectomy. Medications taken at the time of the event included Prilosec®, oxycodone, nifedipine, and metoprolol.

There have been 18 other cases of ARDS 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 |
|---------------|-------|---|
| ARDS (n=18) | 5 | 5 Unlikely |
| | 4 | 4 Unrelated, 4 Unlikely, 1 Possible, 2 Probable |
| | 3 | 2 Unlikely |

There have been 31,495 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, a possible relationship exists between the event and bevacizumab therapy.

| | ARDS |
|------------------------------------|----------|
| Bevacizumab | Possible |
| Nab-paclitaxel | Unlikely |
| Invasive breast carcinoma | Possible |
| Pleural effusion | Possible |
| Bilateral pneumothoraces | Probable |
| Post-thoracentesis pulmonary edema | Possible |
| Pneumonia | Possible |

Date: 3/28/11

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.