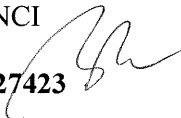




DATE: JUN 28 2011

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1727423 

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 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 59-year-old female with invasive breast carcinoma experienced grade 4 pneumonitis/pulmonary infiltrates and grade 4 adult respiratory distress syndrome while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, paclitaxel and filgrastim/pegfilgrastim.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMab VEGF)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 4: Pneumonitis/pulmonary infiltrates Gr. 4: Adult respiratory distress syndrome
AE: 1727423	Protocol: E5103

The patient is a 59-year-old female with invasive breast carcinoma who experienced pneumonitis/pulmonary infiltrates and adult respiratory distress syndrome while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, filgrastim or pegfilgrastim, and paclitaxel. The planned protocol therapy the patient was assigned is as follows:

Cycle = 14 Days (Cycles 1-4)
Doxorubicin: 60 mg/m² IVP on Day 1
Cyclophosphamide: 600 mg/m² IV over 20-30 minutes on Day 1
Bevacizumab/Placebo: 10 mg/kg IV over 30-90 minutes on Day 1
Filgrastim: 5 mcg/kg SQ on Days 2-11 OR
Pegfilgrastim: 6 mg SQ on Day 2

Cycle = 21 Days (Cycles 5-8)
Paclitaxel: 80 mg/m² IV over 1 hour on Days 1, 8 and 15
Bevacizumab/Placebo: 15mg/kg IV over 30-90 minutes on Day 1

The patient was diagnosed with invasive breast carcinoma in December 2010, and is status post partial mastectomy with port placement at that time. On January 19, 2011, a MUGA scan revealed a calculated left ventricular ejection fraction of 65.8 %. She began the investigational agent on February 3, 2011. She received the last dose of bevacizumab/placebo on February 17, 2011 (Cycle 2, Day 1), the last doses of doxorubicin and cyclophosphamide on March 17, 2011 (Cycle 4, Day 1), the last dose of pegfilgrastim on March 18, 2011 (Cycle 4, Day 2), and the last dose of paclitaxel on April 12, 2011 (Cycle 5, Day 8).

On February 25, 2011 (Cycle 2, Day 9), a chest CT scan revealed multiple bilateral pulmonary vessel filling defects consistent with pulmonary emboli, and small peripheral wedge-shaped areas of consolidation within the left lower lobe which may have been areas of subsegmental atelectasis. She developed pulmonary embolism and was receiving Coumadin[®]. On March 28, 2011, a MUGA scan prior to cycle 5, revealed a normal left ventricular wall motion and a left ventricular ejection fraction of 66%.

On April 16, 2011, (Cycle 5, Day 12), the patient was found unresponsive. She was intubated in the field as she was significantly hypoxic. Upon arrival to the emergency room, she was not ventilating well, and required Ambu[®] bag ventilation with a PEEP of 10-cm water. A chest X-ray showed diffuse alveolar infiltrates with vascular congestion. This was suggestive of pneumonia or adult respiratory distress syndrome (ARDS) of uncertain etiology. She was switched to mechanical ventilation and started on IV antibiotics. The patient had an elevated blood pressure of 150/102 mmHg, and given the vascular congestion which was seen on the chest X-ray, the patient was administered a spray of nitroglycerin. She became hypotensive, was given more IV fluids and admitted to the intensive care unit. Her PT was 22.0

seconds (reference range: 11.0-12.5 seconds) with an INR of 1.93 and APTT was 30.8 seconds (reference range: 30-40 seconds). There was no indication of a recurrence of PE since the INR was almost in the therapeutic range.

On April 17, 2011, a chest X-ray revealed a greater bilateral alveolar consolidation compared to the prior study done on April 16, 2011. BNP was elevated at 484 pg/mL (reference range: 0-100 pg/mL). On April 19, 2011, the patient was still in respiratory failure. Blood and sputum cultures remained negative, and she continued to receive broad spectrum antibiotics. The patient was started on steroids with Solu-Medrol®. On April 24, 2011, the laboratory findings were significant for a BNP of 960 pg/mL. By April 25, 2011, the chest X-rays continued to show persistent bilateral infiltrates with a moderate increase in the right middle lobe. The patient was continued on meropenem, ciprofloxacin, caspofungin and IV steroid for a possible drug induced pulmonary disease (PIPD). The patient was evaluated daily for a spontaneous breathing trial. Daily chest x-rays were continued along with a bronchoalveolar lavage. A lung biopsy was not performed.

The patient’s past medical and surgical history is significant for hypertension, pulmonary embolism, eye surgery at age 5, tonsillectomy and adenoidectomy at age 7, ligature of fallopian tube, as well as bilateral cataract surgery. Medications taken at the time of the event included alprazolam, aprepitant, calcium-vitamin D, dexamethasone, hydrocodone, metoprolol, metronidazole, ondansetron, warfarin, cephalexin, rabeprazole, tazarotene, doxycycline, and enoxaparin.

There have been 199 other cases of pneumonitis/pulmonary infiltrates and 19 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
Pneumonitis/pulmonary infiltrates (n=199)	5	12 Unlikely, 3 Possible
	4	2 Unrelated, 14 Unlikely, 13 Possible, 3 Probable
	3	20 Unrelated, 46 Unlikely, 55 Possible, 7 Probable, 1 Definite
	2	6 Unrelated, 7 Unlikely, 5 Possible, 3 Probable
	1	1 Unrelated, 1 Possible
ARDS (n=19)	5	5 Unlikely, 1 Possible
	4	4 Unrelated, 4 Unlikely, 1 Possible, 2 Probable
	3	2 Unlikely

There have been 32,949 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, a causal relationship between the events and bevacizumab cannot be excluded.

	Pneumonitis/pulmonary infiltrates	ARDS
Bevacizumab/placebo	Possible	Possible
Cyclophosphamide	Unrelated	Unrelated
Doxorubicin hydrochloride	Unrelated	Unrelated
Paclitaxel	Possible	Possible
Pegfilgrastim	Unrelated	Unrelated
Invasive breast carcinoma	Unlikely	Unrelated
Possible CHF	Possible	Possible

Date: 6/23/11

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

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

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