



DATE: FEB 28 2011

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1803480

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 64-year-old female with invasive breast carcinoma experienced grade 4 cerebritis, grade 4 orbital cellulitis and grade 4 pneumonia, while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with nab-paclitaxel.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMab VEGF)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 4: Infection with normal ANC: Left orbital cellulitis Gr. 4: Infection: Cerebritis Gr. 4: Infection with normal ANC: Lung (pneumonia)
AE: 1803480	Protocol: CALGB-40502

The patient is a 64-year-old female with invasive breast carcinoma who experienced cerebritis, ARDS, left orbital cellulitis, pneumonia, and asystole while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with nab-paclitaxel. She began her first course of treatment on September 21, 2009, receiving 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 doses of bevacizumab and nab-paclitaxel on July 1, 2010 (Cycle 10, Day 15).

The patient was diagnosed with invasive breast carcinoma in August 2009. She began the investigational treatment on September 21, 2009.

On July 21, 2010, the patient presented to the clinic with a tooth abscess, and she was treated with oral antibiotics prescribed by her primary care physician. On July 29, 2010, the patient returned to the clinic for treatment. Although she had been scheduled for a dental appointment that day, the patient refused to keep that appointment, stating that her tooth was better. She reported a 1-week history of pain, itching, and swelling of her left eyelid that had become progressively worse. She had a markedly reddened, swollen, and draining left eyelid. She was referred to the emergency room where she underwent incision and drainage of her left eyelid abscess, and she was given clindamycin. The patient was admitted to the hospital and started on IV vancomycin and Unasyn[®]. A CT scan of the orbit, sella, and internal auditory canal later that day showed a pre-existing large destructive process at the base of the skull with destroyed left clivus and left sphenoid bone at the base of the middle cranial fossa, complete opacification or near complete opacification of the left maxillary, left ethmoid and left frontal sinuses, and an abscess in the left superior eyelid which extended into the postseptal upper orbit adjacent to the superior rectus muscle. These findings were confirmed by an MRI of the orbits on July 30, 2010. Her antibiotic therapy was switched to vancomycin, ceftriaxone, and Flagyl[®].

On August 4, 2010, the patient had the following surgical procedures performed: a left frontal craniotomy, irrigation and debridement of the left frontal epidural and subdural abscess, excision of the left frontal pole cerebritis and early abscess formation, irrigation and debridement of the left frontal and ethmoidal sinus infection, cranialization of frontal sinus, dural patch grafting, autologous tissue harvesting of the right contralateral pericranium, and placement of a lumbar drain. The left eyelid abscess culture grew *Streptococcus aeruginosa* and the patient was to be continued on ceftriaxone for six weeks from the date of surgery.

After surgery, the patient experienced hypoventilation requiring ventilation overnight. On August 5, 2010, the patient suffered a seizure and she was given Ativan[®] and started on Dilantin[®]. On August 7, 2010, a chest X-ray showed increasing nonspecific opacities at the lung bases which were considered to possibly be pulmonary edema. On August 8, 2010, the patient became hypotensive and developed acute respiratory failure. She was unresponsive but had a pulse. An emergent endotracheal intubation was performed and she was placed on mechanical ventilation. The patient was started on Levophed, IV hydrocortisone, cefepime, and Levaquin[®]. A CT scan of the chest that day showed new bilateral pleural

effusions as well compressive atelectasis. A portable chest X-ray later suggested new infiltrate/consolidation within the right mid lung, and the left lung. On August 15, 2010, a repeat portable chest X-ray showed worsened interstitial infiltrates that were likely pulmonary edema. On August 17, 2010, the patient's condition improved, and the tracheotomy tube was removed. She was discharged to a rehabilitation facility on August 19, 2010.

Repeat CT scans of the brain on August 12, 2010, showed persistent bifrontal extra axial fluid collections, resolving pneumocephalus, subdural blood, and left frontal lobe edema and/or post-operative change. Another follow-up CT scan on August 27, 2010, showed decreasing edema within the inferior aspect of the left frontal lobe, improving aeration of the ethmoid air cells, and persistent opacification of the left frontal sinus as compared to the study of August 12, 2010. Per site, there is no further information available.


The patient's past medical and surgical history is unremarkable. Medications taken at the time of the event included Ultram®, cyanocobalamin, pyridoxine, and cholecalciferol.

There have been 31,384 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, a causal relationship between the orbital cellulitis and bevacizumab cannot be excluded. The pulmonary complications are likely related to the surgery and unlikely related to bevacizumab.

	Cerebritis	Left orbital cellulitis	Pneumonia
Bevacizumab	Possible	Possible	Unlikely
Nab-Paclitaxel	Unlikely	Unrelated	Unlikely
Invasive breast carcinoma	unrelated	Unrelated	Unrelated
Post-surgical complications	Unrelated	Probable	Possible
Tooth abscess	Probable	Probably	unrelated

Date: 2/24/11

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.