



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: January 30, 2009

To: NCCTG Primary Clinical Research Associates

From: Lynn Flickinger
Protocol Development Coordinator

Re: N0735, Phase II Trial of Albumin-Bound Paclitaxel in Combination with Gemcitabine and Bevacizumab in Patients with Metastatic Breast Cancer

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with Bevacizumab for a study where the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) is distributing this agent. You may have also received this communication directly from DCTD.

AE_267119_F2

Please note that all risks currently cited in the NCCTG consent form cannot be omitted; it is at the discretion of your local IRB as to whether they wish to add risks based on the enclosed information. If a determination has been made by the NCCTG Research Base that a protocol amendment is necessary, you will receive the NCI-approved protocol addendum at a later date; for purposes of cross-reference, this communication will cite the adverse event noted above.

Please submit this adverse event to your Institutional Review Board.

If you have any questions concerning this communication, please contact Lynn Flickinger at Flickinger.lynn@mayo.edu or 507-538-7034.

LF/kjm
enclosure



National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

DATE: November 6, 2008

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

SUBJECT: Bevacizumab (rhuMAb VEGF) Investigator Notification: **Myelodysplastic Syndrome**
Genentech Manufacturer Report # 267119

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. A MedWatch report and CIOMS form, which describe myelodysplastic syndrome in a patient participating in a Genentech-sponsored clinical trial utilizing the investigational agent bevacizumab and chemotherapy, was recently distributed to investigators.

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) according to your local IRB's policies and procedures.
- File a copy of this letter in your protocol file.

If your study is not covered under INDs 7921 or 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 MedWatch Report and CIOMS Form that describe the following adverse event are attached:

A 65-year-old female with metastatic breast cancer experienced Grade 4 myelodysplastic syndrome while on a phase 3 study utilizing the investigational agent bevacizumab in combination with chemotherapy.

There have been 3 cases of myelodysplastic syndrome reported to the NCI for bevacizumab trials.

Attachments: MedWatch Report
CIOMS Form

For use by user-facilities,
importers, distributors and manufacturers
for MANDATORY reporting

MEDWATCH
3500A Facsimile

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Mfr Report #	267119
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A. PATIENT INFORMATION			
1. Patient Identifier	2. Age at Time of Event: 65 Years or _____ Date of Birth:	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight _____ lbs or _____ kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input type="checkbox"/> Death: _____ (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect <input type="checkbox"/> Hospitalization - initial or prolonged <input checked="" type="checkbox"/> Other Serious (Important Medical Events) <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) 06/25/2008		4. Date of This Report (mm/dd/yyyy) 10/14/2008	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) myeloid dysplasia [MYELODYSPLASTIC SYNDROME] Case Description: IND SAFETY REPORT This case, manufacturer control number 267119, is a report from FRANCE referring to a 65-year-old Female subject (D # _____). An Investigator reported this case from Genentech-sponsored study AVF3694G-B, a multi-center, phase III, randomized placebo-controlled trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy regimens in subjects with previously untreated metastatic breast cancer. On 28-APR-2007, the subject received BEVACIZUMAB OR PLACEBO (1080 mg, Q3W, Intravenous), continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates #1 06/25/2008 BIOPSY BONE MARROW (continued) #2 06/25/2008 HAEMATOCRIT 0.28 µL #3 06/25/2008 HAEMOGLOBIN 85 g/L #4 06/25/2008 NEUTROPHIL COUNT (continued) #5 06/23/2008 PLATELET COUNT (continued) #6 06/25/2008 PLATELET COUNT (continued) continued in additional info section...			
7. Other Relevant History, including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Caucasian			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler)			
#1. BEVACIZUMAB OR PLACEBO (Bevacizumab) (Continued)			
#2. ADRIAMYCIN (DOXORUBICIN/DOXORUBICIN HYDROCHLORIDE)			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. 1080 mg, Q3W, Intravenous		#1. 04/28/2007 to 10/09/2007	
#2. 75 mg, UNK		#2. 04/28/2007 to UNK	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced? Doesn't Apply	
#1. metastatic breast (Continued)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. metastatic breast (Continued)		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction? Doesn't Apply	
#1. 78776	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2.	#2.	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
#1. FEMARA (LETROZOLE)			
#2. CLASTOBAN (CLODRONIC ACID)			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices)		2. Phone Number	
Genentech, Inc. James Nickas Pharm.D. 1 DNA Way South San Francisco, CA 94080 UNITED STATES		6502255591	
4. Date Received by Manufacturer (mm/dd/yyyy) 10/08/2008		3. Report Source (Check all that apply)	
5. (A)NDA # IND # BB 7023		<input checked="" type="checkbox"/> Foreign FRA	
6. If IND, Give Protocol # AVF3694G-B		<input checked="" type="checkbox"/> Study	
7. Type of Report (Check all that apply)		<input type="checkbox"/> Literature	
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day		<input type="checkbox"/> Consumer	
<input type="checkbox"/> 7-day <input type="checkbox"/> Periodic		<input checked="" type="checkbox"/> Health Professional	
<input type="checkbox"/> 10-day <input type="checkbox"/> Initial		<input type="checkbox"/> User Facility	
<input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up #2		<input type="checkbox"/> Company Representative	
8. Adverse Event Term(s) MYELODYSPLASTIC SYNDROME		<input type="checkbox"/> Distributor	
9. Manufacturer Report Number 267119		<input type="checkbox"/> Other:	
E. INITIAL REPORTER			
1. Name and Address		Phone #	
2. Health Professional?		3. Occupation	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
4. Initial Reporter Also Sent Report to FDA			
<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Unk			

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

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C. SUSPECT PRODUCT(S)	
1. Name (Give labeled strength & mfr/labeler)	
#3. CYCLOPHOSPHAMIDE (CYCLOPHOSPHAMIDE)	
#4.	
2. Dose, Frequency & Route Used	3. Therapy Dates (if unknown, give duration from/to (or best estimate))
#3. 780 mg, UNK	#3. 04/28/2007 to UNK
#4.	#4.
4. Diagnosis for Use (Indication)	5. Event Abated After Use Stopped or Dose Reduced?
#3. metastatic breast (Continued)	#3. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply
#4.	#4. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
6. Lot #	7. Exp. Date
#3.	#3.
#4.	#4.
9. NDC# or Unique ID	8. Event Reappeared After Reintroduction?
NA	#3. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply
	#4. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)	

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MEDWATCH

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ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

DOXORUBICIN/DOXORUBICIN HYDROCHLORIDE (75 mg, frequency and route not reported) and CYCLOPHOSPHAMIDE (780 mg, frequency and route note reported). The last doses prior to the event of doxorubicin/ doxorubicin hydrochloride and cyclophosphamide were administered on 27-AUG-2007. The last dose prior to the event of bevacizumab or placebo was administered on 09-OCT-2007. The lot number for bevacizumab or placebo was reported as 78776.

It was reported that the subject was hospitalized on 25-JUN-2008. A bone marrow exam on the same day revealed myeloid dysplasia. Conflicting information reported that on 03-JUL-2008, the subject experienced myeloid dysplasia (MYELOID DYSPLASIA). Action taken with bevacizumab or placebo due to the event was reported as not applicable. Conflicting information was reported indicating that the subject was discontinued from the blinded study medication. Action taken with doxorubicin/doxorubicin hydrochloride and cyclophosphamide was not reported. The subject received unspecified medication for treatment of the event.

At the time of the report, the event remained ongoing.

The Investigator assessed the event MYELOID DYSPLASIA as related to BEVACIZUMAB OR PLACEBO. In the reporter's opinion, other possible etiological factors included protocol-specified chemotherapy of doxorubicin/doxorubicin hydrochloride and cyclophosphamide.

The event was identified as medically significant by the reporter.

On 03-SEP-2008, the subject was unblinded and found to be on bevacizumab.

This report contains case details known at the time of the submission.

Additional follow-up is being requested. If received, the case will be updated accordingly.

ON 15-SEP-2008: AFTER FURTHER REVIEW OF THE REPORT, ADDITIONAL CLARIFICATION IS REQUIRED.

The subject ID# was previously reported as _____ and should be _____.

ADDITIONAL INFORMATION RECEIVED ON 15-SEP-2008

Concomitant medications included letrozole and clodronic acid. Additionally, it was reported that the subject had no significant past medical history.

On an unspecified date in OCT-2007, it was reported that the subject decided to discontinue the study. The last dose of bevacizumab was administered on 09-OCT-2007.

On 23-JUN-2008, the subject experienced thrombocytopenia. Relevant laboratory tests included: PLT ($28 \times 10^9/L$).

On 24-JUN-2008, the subject was hospitalized due thrombocytopenia.

On 25-JUN-2008, the subject experienced myeloid dysplasia (MYELOID DYSPLASIA). Relevant diagnostic tests performed that day included a bone marrow biopsy which revealed "myeloid dysplasia, hematopoietic bone marrow is rich (level 4), active with elements of megacaryocyte line in particular, no metastatic extension was shown". Additionally, relevant laboratory tests included: WBC (5.3, units reported, however were illegible), HGB (85 g/l), HCT (0.28 ul), PLT ($45 \times 10^9/L$), and NEUT ($1.8 \times 10^9/L$). Treatment for the event included prednisone and vidarabine. Action taken with the study drugs was not applicable.

This report contains case details known at the time of the submission.

No further information is available.

ADDITIONAL INFORMATION RECEIVED 08-OCT-2008

It was reported that this subject was not hospitalized for the event. The event was reported as medically significant by the reporter.

This case contains details known at the time of the submission.

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No further follow up is expected.

PREVIOUSLY FILED IND SAFETY REPORTS OF SIMILAR EVENTS:

Genentech has previously filed IND safety reports of similar events of myeloid dysplasia from studies of Bevacizumab.

Manufacturer control number~ISR primary event term~~~~~Date submitted
265261~~~~~myelodysplastic syndrome~~~~~5-AUG-2008

SPONSOR ASSESSMENT

Based on review of available data, the sponsors cannot establish or exclude the possibility of a cause-and-effect relationship between administration of Bevacizumab and the occurrence of myeloid dysplasia.

At this time, the Sponsors do not believe changes to the conduct of this clinical trial are warranted.

B6. LABORATORY DATA

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	06/25/2008	BIOPSY BONE MARROW myeloid dysplasia; hematopoietic bone marrow is rich (level 4) with active elements of megacaryocyte line in particular, no metastatic extension shown on bone marrow	see notes	
4	06/25/2008	NEUTROPHIL COUNT	1.8 x10 ⁹ /L	
5	06/23/2008	PLATELET COUNT	28 x10 ⁹ /L	
6	06/25/2008	PLATELET COUNT	45 x10 ⁹ /L	
7	06/25/2008	WHITE BLOOD CELL COUNT	5.3	

C1. NAME (Continued)

Suspect Medication #1: BEVACIZUMAB OR PLACEBO(Bevacizumab) Powder and solvent for solution for infusion, 100mg

C4. DIAGNOSIS FOR USE (Continued)

#1:metastatic breast cancer (METASTATIC BREAST CANCER)
#2:metastatic breast cancer (METASTATIC BREAST CANCER)
#3:metastatic breast cancer (METASTATIC BREAST CANCER)

0005

ADDITIONAL INFORMATION**7+13. DESCRIBE REACTION(S) continued**

An Investigator reported this case from Genentech-sponsored study AVF3694G-B, a multi-center, phase III, randomized placebo-controlled trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy regimens in subjects with previously untreated metastatic breast cancer.

On 28-APR-2007, the subject received BEVACIZUMAB OR PLACEBO (1080 mg, Q3W, Intravenous), DOXORUBICIN/DOXORUBICIN HYDROCHLORIDE (75 mg, frequency and route not reported) and CYCLOPHOSPHAMIDE (780 mg, frequency and route not reported). The last doses prior to the event of doxorubicin/ doxorubicin hydrochloride and cyclophosphamide were administered on 27-AUG-2007. The last dose prior to the event of bevacizumab or placebo was administered on 09-OCT-2007. The lot number for bevacizumab or placebo was reported as 78776.

It was reported that the subject was hospitalized on 25-JUN-2008. A bone marrow exam on the same day revealed myeloid dysplasia. Conflicting information reported that on 03-JUL-2008, the subject experienced myeloid dysplasia (MYELOID DYSPLASIA). Action taken with bevacizumab or placebo due to the event was reported as not applicable. Conflicting information was reported indicating that the subject was discontinued from the blinded study medication. Action taken with doxorubicin/doxorubicin hydrochloride and cyclophosphamide was not reported. The subject received unspecified medication for treatment of the event.

At the time of the report, the event remained ongoing.

The Investigator assessed the event MYELOID DYSPLASIA as related to BEVACIZUMAB OR PLACEBO. In the reporter's opinion, other possible etiological factors included protocol-specified chemotherapy of doxorubicin/doxorubicin hydrochloride and cyclophosphamide.

The event was identified as medically significant by the reporter.

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This report contains case details known at the time of the submission.

Additional follow-up is being requested. If received, the case will be updated accordingly.

ON 15-SEP-2008: AFTER FURTHER REVIEW OF THE REPORT, ADDITIONAL CLARIFICATION IS REQUIRED.

The subject ID# was previously reported as _____ and should be _____

ADDITIONAL INFORMATION RECEIVED ON 15-SEP-2008

Concomitant medications included letrozole and clodronic acid. Additionally, it was reported that the subject had no significant past medical history.

On an unspecified date in OCT-2007, it was reported that the subject decided to discontinue the study. The last dose of bevacizumab was administered on 09-OCT-2007.

On 23-JUN-2008, the subject experienced thrombocytopenia. Relevant laboratory tests included: PLT ($28 \times 10^9/L$).

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ADDITIONAL INFORMATION RECEIVED 08-OCT-2008

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No further follow up is expected.

ADDITIONAL INFORMATION**7+13. DESCRIBE REACTION(S) continued****PREVIOUSLY FILED IND SAFETY REPORTS OF SIMILAR EVENTS:**

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Manufacturer control number~ISR primary event term~~~~~Date submitted
265261~myelodysplastic syndrome~~~~~5-AUG-2008

SPONSOR ASSESSMENT

Based on review of available data, the sponsors cannot establish or exclude the possibility of a cause-and-effect relationship between administration of Bevacizumab and the occurrence of myeloid dysplasia.

At this time, the Sponsors do not believe changes to the conduct of this clinical trial are warranted.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	25-JUN-2008	BIOPSY BONE MARROW	see notes	
		myeloid dysplasia; hematopoietic bone marrow is rich (level 4) with active elements of megacaryocyte line in particular, no metastatic extension shown on bone marrow		
2	25-JUN-2008	HAEMATOCRIT	0.28 µL	
3	25-JUN-2008	HAEMOGLOBIN	85 g/L	
4	25-JUN-2008	NEUTROPHIL COUNT	1.8 x10 ⁹ /L	
5	23-JUN-2008	PLATELET COUNT	28 x10 ⁹ /L	
6	25-JUN-2008	PLATELET COUNT	45 x10 ⁹ /L	
7	25-JUN-2008	WHITE BLOOD CELL COUNT	5.3	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) BEVACIZUMAB OR PLACEBO (Bevacizumab) Powder and solvent for solution for infusion, 100 mg (Lot # 78776); Regimen #1	1080 mg, Q3W; Intravenous	metastatic breast cancer (METASTATIC BREAST CANCER)	28-APR-2007 / 09-OCT-2007; 165 days
#3) CYCLOPHOSPHAMIDE (CYCLOPHOSPHAMIDE) ; Regimen #1	780 mg, UNK; Unknown	metastatic breast cancer (METASTATIC BREAST CANCER)	28-APR-2007 / Unknown; Unknown