

IND SAFETY REPORT: INITIAL WRITTEN REPORT

TO: 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 September 29, 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						
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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/m² IVP on Day 1 Cyclophosphamide: 600 mg/m² 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/m² 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 10³/μL (reference range: 4.2-10.2 x 10³/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 10³/μL (reference range: 140-450 x 10³/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.								
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.								
<table border="1" style="margin: auto; border-collapse: collapse;"> <thead> <tr> <th style="width: 40%;">Adverse Event</th> <th style="width: 10%;">Grade</th> <th style="width: 50%;">Attribution</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">Secondary malignancies (n=4)</td> <td style="text-align: center;">4</td> <td style="text-align: center;">1 Unrelated, 3 Unlikely</td> </tr> </tbody> </table>			Adverse Event	Grade	Attribution	Secondary malignancies (n=4)	4	1 Unrelated, 3 Unlikely
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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.