



DATE: JUN 20 2011

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE#, 1173562

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 50-year-old female with stage III ovarian cancer suddenly expired while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with paclitaxel and carboplatin.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF) AE: 1173562	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 5: Sudden death Protocol: GOG-0252
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The patient was a 50-year-old female with stage III ovarian cancer who suddenly expired while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with paclitaxel and carboplatin. The planned protocol therapy was as follows:

Cycle = 3 weeks:

Phase A (Cycles 1-6):

Paclitaxel: 80 mg/m² IV over 1 hr on days 1, 8 & 15

Carboplatin: AUC 6 IV on day 1

Bevacizumab: 15 mg/kg IV over 30-90 min on day 1, beginning with cycle 2

Phase B (Cycles 7-22):

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

The patient was diagnosed with stage III ovarian cancer in May 2010. She was status post total abdominal hysterectomy and bilateral salpingo-oophorectomy, omentectomy, and tumor debulking. The patient began the investigational therapy on August 31, 2010. She received her last doses of bevacizumab, paclitaxel, and carboplatin on January 4, 2011 (Cycle 6, Day 1).

On January 12, 2011 (Cycle 6, Day 9), the patient presented to the hospital for fever with a temperature of 39.2 °C. She was admitted and treated with empiric antibiotics. Her white blood cell count and absolute neutrophil count were normal initially, then the counts dropped to 2.0 x 10⁹/L (reference range: 5-10 x 10⁹/L) and 1.08 x 10⁹/L (reference range: 2.5-8 x 10⁹/L), respectively. The chest X-ray was consistent with pneumonia. The patient received supplemental oxygen and aggressive pulmonary hygiene nebulizers. Her condition improved, and her chest X-ray showed improving left pleural effusion and left lower lobe infiltrate. The patient also developed dyspnea, but a CTA of the pulmonary arteries performed on January 17, 2011 was not suggestive of pulmonary embolus. On the same day, an ECG revealed left posterior fascicular block, low voltage throughout and borderline repolarization abnormality, which were all new findings since the previous ECG recorded on November 14, 2010. An echocardiogram showed trivial pericardial effusion. Blood culture results were negative. On January 19, 2011, a chest X-ray showed increased density at the lung bases which may reflect increased atelectasis or infiltrates. A MUGA scan on January 20, 2011 showed that her left ventricular ejection fraction was normal (74%). The patient also had been suffering from depression for about a year. The patient was discharged on January 21, 2011.

During a follow-up clinic visit on February 15, 2011, the patient was weak but in no distress and her blood pressure was 127/78 mmHg. She had grade 2 peripheral neuropathy on the soles of her feet; she also had pain and mild stiffness in both knees. On March 7, 2011, a CT scan with contrast of the abdomen and pelvis showed small bilateral pleural effusions and small pericardial effusion.

On March 11, 2011 (Cycle 6, Day 67), the patient fell at home and went into asystole. Cardiopulmonary resuscitation was performed by a family member; she was then transported to the emergency room (ER). During physical examination in ER, she was not responsive; her heart rate was 12 beats/min, her temperature was 35.6 °C, and her lungs were clear. The patient was intubated and resuscitated. Her pulse then returned and her heart rate was 120 beats/min; her systolic blood pressure was kept around 120 mmHg with the application of dopamine. The laboratory results revealed a normal white blood cell

count, a creatine kinase level of 266 U/L (reference range: 30-135 U/L), a troponin I level of 0.8 ng/mL (reference range: 0-0.03 ng/mL), and D-dimer of 3.1 mg/L (reference range: 0.5-2.1 mg/L). The arterial blood gases test revealed a pH < 6.8 (reference range: 7.35-7.45), PCO₂ of 78 mmHg (reference range: 35-45 mmHg), and PO₂ of 54 mmHg (reference range: 80-100 mmHg). A chest X-ray showed a left retrocardiac infiltrate, but the remainder of the lungs was clear and the heart was within normal limits. A noncontrast CT scan of the brain was normal and there was no evidence of acute hemorrhage, mass lesion, or findings which suggested acute infarction. The patient never regained consciousness and she passed away on March 12, 2011. Her blood culture results were not significant. The cause of her death was considered to be cardiac arrest.

The patient's past medical and surgical history was remarkable for anxiety, depression, hypertension, urinary tract infection, pneumonia, arthroscopy, loop electrical excision procedure, and port-a-cath insertion. Medications taken at the time of the event included Klonopin[®], Paxil[®], Compazine[®], Zofran[®], Dilaudid[®], Colace[®], and Valium[®].

There have been 56 other cases of sudden death and 164 other cases of death NOS reported to NCI as a serious adverse event through AdEERS under the bevacizumab NSC and/or IND.


Adverse Event	Grade	Attribution
Sudden death (n=56)	5	6 Unrelated, 11 Unlikely, 37 Possible, 2 Probable
Death NOS (n=164)	5	60 Unrelated, 69 Unlikely, 34 Possible, 1 Probable

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

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

	Sudden death
Bevacizumab	Possible
Carboplatin	Possible
Paclitaxel	Possible
Ovarian epithelial cancer	Unlikely

Date: 6/16/11

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.