



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: October 31, 2008

To: NCCTG Primary Clinical Research Associates

From: Janis Wobschall

Re: N0776, Phase II Trial of Avastin® in Combination with Sorafenib in Recurrent Glioblastoma Multiforme

The purpose of this memorandum is to provide investigators with a recent industry report of an adverse event that has occurred in association with Bevacizumab at a non-NCCTG institution. You may have also received this communication directly from the drug manufacturer.

AE_267119

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 Janis Wobschall at wobschall.janis@mayo.edu or 507-284-4852.

JW/kjm
enclosure

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

MEDWATCH
3500A Facsimile

Mfr Report #	267119
UF/Importer Report #	
FDA Use Only	

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
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B. ADVERSE EVENT OR PRODUCT PROBLEM

1. Adverse Event and/or Product Problem (e.g., defects/malfunctions)

2. Outcomes Attributed to Adverse Event (Check all that apply)

Death: _____ (mm/dd/yyyy) Disability or Permanent Damage

Life-threatening Congenital Anomaly/Birth Defect

Hospitalization - initial or prolonged Other Serious (Important Medical Events)

Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy) 07/03/2008

4. Date of This Report (mm/dd/yyyy) 09/05/2008

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)

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

#1. 1080 mg, Q3W, Intravenous

#2. 75 mg, UNK

3. Therapy Dates (if unknown, give duration from/to (or best estimate))

#1. 04/28/2007 to UNK

#2. 04/28/2007 to UNK

4. Diagnosis for Use (Indication)

#1. metastatic breast (Continued)

#2. metastatic breast (Continued)

5. Event Abated After Use Stopped or Dose Reduced?

#1. Yes No Doesn't Apply

#2. Yes No Doesn't Apply

6. Lot #

#1. 78776

7. Exp. Date

#1. _____

8. Event Reappeared After Reintroduction?

#1. Yes No Doesn't Apply

#2. Yes No Doesn't Apply

9. NDC# or Unique ID

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

G. ALL MANUFACTURERS

1. Contact Office - Name/Address (and Manufacturing Site for Devices)

Genentech, Inc.
James Nickas
Pharm.D.
1 DNA Way
South San Francisco, CA 94080 UNITED STATES

2. Phone Number
6502255591

3. Report Source (Check all that apply)

Foreign FRA

Study

Literature

Consumer

Health Professional

User Facility

Company Representative

Distributor

Other: _____

4. Date Received by Manufacturer (mm/dd/yyyy)
08/29/2008

5. (A)NDA # _____

IND # BB 7023

6. If IND, Give Protocol #
AVF3694G-B

7. Type of Report (Check all that apply)

5-day 30-day

7-day Periodic

10-day Initial

15-day Follow-up # _____

8. Adverse Event Term(s)
MYELODYSPLASTIC SYNDROME

9. Manufacturer Report Number
267119

E. INITIAL REPORTER

1. Name and Address _____ Phone # _____

2. Health Professional? Yes No

3. Occupation _____

4. Initial Reporter Also Sent Report to FDA Yes No 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

3500A Facsimile (Back) (Continued)

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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 type="checkbox"/> Doesn't Apply
#4.	UNK
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)	

MEDWATCH

3500A Facsimile (Back) (Continued)

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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.

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	see notes	

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)

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY FRANCE	2. DATE OF BIRTH			2a. AGE 65 Years	3. SEX Female	3a. WEIGHT Unk	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year				Day	Month	Year	<input type="checkbox"/> PATIENT DIED <input type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING
							03	JUL	2008		

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)
**Other Serious Criteria: Medically Significant
myeloid dysplasia [MYELOYDYSPLASTIC 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 #).

(Continued on Additional Information Page)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1) BEVACIZUMAB OR PLACEBO (Bevacizumab) Powder and solvent for solution for infusion, 100 mg {Lot # #2) ADRIAMYCIN (DOXORUBICIN/DOXORUBICIN HYDROCHLORIDE) (Continued on Additional Information Page)		20. DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
15. DAILY DOSE(S) #1) 1080 mg, Q3W #2) 75 mg, UNK	16. ROUTE(S) OF ADMINISTRATION #1) Intravenous #2) Unknown	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
17. INDICATION(S) FOR USE #1) metastatic breast cancer (METASTATI #2) metastatic breast cancer (METASTATIC BREAST CANCER) (Continued on Additional Information Page)		
18. THERAPY DATES (from/to) #1) 28-APR-2007 / Unknown #2) 28-APR-2007 / Unknown	19. THERAPY DURATION #1) Unknown #2) Unknown	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) From/To Dates Type of History / Notes Description Unknown

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Genentech, Inc. James Nickas 1 DNA Way South San Francisco, CA 94080 UNITED STATES Phone: 6502255591		26. REMARKS
	24b. MFR CONTROL NO. 267119	25b. NAME AND ADDRESS OF REPORTER
24c. DATE RECEIVED BY MANUFACTURER 29-AUG-2008	24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER:	
DATE OF THIS REPORT 05-SEP-2008	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

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13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	25-JUN-2008	BIOPSY BONE MARROW myeloid dysplasia	see notes	

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 / Unknown; Unknown

ADDITIONAL INFORMATION**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
#3) CYCLOPHOSPHAMIDE (CYCLOPHOSPHAMIDE) ; Regimen #1	780 mg, UNK; Unknown	metastatic breast cancer (METASTATIC BREAST CANCER)	28-APR-2007 / Unknown; Unknown