



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: September 12, 2008

To: NCCTG Primary Clinical Research Associates

From: Sara Braun

Re: N0775, A Randomized Phase II Trial of Temozolomide (TMZ) and Avastin® or ABI-007/Carboplatin (CBDCA) and Avastin® in Patients with Unresectable Stage IV Malignant Melanoma

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_249327

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 Sara Braun at braun.sara@mayo.edu or 507-538-8226.

SB/kjm
enclosure

Genentech

IN BUSINESS FOR LIFE

Date: 1 August 2008

Axel Grothey, MD
Mayo Clinic
200 First Street S.W.
Rochester, MN 55905

RE: IND Safety Report/Expedited Case Safety Report

Investigational Product(s): **Bevacizumab**

GNE MCN: **249327 Initial** Other Reference Number(s):

Dear Dr. Grothey,

Attached is a case summary of a serious and unexpected adverse drug reaction that occurred in a subject exposed to bevacizumab. Good Clinical Practice regulations require that you promptly submit a copy of this IND safety report/expedited case safety report to your Institutional Review Board or Independent Ethics Committee. File a copy of this IND safety report/expedited case safety report in your protocol file so that it is available for review during a Sponsor monitoring visit and/or regulatory audit.

In the European Economic Area (EEA) Genentech, Inc. or its designee will directly inform the Institutional Review Boards/Ethics Committees, as appropriate.

This IND safety report/expedited case safety report must be filed with your Investigator Brochure (IB) for information only. This IND safety report/expedited case safety report is not considered an addendum to your safety reference document.

Although this adverse event has been documented and reported to the appropriate Regulatory agencies, the report does not necessarily reflect a conclusion by Genentech or the Regulatory agencies that bevacizumab contributed to the adverse event.

If questions arise, please contact the undersigned.

Sincerely,



Eric Hedrick
Medical Monitor
AVF3918s AVF3870s

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

MEDWATCH
3500A Facsimile

Mfr Report #	249327
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier	2. Age at Time of Event: 74 Years or Date of Birth:	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 120.0 lbs or 54.4 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 checked="" type="checkbox"/> Hospitalization - initial or prolonged		<input 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) 10/08/2007		4. Date of This Report (mm/dd/yyyy) 07/30/2008	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) gastroenteritis [GASTROENTERITIS]			
Case Description: This case, manufacturer control number 249327, is a report from the UNITED STATES referring to a 74 Year-old Female subject (ID#). An investigator reported this case from a Genentech-sponsored study AVF3694g (Eudract number 2006-000378-61), a multicenter, 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.			
Past medical history, concurrent illnesses, concomitant medications and allergies were not reported.			
continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates			
#1 10/08/2007 URINARY SYSTEM X-RAY (continued)			
#2 10/09/2007 CULTURE STOOL Negative			
#3 10/09/2007 BLOOD CULTURE Negative			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Caucasian			
#1 Historical Drug, NICOTINE (20 years ago)			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler)			
#1. BEVACIZUMAB OR PLACEBO (Bevacizumab) (Continued)			
#2. CAPECITABINE (CAPECITABINE)			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. 880 mg, Q3W, Intravenous		#1. 07/24/2007 to UNK	
#2. 1000 mg/m2, UNK		#2. 07/24/2007 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 checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
#2. metastatic breast (Continued)			#2. <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
6. Lot #	7. Exp. Date		8. Event Reappeared After Reintroduction? Doesn't Apply
#1. 19961, 19964	#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. IMODIUM (LOPERAMIDE HYDROCHLORIDE)			
#2. TENORMIN (ATENOLOL)			
continued in additional info section...			
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
4. Date Received by Manufacturer (mm/dd/yyyy) 07/25/2008			3. Report Source (Check all that apply)
6. If IND, Give Protocol # AVF3694G-B			<input type="checkbox"/> Foreign
7. Type of Report (Check all that apply)			<input checked="" type="checkbox"/> Study
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day			<input type="checkbox"/> Literature
<input type="checkbox"/> 7-day <input type="checkbox"/> Periodic			<input type="checkbox"/> Consumer
<input type="checkbox"/> 10-day <input checked="" type="checkbox"/> Initial			<input checked="" type="checkbox"/> Health Professional
<input checked="" type="checkbox"/> 15-day <input type="checkbox"/> Follow-up #			<input type="checkbox"/> User Facility
5. (A)NDA #			<input type="checkbox"/> Company Representative
IND # BB 7023			<input type="checkbox"/> Distributor
STN #			<input type="checkbox"/> Other:
PMA/ 510(k) #			
Combination Product <input type="checkbox"/> Yes			
Pre-1938 <input type="checkbox"/> Yes			
OTC Product <input type="checkbox"/> Yes			
9. Manufacturer Report Number 249327		8. Adverse Event Term(s) GASTROENTERITIS	
E. INITIAL REPORTER			
1. Name and Address			Phone #
2. Health Professional? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
3. Occupation		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

3500A Facsimile (Back) (Continued)

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

On 24-JUL-2007, the subject initiated treatment with BEVACIZUMAB OR PLACEBO (880 mg, Q3W, Intravenous) and CAPECITABINE (1000 mg/m², Route and frequency not reported). The lot numbers of the Bevacizumab or Placebo were 19961 and 19964. The last dose of Bevacizumab or Placebo, prior to onset of the event, was administered on 19-SEP-2007 and the last dose of Capecitabine was administered on 02-OCT-2007.

On 08-OCT-2007, the subject experienced abdominal cramping, nausea and vomiting and diarrhea (DIARRHEA) and was admitted to the hospital. On 08-OCT-2007, the subject had a KUB x-ray that was negative. On 09-OCT-2007, the subject had negative blood and stool cultures. No further clinical information was reported. Treatment for the event included Capecitabine being held. Treatment with Bevacizumab or Placebo was also held.

At the time of this report, the event outcome was not known.

The Investigator assessed the event DIARRHEA as related to BEVACIZUMAB OR PLACEBO. In the reporter's opinion, other possible etiological factors included treatment with Capecitabine.

Additional information has been requested.

ADDITIONAL INFORMATION RECEIVED ON 19-OCT-2007:

Concomitant medications included Imodium, Tenormin, Norvasc, and Prilosec.

Treatment for the event included Cipro, metronidazole, ondansetron and Protonix. At the time of this report, BEVACIZUMAB OR PLACEBO had not been restarted.

On 13-OCT-2007, the event was resolving. The subject was discharged with some loose bowel movements. Her abdominal tenderness and nausea and vomiting had disappeared.

Further information is not available.

ADDITIONAL INFORMATION RECEIVED ON 29-JUL-2008:

The event was amended to GASTROENTERITIS from DIARRHEA and the case now qualifies as an expedited report.

On 29-JUL-2008, the subject was unblinded and found to be on BEVACIZUMAB.

The investigator assessed the event GASTROENTERITIS as related to BEVACIZUMAB.

No further information was available.

REPORTS OF SIMILAR EVENTS

Genentech has not filed previous IND safety reports of GASTROENTERITIS or IND safety reports of similar events for subjects receiving BEVACIZUMAB.

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 GASTROENTERITIS.

In regards this case, the concomitant treatment with Capecitabine is a contributing factor.

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	10/08/2007	URINARY SYSTEM X-RAY Negative		

MEDWATCH

3500A Facsimile (Back) (Continued)

Mfr Report #	249327
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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)

C10. CONCOMITANT MEDICAL PRODUCTS (Continued)

- #3. NORVASC (AMLODIPINE BESYLATE)
- #4. PRILOSEC (OMEPRAZOLE)

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY UNITED STATES	2. DATE OF BIRTH Day Month Year	2a. AGE 74 Years	3. SEX Female	3a. WEIGHT 54.42 kg	4-6 REACTION ONSET Day Month Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION		
						Day 08	Month OCT	Year 2007	<input type="checkbox"/> PATIENT DIED <input checked="" type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) gastroenteritis [GASTROENTERITIS] Case Description: This case, manufacturer control number 249327, is a report from the UNITED STATES referring to a 74 Year-old Female subject (ID#). An investigator reported this case from a Genentech-sponsored study AVF3694g (Eudract number 2006-000378-61), a multicenter, 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.									
(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) CAPECITABINE (CAPECITABINE) (Continued on Additional Information Page)		20. DID REACTION ABATE AFTER STOPPING DRUG? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
15. DAILY DOSE(S) #1) 880 mg, Q3W #2) 1000 mg/m2, UNK	16. ROUTE(S) OF ADMINISTRATION #1) Intravenous #2) Unknown	
17. INDICATION(S) FOR USE #1) metastatic breast cancer (METASTATI #2) metastatic breast cancer (METASTATIC BREAST CANCER) (Continued on Additional Information Page)		21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
18. THERAPY DATES(from/to) #1) 24-JUL-2007 / Unknown #2) 24-JUL-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) #1) IMODIUM (LOPERAMIDE HYDROCHLORIDE) ; Unknown #2) TENORMIN (ATENOLOL) ; Unknown #3) NORVASC (AMLODIPINE BESYLATE) ; Unknown #4) PRILOSEC (OMEPRAZOLE) ; Unknown		
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)		
From/To Dates Unknown	Type of History / Notes Historical Drug 20 years ago	Description
(Continued on Additional Information Page)		

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. 249327		
24c. DATE RECEIVED BY MANUFACTURER 25-JUL-2008	24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER:	25b. NAME AND ADDRESS OF REPORTER
DATE OF THIS REPORT 30-JUL-2008	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	
(Continued on Additional Information Page)		

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

Past medical history, concurrent illnesses, concomitant medications and allergies were not reported.

On 24-JUL-2007, the subject initiated treatment with BEVACIZUMAB OR PLACEBO (880 mg, Q3W, Intravenous) and CAPECITABINE (1000 mg/m², Route and frequency not reported). The lot numbers of the Bevacizumab or Placebo were 19961 and 19964. The last dose of Bevacizumab or Placebo, prior to onset of the event, was administered on 19-SEP-2007 and the last dose of Capecitabine was administered on 02-OCT-2007.

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The investigator assessed the event GASTROENTERITIS as related to BEVACIZUMAB.

No further information was available.

REPORTS OF SIMILAR EVENTS

Genentech has not filed previous IND safety reports of GASTROENTERITIS or IND safety reports of similar events for subjects receiving BEVACIZUMAB.

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 GASTROENTERITIS.

In regards this case, the concomitant treatment with Capecitabine is a contributing factor.

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	08-OCT-2007	URINARY SYSTEM X-RAY Negative		
2	09-OCT-2007	CULTURE STOOL Negative		
3	09-OCT-2007	BLOOD CULTURE Negative		

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
#1) BEVACIZUMAB OR PLACEBO (Bevacizumab) Powder and solvent for solution for infusion, 100 mg {Lot # 19961, 19964}; Regimen #1	880 mg, Q3W; Intravenous	metastatic breast cancer (METASTATIC BREAST CANCER)	24-JUL-2007 / Unknown; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Historical Drug 20 years ago	(NICOTINE); Drug Indication: (), Drug Reaction: ()

25b. Name And Address of Reporters continued