



DATE: JAN 31 2011

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, #2 AE# 1003452

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 76-year-old female with ovarian epithelial cancer experienced grade 4 atrial fibrillation *and later died* while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with carboplatin and paclitaxel.

The attached report has been amended to reflect new information. 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 Event	Grade	Attribution
Sudden death (48)	5	6 Unrelated, 5 Unlikely, 34 Possible, 3 Probable
Death NOS (123)	5	42 Unrelated, 51 Unlikely, 30 Possible,
Atrial fibrillation (n=8285)	4	1 Unrelated, 43 Unlikely, 911 Possible, 1 Probable
	3	34 Unrelated, 810 Unlikely, 2325 Possible, 4 Probable
	2	4-6 Unrelated, 87 Unlikely, 911 Possible
	1	1 Possible, 1 Unrelated

There have been ~~30,180~~**30,255** patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

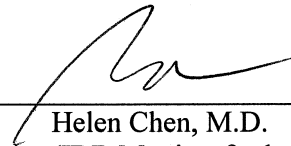
In this case, a causal relationship between the events and bevacizumab cannot be excluded.

	Atrial fibrillation	Death NOS
Bevacizumab (rhuMAb VEGF)	Possible	<i>Possible</i>
Carboplatin	Unlikely	<i>Possible</i>
Paclitaxel (Taxol)	Unlikely	<i>Possible</i>
Ovarian epithelial cancer	Unlikely	<i>Possible</i>
Hypertension	Possible	<i>Possible</i>
Atrial fibrillation	N/A	<i>Probable</i>

Date: _____

1/12/10

Signature: _____



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

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

cc: Arther Cannon
Safety Contact: onc_drug.safety@gene.com
Genentech, Inc.