



DATE: DEC 15 2010

FROM: Kevin Conlon, M.D., Senior Investigator, Investigational Drug Branch, CTEP, DCTD, NCI *Kevin Conlon*

SUBJECT: Bevacizumab (rhuMab VEGF) NCI IND Safety Report, #2 AE# 1449190

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 52-year-old female with head and neck squamous cell carcinoma ~~experienced a conduction abnormality/atrioventricular heart block and subsequently~~ expired *suddenly* while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with cisplatin and docetaxel.

The attached report has been amended to reflect a change in the adverse event term. Changes to the original summary are indicated by bold and italics (new information) and/or strikethrough (deleted information). If this assessment is changed further, we will notify your office. Please note that this modified report will be distributed to investigators.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF) AE: 1449190	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #2 Event: Gr. 5: Conduction abnormality/atrioventricular heart block: Asystole Sudden death Protocol: E1305
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This AdEERS report was initially reported on AdEERS ticket # 1858857.

The patient was a 52-year-old female with head and neck squamous cell carcinoma who ~~experienced a conduction abnormality/atrioventricular heart block and subsequently~~ expired *suddenly* while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with cisplatin and docetaxel. She began the first and only course of the investigational treatment on December 16, 2009, receiving bevacizumab 15 mg/Kg IV over 30-90 minutes on Day 1, docetaxel 75 mg/m² IV over 1 hour on Day 1 and cisplatin 75 mg/m² IV over 1-2 hours on Day 1.

The patient was diagnosed with head and neck squamous cell carcinoma in October 2008, and was status post maxillectomy and palatectomy with adjuvant radiation therapy. A post radiation CT scan of the paranasal sinus and the neck with IV contrast done on November 18, 2009, revealed a large heterogeneous mass arising from the left mastoid space and nasopharyngeal area with epidural extension through the left foramen ovale into the inferior aspect of the left cavernous carotid. This mass was causing erosion of the base of the skull that had increased in size compared to a prior CT scan. The patient underwent a biopsy from the nasopharynx and mouth on November 20, 2009, which showed an infiltrating, well-differentiated squamous cell carcinoma. She began the first and only course of the investigational treatment on December 16, 2009.

On December 10, 2009, the patient complained of left ear pain and numbness in the left side of the face during a review for further therapy. The physical examination revealed limitations in buccal opening, fungating lesion in the left side of the oral cavity, and myosis in the left eye. At this time, it was felt that further radiation therapy would not be of any benefit to the patient, and she was offered the choice of chemotherapy.

On December 16, 2009 (Cycle 1, Day 1), the patient received the first and the only course of the investigational therapy and tolerated it well. On December 24, 2009 (Cycle 1, Day 9), the patient complained of weakness without apparent chest pain or shortness of breath during ambulation, requiring assistance from family members to perform self care in the very early morning. Soon after returning to bed, she was noted to have a respiratory arrest that prompted an emergency call. Attempts to resuscitate the patient in the field by paramedics and hospital staff in the emergency room were unsuccessful. Of note, no evidence of hemorrhage or hemoptysis was noted by the ER physicians during the attempts to resuscitate the patient. An autopsy was not obtained.

The patient's past medical/surgical history is significant for maxillectomy, palatectomy, and cholecystectomy. Her family history is significant for neck cancer in her father and a benign brain tumor in her sister. Medications taken at the time of the event included Roxicet[®], fentanyl patch, and amoxicillin.

There *have been 55 other cases of sudden death and 95 other cases of death NOS* ~~has been one other case of conduction abnormality/atrioventricular heart block (Grade 4, Unlikely)~~ reported to the NCI as a serious adverse event through AdEERS under the bevacizumab IND and/or NSC.


Adverse Event	Grade	Attribution
Sudden death (n=55)	5	6 Unrelated, 11 Unlikely, 35 Possible, 3 Probable
Death NOS (n=95)	5	27 Unrelated, 41 Unlikely, 27 Possible

There have been ~~25,513~~ **30,180** patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, it is felt that a possible relationship between bevacizumab and the event exists. The event may be related to extent of disease (proximity to the left cavernous carotid artery detected by CT scan) although no bleeding was reported.

	Conduction abnormality/atrioventricular heart block: Asystole Sudden death
Bevacizumab (rhuMAb VEGF)	Possible
Cisplatin	Possible
Docetaxel (Taxotere)	Possible
Head and neck squamous cell carcinoma, NOS	Possible
Hemorrhage or thrombosis related to tumor invading carotid artery	Probable

Date: 13 December 2010

Signature: 
 Kevin Conlon, M.D.
 (IDB Monitor for bevacizumab)

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

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 Genentech, Inc.