



MAR 29 2011

**DATE:**

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

**SUBJECT:** Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1897814

**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 ovarian stromal cancer experienced grade 2 tinnitus and hearing impairment while on a phase 2 study utilizing the investigational agent bevacizumab.

## ADVERSE EVENTS ASSESSMENT

IND <b>7921</b> NSC <b>704865</b> <b>Bevacizumab</b> <b>(rhuMab VEGF)</b>	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # <b>1</b> Event: <b>Gr. 2: Tinnitus</b> <b>Gr. 2: Hearing: patients without baseline audiogram and not enrolled in a monitoring program</b> Protocol: <b>GOG-0251</b>
AE: <b>1897814</b>	

The patient is a 55-year-old female with ovarian stromal cancer who experienced tinnitus and hearing impairment while on a phase 2 trial utilizing the investigational agent bevacizumab. She began the first course of the investigational therapy on December 21, 2009, receiving bevacizumab 15 mg/kg IV over 30-90 min on Day 1, every 21 days. She received her last dose of bevacizumab on December 30, 2010 (Cycle 18, Day 1).

The patient was diagnosed with ovarian stromal cancer in November 2006, and is status post laparoscopic bilateral salpingo-oophorectomy performed in November 2006, staging surgery performed in January 2007, 6 courses of Taxol<sup>®</sup> and carboplatin completed in May 2007, 4 courses of BEP (bleomycin, etoposide and cisplatin) treatment from July to September 2008, cryoreductive surgery performed in November 2008, and pelvic radiation therapy of 50 Gy completed in January 2009. Of note, the patient does not have baseline tinnitus. She began the investigational therapy on December 21, 2009.

On July 15, 2010 (Cycle 10, Day 14), the patient reported the presence of constant bilateral tinnitus. She was seen on September 16, 2010, for an audiology evaluation. The patient was unaware of any significant hearing difficulty from either ear. She also denied the presence of otalgia, aural fullness, otorrhea, dizziness and/or imbalance, or any significant history of noise exposure. Pure tone test results revealed a moderate high-frequency sensorineural hearing loss, as well as a moderately severe rising to moderate ultra high frequency hearing loss for the right ear, and a moderate to moderately severe high-frequency sensorineural hearing loss, as well as a moderately severe ultra high frequency hearing loss for the left ear, with essentially normal middle ear mobility bilaterally. Distortion product otoacoustic emissions test results were in essential agreement with the audiometric configuration. It was determined that the patient would experience significant difficulty with normal conversation, primarily when in a noisy listening environment. She was recommended to avoid noise exposure and use ear protection as appropriate. A follow-up audiology evaluation was performed on December 10, 2010; it revealed that both test results and patient's symptoms were overall not significantly different from the last evaluation.

The patient's past medical and surgical history is significant for hypertension, gastric reflux, hypercholesterolemia, depression, laparoscopic bilateral salpingo-oophorectomy, staging surgery, and secondary cryoreductive surgery. Medications taken at the time of the event included Crestor<sup>®</sup>, Dynacirc<sup>®</sup>, iron supplement, Lexapro<sup>®</sup>, magnesium, Prevacid<sup>®</sup>, and Toprol<sup>®</sup>.

There have been 5 other cases of tinnitus and 3 other cases of hearing impairment reported as serious adverse events through AdEERS under the bevacizumab NSC and/or IND as shown in the table below.


Adverse Event	Grade	Attribution
Tinnitus (n=5)	2	2 Unrelated, 2 Possible, 1 Probable
Hearing impaired (n=3)	2	1 Possible
	3	1 Unlikely
	4	1 Unlikely

To date, a total of 31,563 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, it is felt that a possible causal relationship exists between the events and the investigational agent.

	<b>Tinnitus</b>	<b>Hearing impaired</b>
<b>Bevacizumab</b>	Possible	Possible
<b>Ovarian stromal cancer</b>	Unrelated	Unrelated
<b>Prior therapy with cisplatin</b>	Possible	Possible

Date: 3/29/11

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.