



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: February 20, 2009

To: NCCTG Primary Clinical Research Associates

From: Lynn Flickinger
Protocol Development Coordinator

Re: N0735, Phase II Trial of Albumin-Bound Paclitaxel in Combination with Gemcitabine and Bevacizumab in Patients with Metastatic Breast Cancer

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with Bevacizumab for a study where the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) is distributing this agent. You may have also received this communication directly from DCTD.

AE_1859262_F1

Please note that all risks currently cited in the NCCTG consent form cannot be omitted; it is at the discretion of your local IRB as to whether they wish to add risks based on the enclosed information. If a determination has been made by the NCCTG Research Base that a protocol amendment is necessary, you will receive the NCI-approved protocol addendum at a later date; for purposes of cross-reference, this communication will cite the adverse event noted above.


Please submit this adverse event to your Institutional Review Board.

If you have any questions concerning this communication, please contact Lynn Flickinger at Flickinger.lynn@mayo.edu or 507-538-7034.

LF/kjm
enclosure



DATE: November 21, 2008

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

SUBJECT: Bevacizumab (rhuMAb VEGF) and OSI-774 (erlotinib; Tarceva[®]) NCI IND Safety Report, AE# **1859262**

TO: Investigators Using Bevacizumab (NSC 704865) and Erlotinib (NSC 718781)

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 agents bevacizumab and erlotinib.

The following must be completed by all investigators using bevacizumab under NCI INDs 7921 and 11460 and erlotinib under NCI IND 63383:

- 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, 11460, and 63383, 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 and erlotinib, there does not appear to be a change in the risk-benefit ratio for bevacizumab and erlotinib 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's, and the total number of patients enrolled in trials under these INDs and/or NSC's.

A 32-year-old male with cholangiocarcinoma metastatic to the liver, retroperitoneum, and lungs experienced a grade 3 **pneumomediastinum** while on a phase 2 study using the investigational agent bevacizumab in combination with erlotinib.

ADVERSE EVENTS ASSESSMENT

IND 7921	63383	ADVERSE EXPERIENCE REPORT NO.
NSC 704865	718781	IND Safety Report: # 1
Bevacizumab (rhuMAb VEGF)	OSI-774 (erlotinib; Tarceva®)	Event: Gr. 3: Pneumomediastinum
AE: 1859262		Protocol: 7024

The patient is a 32-year-old male with cholangiocarcinoma metastatic to the liver, retroperitoneum, and lungs who experienced a pneumomediastinum while on a phase 2 study using the investigational agent bevacizumab in combination with erlotinib. He began his first course of treatment on August 28, 2007, receiving bevacizumab 5 mg/kg IV over 30 to 90 minutes on Days 1 and 15 and erlotinib 150 mg PO daily, every 28 days. The patient received his last dose of bevacizumab on August 26, 2008 (Cycle 14, Day 1), and the last dose of erlotinib on September 23, 2008 (Cycle 14, Day 29).

The patient was initially diagnosed with cholangiocarcinoma in May 2007, and is status post exploratory laparotomy and biopsy (the mass was found to be unresectable due to its vascular supply and proximity to the inferior vena cava). He began the investigational therapy on August 28, 2007, and completed 14 cycles of treatment (the Day 15 dose of bevacizumab was missed due to transportation issues) with no other serious adverse events.

On September 22, 2008 (Cycle 14, Day 28), the patient had routine chest, abdomen, and pelvic CT scans which revealed extensive mediastinal air extending from the gastroesophageal junction throughout the mediastinum and surrounding the pericardium with air extending into the supraclavicular regions bilaterally along the great vessels, greater on the right, and extremely tiny anterior pneumothoraces. On September 23, 2008, the patient was admitted to the hospital for a pneumomediastinum and possible esophageal tear (Boerhaave syndrome). The patient reported that 3 nights prior to his admission, he experienced increased pain related to his cancer with subsequent nausea and vomiting and noticed some blood-tinged vomitus which he had not seen before. These episodes were associated with severe retching. Later that night, he awoke with unusual discomfort in his neck and upper sternum, radiating to his back. That pain subsided over the following day and a half, although he continued to have his chronic right upper quadrant pain related to the cholangiocarcinoma. He also reported not being able to keep any food down and severe constipation despite taking stool softeners. Upon examination, the patient was afebrile, his blood pressure was 162/111 mmHg, his heart rate was 69 bpm and regular, his lungs were clear to auscultation bilaterally, his abdomen was soft, nondistended, tender to palpation in all quadrants (greatest in the right upper quadrant), and he had normoactive bowel sounds. His WBC was normal. A gastrograffin esophagram showed the esophagus to be normal in caliber and mucosal pattern, with no evidence for an esophageal leak that would have provided a cause for the pneumomediastinum seen on the CT scan. Investigational treatment was held, a nasogastric tube was inserted for bowel decompression, and he was given intravenous fluids, analgesics, ondansetron, Lopressor®, and prophylactic treatment for mediastinitis with Levaquin® and metronidazole.

During the remainder of his hospital stay the patient's pain and vomiting improved, he remained clinically stable, and he was able to progress to a soft diet. The pneumomediastinum was thought to have been caused by a small esophageal perforation brought on by retching which resolved on its own. He was discharged home on September 25, 2008 (Cycle 14, Day 31). At a follow-up visit on October 7, 2008, the patient reported that he had significant improvement of his nausea, vomiting, diarrhea, constipation, and hypertension. His abdominal exam revealed active bowel sounds and was nontender. It was decided that if the pneumomediastinum had resolved on a CT scan to be done that day, the patient would restart the investigational therapy. The chest CT scan showed interval resolution of the mediastinal, pericardial, subcutaneous, and intramuscular gas as compared to the images from September 22, 2008. No pneumothoraces were seen. These findings were communicated to the patient's physician.

The patient's past medical history is significant for hypertension and smoking (1 pack per day for 10 years; now 1 pack per week). Medications taken at the time of the event include OxyContin®, Lisinopril®, Ambien®, Actiq®, and methadone.

There have been no other cases of pneumomediastinum reported to the NCI through AdEERS as serious adverse events for bevacizumab or erlotinib; however, there have been 22 other cases of pneumothorax reported to the NCI through AdEERS under the bevacizumab NSC and 6 other cases of pneumothorax reported under erlotinib NSC as summarized in the table below.


Adverse Event	Grade	Attribution
<i>Bevacizumab</i>		
Pneumothorax (n=22)	4	1 Possible, 1 Unlikely
	3	1 Unlikely, 5 Unrelated
	2	1 Possible, 8 Unlikely, 5 Unrelated
<i>Erlotinib</i>		
Pneumothorax (n=6)	2	4 Unlikely, 2 Unrelated

A total of 17,627 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab NSC, and a total of 2681 patients have been enrolled in NCI-sponsored clinical trials under the erlotinib NSC.

In this case, it is felt that a possible causal relationship between bevacizumab and the pneumomediastinum and between erlotinib and the pneumomediastinum could not be excluded.

	Pneumomediastinum
Bevacizumab	Possible
Erlotinib	Possible
Cholangiocarcinoma	Possible
Possible esophageal perforation	Possible

Date: 11/21/08

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

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

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