



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: April 3, 2009

To: NCCTG Primary Clinical Research Associates

From: Sara Braun
Protocol Development Coordinator

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 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.

269963_F1_03Apr2009

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: 28 October 2008

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

→ AP2B
NC
AC

RE: IND Safety Report/Expedited Case Safety Report

Investigational Product(s): **Bevacizumab**

GNE MCN: **269963**

Other Reference Number(s):

Follow Up #1

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

Mfr Report #	269963
UF/Importer Report #	
FDA Use Only	

MEDWATCH
3500A Facsimile

A. PATIENT INFORMATION			
1. Patient Identifier	2. Age at Time of Event: 75 Years or Date of Birth:	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 119.0 lbs or 54.0 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 checked="" 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 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)		4. Date of This Report (mm/dd/yyyy) 10/27/2008	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) memory impairment [MEMORY IMPAIRMENT]			
Case Description: IND SAFETY REPORT			
This case, manufacturer control number 269963, is a study report from the United States referring to a 75 Year-old Male subject (ID# _____). An investigator reported this case from study AVF3671G-B, a randomized, double-blind, placebo-controlled, phase IIIb trial comparing bevacizumab therapy with or without erlotinib after completion of chemotherapy with bevacizumab for the first-line treatment of locally advanced or metastatic non-squamous non-small cell lung cancer, sponsored by Genentech, Inc.			
continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates			
#1 10/16/2008 BLOOD CREATININE (continued)			
#2 10/16/2008 BLOOD GLUCOSE (continued)			
#3 10/16/2008 BLOOD POTASSIUM (continued)			
#4 10/16/2008 BLOOD SODIUM (continued)			
#5 10/16/2008 BLOOD UREA (continued)			
#6 10/16/2008 HAEMATOCRIT (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.)			
#1 Historical Condition, PROSTATE CANCER			
#2 -/-/2006 to UNK, Historical Condition, OSTEOPOROSIS			
#3 Historical Condition, ATELECTASIS			
#4 Current Condition, HYPOTHYROIDISM			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler)			
#1. ERLOTINIB OR PLACEBO (Erlotinib) Tablet			
#2. Bevacizumab (BEVACIZUMAB) Powder and solvent for (Continued)			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. 150 mg, qd, Oral		#1. 10/03/2008 to UNK	
#2. 900 UNK, Q3W, Intravenous		#2. 11/01/2007 to UNK	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. nslc (NSCLC)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2. nslc (NSCLC)		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
6. Lot #		7. Exp. Date	
#1. 2007365		#1. _____	
#2. Not reported		#2. _____	
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)		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)		5. (A)NDA #	
10/20/2008		IND # BB 7023	
6. If IND, Give Protocol #		STN #	
AVF3671G-B		PMA/ 510(k) #	
7. Type of Report (Check all that apply)		Combination Product <input type="checkbox"/> Yes	
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day		Pre-1938 <input type="checkbox"/> Yes	
<input type="checkbox"/> 7-day <input type="checkbox"/> Periodic		OTC Product <input type="checkbox"/> Yes	
<input type="checkbox"/> 10-day <input type="checkbox"/> Initial			
<input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up #1			
9. Manufacturer Report Number		8. Adverse Event Term(s)	
269963		MEMORY IMPAIRMENT	
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

3500A Facsimile (Back) (Continued)

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Mfr Report #	269963
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ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

On 01-NOV-2007, the subject initiated treatment with Bevacizumab (900, units not reported, Intravenous, Q3 Wks). On 03-OCT-2008, the subject initiated treatment with Erlotinib or Placebo (150 mg, qd, Oral). The lot number of the Bevacizumab was not reported. The lot number of the Erlotinib or Placebo was 2007365. The last dose of Bevacizumab, prior to onset of the event, was administered on 02-OCT-2008 and the last dose of Erlotinib or Placebo was administered on 16-OCT-2008.

On a date reported as "13-OCT", the subject developed disabling memory impairment (MEMORY IMPAIRMENT). On 16-OCT-2008, the subject had an unspecified blood test, the results of which were not available at the time of this report. Treatment with Bevacizumab and Erlotinib or Placebo was interrupted. The subject did not receive treatment for the memory impairment.

At the time of this report, the event outcome was unknown.

On 17-OCT-2008 the subject was unblinded and was receiving Erlotinib.

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

The Investigator assessed the event memory impairment as related to Erlotinib and Bevacizumab. Other possible etiological factors included disease under study.

Additional information has been requested, if received the case will be updated accordingly.

ADDITIONAL INFORMATION RECEIVED ON 20-OCT-2008:

Past medical history included prostate cancer, osteoporosis and atelectasis. Concurrent condition at the time of event onset included hypothyroidism.

The subject was status post four cycles of study treatment and has done well on the maintenance phase except for a strep viridans bacteremia from which he has now recovered. He continued to complain of very limited appetite and short term memory loss which he feels is getting very bad. Lab test included WBC 8.85 x10E3/uL, Hgb 14.2 g/dl, Hct 45.3%, neutrophil percentage 61.9%, absolute neutrophil 5.5 X10E3/uL, sodium 140 mmol/L, potassium 4 mmol/L, glucose 104 mg/dl, creatinine 1.4 mg/dl and urea nitrogen 36 mg/dl. He had received multiple CT scans which have been unremarkable. An MRI could not be performed as the subject has a pacemaker. No additional details pertaining to the event was provided.

The investigator assessed the event as possibly related to Bevacizumab or study drug or the combination of the two.

Additional information has been requested, if received the case will be updated accordingly.

PREVIOUSLY FILED IND SAFETY REPORTS OF SIMILAR EVENTS

Genentech has previously filed the following IND safety reports of similar events from studies of Bevacizumab and Erlotinib.

Manufacturer Control Number (MCN)	ISR Primary Event	Date Submitted
269963	Memory Impairment	31-OCT-2008

SPONSOR ASSESSMENT: Based on review of available data, no compelling evidence of a cause-and-effect relationship between administration of Bevacizumab and Erlotinib and the occurrence of Memory Impairment can be identified. At this time, the sponsor does not believe changes to the conduct of the trial are warranted.

Pharmacovigilance:

Memory impairment is unlisted per the erlotinib IB and unlisted and unlabeled per the bevacizumab IB and USPI.

B6. LABORATORY DATA

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	10/16/2008	BLOOD CREATININE	1.4 mg/dL	1.3 0.5

MEDWATCH

3500A Facsimile (Back) (Continued)

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Mfr Report #	269963
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2	10/16/2008	BLOOD GLUCOSE	104 mg/dL	100 65
3	10/16/2008	BLOOD POTASSIUM	4.0 mmol/L	5.4 3.6
4	10/16/2008	BLOOD SODIUM	140 mmol/L	145 135
5	10/16/2008	BLOOD UREA	36 mg/dL	23 7
6	10/16/2008	HAEMATOCRIT	45.3 %	47 37.4
7	10/16/2008	HAEMOGLOBIN	14.9 g/dL	16.3 12.3
8	10/16/2008	INVESTIGATION	see notes	
		Unspecified blood test. Results pending at time of report.		
9	10/16/2008	NEUTROPHIL COUNT	5.5 x10 ³ /μL	7 1.3
10	10/16/2008	NEUTROPHIL PERCENTAGE	61.9 %	75.9 40.1
11	10/16/2008	WHITE BLOOD CELL COUNT	8.86 x10 ³ /μL	9.29 3.28

C1. NAME (Continued)

Suspect Medication #2: Bevacizumab(BEVACIZUMAB) Powder and solvent for solution for infusion, 100mg

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY UNITED STATES	2. DATE OF BIRTH			2a. AGE 75 Years	3. SEX Male	3a. WEIGHT 53.97 kg	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 checked="" 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) memory impairment [MEMORY IMPAIRMENT] Case Description: IND SAFETY REPORT This case, manufacturer control number 269963, is a study report from the United States referring to a 75 Year-old Male subject (ID#).											
(Continued on Additional Information Page)											

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1) ERLOTINIB OR PLACEBO (Erlotinib) Tablet {Lot # 2007365} #2) Bevacizumab (BEVACIZUMAB) Powder and solvent for solution for infusion, 100 mg {Lot # Not reported}		20. DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA Unknown
15. DAILY DOSE(S) #1) 150 mg, qd #2) 900 UNK, Q3W	16. ROUTE(S) OF ADMINISTRATION #1) Oral #2) Intravenous	
17. INDICATION(S) FOR USE #1) nslc (NSCLC) #2) nslc (NSCLC)		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) 03-OCT-2008 / Unknown #2) 01-NOV-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 Unknown 2006 to Unknown	Type of History / Notes Historical Condition Historical Condition	Description PROSTATE CANCER (PROSTATE CANCER) OSTEOPOROSIS (OSTEOPOROSIS)

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
24c. DATE RECEIVED BY MANUFACTURER 20-OCT-2008	24b. MFR CONTROL NO. 269963	25b. NAME AND ADDRESS OF REPORTER
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 27-OCT-2008	25a. REPORT TYPE <input type="checkbox"/> INITIAL <input checked="" type="checkbox"/> FOLLOWUP: 1	

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

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The subject was status post four cycles of study treatment and has done well on the maintenance phase except for a strep viridans bacteremia from which he has now recovered. He continued to complain of very limited appetite and short term memory loss which he feels is getting very bad. Lab test included WBC 8.85 x10E3/uL, Hgb 14.2 g/dl, Hct 45.3%, neutrophil percentage 61.9%, absolute neutrophil 5.5 X10E3/uL, sodium 140 mmol/L, potassium 4 mmol/L, glucose 104 mg/dl, creatinine 1.4 mg/dl and urea nitrogen 36 mg/dl. He had received multiple CT scans which have been unremarkable. An MRI could not be performed as the subject has a pacemaker. No additional details pertaining to the event was provided.

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Pharmacovigilance: Memory impairment is unlisted per the erlotinib IB and unlisted and unlabeled per the bevacizumab IB and USPI.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	16-OCT-2008	BLOOD CREATININE	1.4 mg/dL	1.3 0.5
2	16-OCT-2008	BLOOD GLUCOSE	104 mg/dL	100 65

ADDITIONAL INFORMATION**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
3	16-OCT-2008	BLOOD POTASSIUM	4.0 mmol/L	5.4 3.6
4	16-OCT-2008	BLOOD SODIUM	140 mmol/L	145 135
5	16-OCT-2008	BLOOD UREA	36 mg/dL	23 7
6	16-OCT-2008	HAEMATOCRIT	45.3 %	47 37.4
7	16-OCT-2008	HAEMOGLOBIN	14.9 g/dL	16.3 12.3
8	16-OCT-2008	INVESTIGATION	see notes	
Unspecified blood test. Results pending at time of report.				
9	16-OCT-2008	NEUTROPHIL COUNT	5.5 x10 ³ /μL	7 1.3
10	16-OCT-2008	NEUTROPHIL PERCENTAGE	61.9 %	75.9 40.1
11	16-OCT-2008	WHITE BLOOD CELL COUNT	8.86 x10 ³ /μL	9.29 3.28

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Historical Condition	ATELECTASIS (ATELECTASIS);
Unknown	Current Condition	HYPOTHYROIDISM (HYPOTHYROIDISM);