



DATE: OCT 18 2011

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1178143

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 this letter 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 50-year-old female with breast carcinoma experienced a grade 4 acute myeloid leukemia after completing a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, pegfilgrastim, paclitaxel, and radiation therapy.

IND SAFETY REPORT: FOLLOW-UP #1TO: *Division of Biologic Oncology Products, Center for Drug Evaluation and Research, FDA*

FAX: 301-796-9849

1. IND NUMBER 7921	2. AGENT NAME Bevacizumab (rhuMAb VEGF)	3. DATE October 12, 2011
4. SPONSOR Division of Cancer Treatment and Diagnosis, National Cancer Institute		
5. REPORTER'S NAME, TITLE, AND INSTITUTION Helen Chen, MD-Associate Branch Chief for Investigational Therapeutics 3, Investigational Drug Branch, CTEP, DCTD, NCI		6. PHONE NUMBER 301-496-1196
		7. EMAIL ADDRESS ctepsupportae@tech-res.com
8a. PROTOCOL NUMBER (AE#) E5103 (AE# 1178143)	8b. AE GRADE: AE Grade 4: Secondary Malignancy-possibly related to cancer treatment: Acute myeloid leukemia (AML)	
9. PATIENT IDENTIFICATION 50805	10. AGE 50 years	11. SEX Female
12. PROTOCOL SPECIFIED Cycle = 14 Days (Cycles 1-4) Doxorubicin: 60 mg/m ² IVP on Day 1 Cyclophosphamide: 600 mg/m ² IV over 20-30 minutes on Day 1 Bevacizumab/Placebo: 10 mg/kg IV over 30-90 minutes on Day 1 Filgrastim: 5 mcg/kg SQ on Days 2-11 OR Pegfilgrastim: 6 mg SQ on Day 2 Cycle = 21 Days (Cycles 5-8) Paclitaxel: 80 mg/m ² IV over 1 hour on Days 1, 8, and 15 Bevacizumab/Placebo: 15 mg/kg IV over 30-90 minutes on Day 1		
13. TREATMENT RECEIVED AND DATES The patient began the investigational therapy on August 20, 2008, receiving the last dose of bevacizumab/placebo December 24, 2008 (Cycle 8, Day 1), the last doses of doxorubicin and cyclophosphamide on October 8, 2008 (Cycle 4, Day 1), the last dose of pegfilgrastim on October 9, 2008 (Cycle 4, Day 2), the last dose of paclitaxel on January 7, 2009 (Cycle 8, Day 15), and the last radiation treatment on March 19, 2009.		
14. DESCRIPTION OF ADVERSE EVENT The patient is a 50-year-old female with breast cancer who experienced a grade 4 AML after completing a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, pegfilgrastim, paclitaxel, and radiation therapy. The total dosages administered to the patient were bevacizumab 7904 mg, doxorubicin 460 mg, cyclophosphamide 4440 mg, and paclitaxel 1587 mg. On June 15, 2011, the patient presented to the hospital with dyspnea, weakness, and fatigue. Laboratory results revealed a white blood cell (WBC) count of 10 x 10 ³ /μL (reference range: 4.2-10.2 x 10 ³ /μL) with a marked shift to the left with 8% blasts, hemoglobin of 5 g/dL (reference range: 12.0-15.0 g/dL), and a platelet count of 13 x 10 ³ /μL (reference range: 140-450 x 10 ³ /μL). She was transfused with packed cells and platelets. The patient also underwent a bone marrow biopsy revealing blast cells between 60-70% of cellular elements, which was approximately 30% based on dim CD45/low side scatter/CD34 expression. The lymphoid cells showed that 67% of the lymphocytes were T-cells with a normal CD4:CD8 ratio and normal pan T-cell antigen expression, 35% were polyclonal B-cells, and the remainder were NK cells. The myeloid cell population comprised 63% of the total recorded events. An immunophenotypic analysis of these cells demonstrated evidence of markedly left-shifted myelopoiesis and CD58 expression. Immunoreactivity for the stem cell markers CD34 and CD117 was 11% and 17%, respectively. This was consistent with acute myeloid leukemia with M2 morphology. On June 20, 2011, the patient was admitted to the hospital to begin treatment with 7 days of low-dose cytarabine in combination with 3 days of idarubicin. On July 5, 2011, the patient underwent a mid-cycle bone marrow biopsy which was markedly hypocellular without evidence of residual leukemia. She was given growth factors with G-CSF, and she experienced timely hematopoietic recovery. Additional information has been requested from the investigational site. There is a reasonable possibility that the experience may have been caused by the drug.		

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IND SAFETY REPORT: FOLLOW-UP #1

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 34,421. There have been 4 other cases of secondary malignancies reported to the NCI through AdEERS as serious adverse events for bevacizumab, **which are summarized in the table below. There were no non-hematological secondary malignancies reported.**

Adverse Event	Grade	Attribution
Secondary malignancies (n=4)	4	1 Unrelated, 3 Unlikely
AML (n=2)	4	2 Unlikely
Myelodysplastic Syndrome (n=2)	4	1 Unrelated, 1 Unlikely

16. ASSESSMENT

In this case, a possible relationship exists between the event and the investigational agent.

	Acute myeloid leukemia
Bevacizumab/placebo	Possible
Cyclophosphamide	Definite
Doxorubicin	Probable
Paclitaxel	Possible
Pegfilgrastim	Possible
Breast cancer	Unlikely

17. COMMENTS

Medications taken at the time of the event included tamoxifen and Geodon®.

AT THIS TIME, NO OTHER INFORMATION IS AVAILABLE. IF UPON FURTHER INVESTIGATION RELEVANT INFORMATION BECOMES AVAILABLE, THEN A FOLLOW-UP REPORT WILL BE SUBMITTED IN ACCORDANCE WITH 21CFR 312.32(d) (2).

DISCLAIMER per 21 CFR 312.32(e): THIS SAFETY REPORT DOES NOT NECESSARILY REFLECT A CONCLUSION OR ADMISSION BY THE CTEP IDB SENIOR INVESTIGATOR/SPONSOR THAT THE INVESTIGATIONAL AGENT/THERAPY CAUSED OR CONTRIBUTED TO THE ADVERSE EXPERIENCE BEING REPORTED.