



DATE: May 20, 2010
FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1996104
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 NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 50-year-old female with ovarian epithelial cancer experienced grade 4 vertigo while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with paclitaxel and carboplatin.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 4: Dizziness (Vertigo)
AE: 1996104	Protocol: GOG-0218

The patient is a 50-year-old female with ovarian epithelial cancer who experienced vertigo while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with paclitaxel and carboplatin. She began her first course of treatment on October 2, 2008, receiving chemotherapy alone in Cycle 1 (paclitaxel 175 mg/m² IV over 3 hours and carboplatin AUC 6 IV over 30 minutes on Day 1, every 21 days for 6 cycles), and chemotherapy plus bevacizumab or placebo 15 mg/kg IV on Day 1 starting with Cycle 2, every 21 days for 5 cycles. She received the last doses of bevacizumab/placebo, paclitaxel, and carboplatin on December 30, 2008 (Cycle 5, Day 6).

The patient was initially diagnosed with stage IIIC papillary serous adenocarcinoma of the ovaries in September 2008, and is status post exploratory laparotomy with subtotal abdominal hysterectomy, bilateral salpingo-oophorectomy, total omentectomy, and radical tumor debulking and staging, all of which was performed on September 5, 2008. She began the investigational therapy on October 2, 2008, and completed 4 successful cycles of treatment without complications.

On December 4, 2008 (Cycle 4, Day 1), the patient presented to the clinic with debilitating dizziness, nausea, and vomiting associated with any type of head movement. These symptoms began a few days prior, and were not relieved with antiemetics.

On January 2, 2009 (Cycle 5, Day 9), the patient was admitted to the hospital for unresolved vertigo, nausea, and vomiting. Vital signs upon admission were as follows: temperature 97.6°F, pulse 57 bpm, respiratory rate 20 breaths per minute, blood pressure 155/88 mmHg, and oxygen saturation 98% on room air. Other physical examination was unremarkable. She received antiemetics and IV hydration. The patient revealed that the vertigo was more pronounced when she turned her head primarily to the right side. She stated that the vertigo had severely affected her balance to the point where she must use a walker. An MRI of the brain with and without contrast was unremarkable; it only showed a mildly decreased T1 marrow signal within the calvarium and skull base, possibly indicative of hematopoietic marrow reconversion (but could not exclude osseous metastatic disease). A whole body bone scan was later performed, which ruled out osseous metastatic disease.

On January 4, 2009 (Cycle 5, Day 11), a neurologist performed an extraocular motor test, during which it was noted that the patient had diplopia and nystagmus when looking to the right and left, although both conditions were more pronounced when the patient looked to the right. A lumbar puncture was performed several days later on January 8, 2009, to test for carcinomatous meningitis, and the results were negative.

On January 9, 2009 (Cycle 5, Day 16), the patient was discharged to home with a diagnosis of neurotoxicity secondary to the investigational agent pending otolaryngological evaluation. During an otolaryngology evaluation on January 16, 2009, the patient was noted to have normal anatomical ear structures. It was felt that her dizziness could be related to her chemotherapy's effect on the inner ear. The patient also displayed continuous head movement during this visit, which was felt by the otolaryngologist to contribute to her dizziness. Although audiological testing was planned, the patient never underwent such testing.

The patient's past medical and surgical history is significant for diabetes mellitus type 2, chronic hypertension, tobacco abuse, depression, morbid obesity, and umbilical hernia repair which was

concurrent with her tumor surgery. Medications taken at the time of the event included Prozac[®], Lisinopril[®], Protonix[®], Reglan[®], Valium[®], meclizine, and glipizide.

Dizziness is a known event for bevacizumab, but there have been 3 other cases of vertigo specifically previously reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND. The incidences of vertigo are shown in the table below:

Adverse Event	Grade	Attribution
Vertigo (n = 3)	4 3	2 possible 1 possible

There have been 26,437 patients enrolled in NCI-sponsored clinical trials under this IND and/or NSC.

In this case, a possible causal relationship between bevacizumab and the vertigo exists.

	Vertigo
Bevacizumab	Possible
Carboplatin	Possible
Paclitaxel	Possible
Ovarian epithelial cancer	Unlikely

Date: 5/26/10

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

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

cc: Arthur Cannon
onc_drug_safety@gene.com
Genentech, Inc.