



DATE: DEC 07 2011
FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1851854
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 61-year-old female with fallopian tube carcinoma experienced grade 4 autoimmune thrombocytopenia while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with carboplatin and paclitaxel.

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

. AGENT NAME

Bevacizumab (rhuMab VEGF)

3. DATE

November 14, 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

ctesupportae@tech-res.com

8a. PROTOCOL NUMBER (AE#)

GOG-0262 (AE# 1851854)

8b. AE GRADE: AE

Grade 4: ~~Platelet count decreased~~ **Blood and lymphatic system disorders: Autoimmune thrombocytopenia**

9. PATIENT IDENTIFICATION

814-0262-005

10. AGE

61 years

11. SEX

Female

12. PROTOCOL SPECIFIED

Cycle = 21 days

Bevacizumab: 15 mg/kg IV over 30-90 minutes on Day 1 of cycles 2+

Paclitaxel: 80 mg/m² IV over 1 hour on Days 1, 8, & 15 (Cycles 1-6)

Carboplatin: AUC = 6 IV on Day 1 (Cycles 1-6)

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on April 21, 2011, receiving the last dose of bevacizumab on June 30, 2011 (Cycle 4, Day 8), the last dose of carboplatin on September 22, 2011 (Cycle 6, Day 1), and the last dose of paclitaxel on September 29, 2011 (Cycle 6, Day 8).

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 61-year-old female with fallopian tube carcinoma who experienced grade 4 ~~thrombocytopenia~~ **idiopathic/immune thrombocytopenic purpura** while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with carboplatin and paclitaxel. Bevacizumab was discontinued during cycle 4 due to a rectovaginal fistula. On October 15, 2011, the patient presented to the ER with a 2-day history of abnormal bleeding and pain on her tongue. She reported noticing a petechial rash on her forearms, particularly on both shoulders, and on her lower extremities. She also reported having minimal vaginal bleeding this same day, as well as a brief nosebleed following blowing her nose. The patient also noticed two blood blisters on her tongue. Laboratory results showed her platelet count was 2 K/ μ L (reference range: 150-400 K/ μ L), and hemoglobin was 9.3 g/dL (reference range: 12-16 g/dL). The patient was admitted to the hospital, given a platelet transfusion, and Solu-Medrol[®]. Post transfusion her platelet count had decreased to 1 K/ μ L. On October 16, 2011, her platelet count had increased to 3 K/ μ L, and the patient reported feeling better. On October 17, 2011, laboratory results revealed her platelet count was 12 K/ μ L. Additional information has been requested from the investigational site. There is a reasonable possibility that the experience may have been caused by the drug.

Follow-up #1: Additional information was received from the investigator on November 3, 2011.

On October 16, 2011, the patient's peripheral blood smear confirmed significant thrombocytopenia. There was no evidence of microangiopathic hemolysis, and no definite myelodysplastic features were seen. The clinical picture was consistent with thrombocytopenia due to peripheral destruction, but the underlying etiology was unclear. Possibilities included: drug reaction, autoimmune disease, viral infections (including HIV and HCV), bacterial infections (including *Helicobacter pylori*), heparin (heparin-induced thrombocytopenia), primary Idiopathic/Immune thrombocytopenic purpura (ITP). The patient was placed on steroid therapy with prednisone, and by October 31, 2011, her platelet count had increased to 167 K/ μ L. The patient did not have a bone marrow biopsy or aspiration, and all workups were negative. However, given the response to steroid, a tentative diagnosis of autoimmune thrombocytopenia was made.

0001

IND SAFETY REPORT: FOLLOW-UP #1

	04/07/11 Baseline	08/09/11 (C5,D1)	09/22/11 (C6,D1)	10/15/11	10/16/11	10/17/11/11
White blood cells +(rr: 3.0-8.9 K/ μ L) (rr: 5-10 K/ μ L) *(rr: 4.5-11.0 K/ μ L)	+4.7 K/ μ L	+11.7 K/ μ L	+3.7 K/ μ L	7.7 K/ μ L	*6.7 K/ μ L	--
Red blood cells +(rr: 3.9-5.1 M/ μ L) (rr: 4.2-5.4 M/ μ L) *(rr: 4.00-5.20)	+ 4.41 M/ μ L	+3.95 M/ μ L)	+4.10 M/ μ L	3.58 M/ μ L	*3.40 M/ μ L	--
Hemoglobin +(rr: 11.3-15.2 g/dL) (rr: 12-16 g/dL)	+10.4 g/dL	+10.1 g/dL	+10.6 g/dL	9.3 g/dL	8.9 g/dL	--
Hematocrit +(rr: 35.0-48.0%) (rr: 37-47%) * (rr: 33.0-51.0%)	+ 34%	+33.7%	+34.6%	30.8%	*29.2%	--
Platelets +(rr: 113.0-364.0 K/ μ L) (rr: 150-400 K/ μ L) *(rr: 140-440 K/ μ L)	+199 K/ μ L	+155 K/ μ L	+164 K/ μ L	2 K/ μ L	*3 K/ μ L	12 K/ μ L
Mean platelet volume +(rr: 9.5-13.4 fL) (rr: 7.4-10.4 fL)	+10.3 fL	+10.4 fL	+9.9 fL	undetectable	undetectable	undetectable
Neutrophils +(rr: 1.3-6.6 K/ μ L) *(rr: 2.5-8.0 K/ μ L)	+2.4 K/ μ L	+8.7 K/ μ L	+1.8 K/ μ L	--	*5.0 K/ μ L	--
Lymphocytes +(rr: 0.4-3.6 K/ μ L) *(rr: 1.0-4.0 K/ μ L)	+1.5 K/ μ L	+1.9 K/ μ L	+1.3 K/ μ L	--	*0.5 K/ μ L	--
Monocytes +(rr: 0.2-1.3 K/ μ L) *(rr: 100-700/mm ³)	+0.6 K/ μ L	+1.0 K/ μ L	+0.2 K/ μ L	--	*0.1/mm ³	--
Eosinophils +(rr: 0.1-0.6 K/ μ L) *(rr: 50-100/mm ³)	+0.3 K/ μ L	+0.0 K/ μ L	+0.1 K/ μ L	--	*0.0 mm ³	--
Basophils +(rr: 0.1-0.2 K/ μ L) *(rr: 25-100/mm ³)	+0.0 K/ μ L	+0.0 K/ μ L	+0.0 K/ μ L	--	*0.0/mm ³	--

+rr: baseline reference range

*rr: reference range for dates as indicated

--: not available

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 35,226. There have been 340 other cases of thrombocytopenia reported to the NCI through AdEERS as serious adverse events for bevacizumab, as summarized in the table below. There have been 2 other cases of idiopathic thrombocytopenic purpura reported to the NCI through AdEERS as serious adverse events for bevacizumab as summarized in the table below:

Adverse Event	Grade	Attribution
Thrombocytopenia (n=340)	4	21 Unrelated, 67 Unlikely, 47 Possible, 8 Probable, 1 Definite
	3	22 Unrelated, 49 Unlikely, 42 Possible, 10 Probable, 4 Definite
	2	6 Unrelated, 30 Unlikely, 31 Possible, 2 Probable
Idiopathic thrombocytopenic purpura (n=2)	4	1 Possible
	3	1 Possible

IND SAFETY REPORT: FOLLOW-UP #1

16. ASSESSMENT

In this case, ~~a possible relationship exists between the event and the investigational agent.~~ **given that bevacizumab was discontinued more than three months before the occurrence of thrombocytopenia, it is unlikely to be related to the adverse event. A possible relationship to chemotherapy or other factors cannot be ruled out.**

	Thromboeytopenia
	Autoimmune thrombocytopenia
Bevacizumab	Possible Unlikely
Carboplatin	Possible
Paclitaxel	Possible
Fallopian tube carcinoma	Unlikely

17. COMMENTS

Medications taken at the time of the event included aspirin, vitamin D3, Lomotil[®], Colace[®], Lexapro[®], multivitamin, magnesium hydroxide, oxycodone/acetaminophen, and Percocet[®].

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).