



DATE: JUL 08 2011
FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1793638
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 55-year-old female with stage IV, grade 2 endometrial adenocarcinoma expired while on a phase 2 trial utilizing the investigational agent bevacizumab in combination with paclitaxel and carboplatin.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF) AE: 1793638	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 5: Death NOS Protocol: GOG-0086P
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The patient was a 55-year-old female with stage IV, grade 2 endometrial adenocarcinoma who expired while on a phase 2 trial utilizing the investigational agent bevacizumab in combination with paclitaxel and carboplatin. The planned protocol therapy was as follows:

Cycle = 3 weeks

Cycles 1-6:

Paclitaxel: 175 mg/m² IV over 3 hours on day 1 x 6 cycles

Carboplatin: AUC 6 IV over 30 minutes on day 1 x 6 cycles

Bevacizumab: 15 mg/kg IV over 30-90 min on day 1 (beginning with cycle 2 for those patients entering post-surgery) x 6 cycles

Maintenance Therapy (Cycles 7+):

Bevacizumab: 15 mg/kg IV over 30-90 min on day 1

The patient was diagnosed with endometrial adenocarcinoma in July 2010, and pulmonary metastasis was found by PET scan in September 2010. She began the investigational therapy on September 16, 2010, and she received her last doses of bevacizumab, paclitaxel, and carboplatin on December 30, 2010 (Cycle 6, Day 1).

On December 30, 2010, the patient was seen in the clinic for her Cycle 6, Day 1 treatment. The patient reported fatigue, mild shortness of breath, cough, vaginal bleeding, and hot flashes. Upon physical examination, the patient's blood pressure was 162/81 mmHg, and her pulse was 121 bpm. Her most recent CT scan prior to the clinic visit showed a decrease in the size of her target lesion from 26.7cm to 21.8 cm. On November 15, 2010, the CT scan of the chest revealed diffuse nodularity along the pleural surface and fissural surfaces of the lungs bilaterally likely representing pleural based metastases. There was also extensive nodularity along the diaphragmatic surfaces and a small left pleural effusion but no pericardial effusion. There were multiple axillary, supraclavicular mediastinal and hilar lymph nodes. The CT scan of the abdomen showed extensive thickening and nodularity throughout the omentum consistent with omental metastases. There was an enlarged uterine mass with possible invasion of the cecum and terminal ileum. The spleen, adrenal glands, kidneys, pancreas, and gallbladder were normal. Her liver function tests, electrolytes, creatinine, WBC, and platelet count were all within normal ranges; her hemoglobin was 10 gm/dL (reference range: 12-16 gm/dL). She received her study treatment and was prescribed nifedipine ER.

On January 16, 2011 (Cycle 6, Day 17), the patient was found unresponsive by her husband. He called EMS and initiated CPR. Emergency personnel made several unsuccessful attempts to intubate the patient. She was transported to the emergency room where she expired. The patient's D-dimer was >5000 ng/mL (reference range: 105-400 ng/ml) and her potassium was 7.5 mmol/L (reference range: 3.5-5.10 mmol/L). Her CO₂ was 18 mmol/L (reference range: 21-32 mmol/L) and creatinine was 1.0 mg/dL

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(reference range: 0.60-1.30 mg/dL). An autopsy was not performed.

The patient's past medical and surgical history was significant for a caesarian section, ovary drilling, D&C, obesity, sleep apnea, anemia, and hypertension. Medications taken at the time of the event included dexamethasone, Percocet[®], metoprolol, ondansetron, prochlorperazine maleate, and senna.

There have been 167 other cases of death NOS and 57 other cases of sudden death reported to NCI as a serious adverse event through AdEERS under the bevacizumab NSC and/or IND.

Adverse Event	Grade	Attribution
Death NOS (n=167)	5	62 Unrelated, 70 Unlikely, 34 Possible, 1 Probable
Sudden death (n=57)	5	6 Unrelated, 11 Unlikely, 37 Possible, 3 Probable

There have been 33,172 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, a possible relationship between the death NOS and bevacizumab cannot be excluded.

	Death NOS
Bevacizumab	Possible
Carboplatin	Possible
Paclitaxel	Possible
Ovarian epithelial cancer	Unlikely

Date:

4/6/11

Signature:

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

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

cc: Arthur Cannon
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Genentech, Inc.