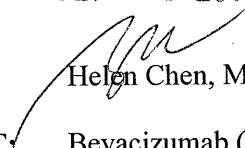




DATE: SEP 29 2011

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report #2, AE# 1874144

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 56-year-old female with stage III cervical carcinoma expired from ~~neerotizing fasciitis~~ ***a skin infection (cellulitis)*** while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with paclitaxel and topotecan.

This report has been amended to reflect revised 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.

The patient's past medical and surgical history was remarkable for asthma, chronic pain, bilateral tubal ligation, hernia repair, right hydronephrosis, right ureteral stent placement, Port-A-Cath[®] placement, and right femoral IM nail. Medications taken at the time of the event included clotrimazole, hydrochlorothiazide, Phenergan[®], Zofran[®], temazepam, dexamethasone, lorazepam, ranitidine, clonazepam, lisinopril, oxycodone, albuterol, methadone, and Symbicort[®].

Infection is an expected adverse event for bevacizumab but is being reported because this event is unusually severe. There have been 7 other cases of necrotizing skin infection, and 1 other case of necrotizing empyema, reported to NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND as shown in the table below:

Adverse Event	Grade	Attribution
Necrotizing skin infection (n=7)	5	2 Possible
	4	1 Unrelated, 2 Possible
	3	2 Possible
Necrotizing empyema (n=1)	4	1 Possible

There have been 34,327 patients 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 event and the investigational agent bevacizumab.

	Necrotizing fasciitis Skin infection (cellulitis)
Bevacizumab	Possible
Paclitaxel	Possible
Topotecan	Possible
Cervical cancer	Unlikely

Date: _____

9/26/11

Signature: _____



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

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

cc: Arthur Cannon
Gilbert Jirau-Lucca
Safety Contact: onc_drug.safety@gene.com
Genentech, Inc.