



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: April 3, 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 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_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 Lynn Flickinger at Flickinger.lynn@mayo.edu or 507-538-7034.

LF/kjm
enclosure

Genentech

IN BUSINESS FOR LIFE

Date: 22 October 2008

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

→? ADLB
CC
AG

RE: IND Safety Report/Expedited Case Safety Report

Investigational Product(s): **Bevacizumab**

GNE MCN: **269963 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 #	269963
UF/Importer Report #	
FDA Use Only	

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
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In confidence

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: _____ Disability or Permanent Damage
 Life-threatening (mm/dd/yyyy) 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)

4. Date of This Report (mm/dd/yyyy)
10/21/2008

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 INVESTIGATION (continued)

7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

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
#1. 150 mg, qd, Oral
#2. 900 UNK, Q3W, Intravenous

3. Therapy Dates (if unknown, give duration from/to (or best estimate))
#1. 10/03/2008 to UNK
#2. 11/01/2007 to UNK

4. Diagnosis for Use (Indication)
#1. nsclc (NSCLC)
#2. nsclc (NSCLC)

5. Event Abated After Use Stopped or Dose Reduced?
#1. Yes No Doesn't Apply
#2. Yes No Doesn't Apply

6. Lot #
#1. 2007365
#2. Not reported

7. Exp. Date
#1.
#2.

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
 Study
 Literature
 Consumer
 Health Professional
 User Facility
 Company Representative
 Distributor
 Other:

4. Date Received by Manufacturer (mm/dd/yyyy)
10/16/2008

5. (A)NDA #
IND # BB 7023
STN #
PMA/ 510(k) #

6. If IND, Give Protocol #
AVF3671G-B

7. Type of Report (Check all that apply)
 5-day 30-day
 7-day Periodic
 10-day Initial
 15-day Follow-up #

Combination Product Yes
Pre-1938 Yes
OTC Product Yes

8. Adverse Event Term(s)
MEMORY IMPAIRMENT

9. Manufacturer Report Number
269963

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)

Mir Report #	269963
UF/Importer Report #	
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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.

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	INVESTIGATION	see notes	
		Unspecified blood test. Results pending at time of report.		

C1. NAME (Continued)

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

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

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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	INVESTIGATION	see notes	

Unspecified blood test. Results pending at time of report.