



DATE: September 24, 2009
FROM: Kevin Conlon, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE # **1950915**
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 67-year-old female with invasive breast carcinoma experienced grade 3 hemolysis while on a phase 3 study utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, paclitaxel, and pegfilgrastim.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMab VEGF)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 3: Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)
AE: 1950915	Protocol: E5103

The patient is a 67-year-old female with synchronous invasive breast carcinomas (Stage IIIC and Stage I) who experienced hemolysis while on a phase 3 study utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, paclitaxel, and pegfilgrastim. She began her first course of treatment on August 27, 2008 receiving bevacizumab/placebo 10 mg/kg IV over 30-90 minutes on Day 1, doxorubicin 60 mg/m² IVP on Day 1, cyclophosphamide 600 mg/m² IV over 20-30 minutes on Day 1, and pegfilgrastim 6 mg SQ on Day 2, every 21 days for Cycles 1-4. For Cycles 5-8 (cycle=21 days), she received bevacizumab/placebo 15 mg/kg IV over 30-90 minutes on Day 1 and paclitaxel 80 mg/m² IV over 1 hour on Days 1, 8, and 15. She was then unblinded and received bevacizumab 15 mg/kg IV over 30-90 minutes on Day 1 with concurrent hormonal therapy every 21 days for Cycles 9-18. The patient received her last doses of cyclophosphamide and doxorubicin on October 22, 2008 (Cycle 4, Day 1), pegfilgrastim on October 23, 2008 (Cycle 4, Day 2), paclitaxel on December 17, 2008 (Cycle 6, Day 8), and bevacizumab on March 4, 2009 (Cycle 10, Day 1).

The patient was diagnosed with synchronous breast cancers, infiltrating ductal carcinoma and infiltrating lobular carcinoma, (ER, PR positive and HER-2 negative) of the right breast in July 2008. She is status post right segmental mastectomy with sentinel lymph node dissection and regional axillary dissection on July 17, 2008 followed by chemotherapy and adjuvant radiation therapy. She began the investigational therapy on August 27, 2008.

On April 12, 2009 (Cycle 10, Day 1), the patient presented to the emergency room of the local hospital via ambulance with complaints of non-radiating chest pain particularly around her port sight. She had been recently hospitalized for dehydration. The patient's blood pressure was 56/36 mmHg en route to the emergency room. On arrival, her vital signs were 97.5° F, pulse 121 bpm, respiration 20 breaths per minute, blood pressure 102/78 mmHg, and oxygen saturation 96% on room air. The physical examination was unremarkable except for dry oral mucosa, tachycardia, and diffuse weakness. There was no evidence of coronary artery disease or acute coronary event. Laboratory reports showed a hemoglobin of 13.6 g/dL (reference range: 11.7-16.1 g/dL), platelet count of 166 × 10³/L (reference range: 150-400 × 10³/L), and a urinary tract infection. The EKG showed a sinus tachycardia with a ventricular rate of 120 bpm and some PVCs without an acute injury pattern. A chest X-ray showed mild cardiomegaly and an Infuse-a-Port, but no acute consolidation or pneumothorax. Her chest pain was felt to be non-cardiac in nature. She was given IV fluids and one dose of IV Rocephin®. The patient was subsequently transferred to another facility for admission and further management on April 13, 2009.

On admission, the patient appeared lethargic with a temperature of 95.8°F, pulse of 102 bpm, and blood pressure of 114/73 mmHg. Her hemoglobin had decreased to 9.7 g/dL and the platelet count was 117 × 10³/L. The blood cultures from the previous day were negative, and the urine cultures grew *E. coli*. A brain MRI revealed an acoustic neuroma. The patient was diagnosed with Coombs negative hemolytic anemia thought to be secondary to urosepsis versus bevacizumab. Within 48 hours the patient's mental status had improved. A bone marrow biopsy on April 20, 2009, was within normal limits and showed no evidence of infiltrative metastatic disease or a myeloproliferative disorder.

The patient's condition improved significantly with treatment and physical therapy. Her hemoglobin and platelet count recovered to 11.6 g/dL and $254 \times 10^3/L$ respectively. A repeat urine culture was negative. She was discharged home on April 24, 2009 (Cycle 10, Day 13), with physical therapy. The patient was removed from the protocol on April 30, 2009.

On May 7, 2009, the patient presented to the clinic feeling better with increased energy levels. Laboratory values showed hemoglobin of 12.9 g/dL and a platelet count of $303 \times 10^3/L$. Epstein-Barr virus titers showed convalescent or previous infections. Her CMV IgG and IgM were positive. The cause of the Coombs negative hemolytic anemia was deemed unclear.

Pertinent laboratory values:

	8/27/09 Baseline	4/12/09 C10, D1	4/13/09 C10, D2	4/24/09 C10, D13	5/1/09 Off-study	5/7/2009 Off-study
WBC (reference range: 4.5-11.0 K/ μ L)	13.4	7.2	5.1	4.0	4.5	5.2
RBC count (reference range: 3.8-5.8 M/ μ L)	4.54	3.88	2.93	3.54	4.18	3.8
Hemoglobin (reference range: 11.7-16.1 g/dL)	12.7	13.6	9.7	11.6	14.1	12.9
Hematocrit (reference range: 35-47%)	38.5	42.3	31.5	37.1	44.7	40.2
LDH (reference range: 110-190 U/L)	*	*	*	322	270	228
Platelets (reference range: 150-400 K/ μ L)	366	166	117	254	364	303
Red cell morphology	*	*	2+ anisocytosis, 1+ macrocytes, 1+ hypochromasia	2+ anisocytosis, 2+ macrocytes, 1+ polychromasia	*	1+ anisocytosis, 1+ macrocytosis, 1+ polychromasia
Reticulocyte ct (reference range: 0.4-2.4%)	*	*	*	6 Corrected 5.3	*	2.2
Haptoglobin (reference range: 40-240 mg/dL)	*	*	*	27	<30	61.7 (37-184)
Urobilinogen (reference range: 0.1-1.0 mg/dL)	*	*	nl	*	*	*
Alkaline phosphatase (reference range: 50-136 U/L)	77	448	*	139 (34-132)	142	95
AST (reference range: 15-37 U/L)	25	146	*	30 (3-45)	37	34
ALT (reference range: 30-65 U/L)	36	60	*	13 (7-40)	27	27
Conj. bilirubin (reference range: 0.0-0.4 mg/dL)	*	*	*	*	*	*
T. bilirubin (reference range: 0.2-1.0 mg/dL)	0.1	1.2	*	0.5	*	0.5
BUN (reference range: 8-21mg/dL)	19.0	7	*	7	8.0	10
Creatinine (reference range: 0.6-1.2 mg/dL)	1.09	0.9	*	0.7	0.92	0.79

* = not done/not provided

The patient's past medical and surgical history is significant for hypertension, arthritis, restless leg syndrome, osteoporosis, cholelithiasis diagnosed in March 2009, right breast biopsy, left knee surgery, hemorrhoidectomy three times, Cesarean section, dilation of a Schatzki's ring, and tonsillectomy. Her father died of prostate cancer at age 72, and her brother has prostate cancer. Medications taken at the time of the event included Diflucan[®], Lortab[®], Mecca[®] solution, Pepcid[®], prednisone, Requip[®], and trazodone.

There have been 2 other cases of hemolysis (both grade 3 and unlikely related) previously reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND.

There have been 23,035 patients enrolled in NCI-sponsored clinical trials under this IND and/or NSC.

In this case, it is felt that a probable causal relationship between bevacizumab and the event exists.

	Hemolysis
Bevacizumab	Probable
Cyclophosphamide	Unrelated
Doxorubicin	Unrelated
Paclitaxel	Unrelated
Pegfilgrastim	Unrelated
Invasive breast carcinoma	Unrelated
E. coli bacteria	Possible
Ceftriaxone (Rocephin®)	Probable

Date:

24 Sept 2009

Signature:



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(IDB Monitor for bevacizumab)

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

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Genentech, Incorporated