



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: April 3, 2009

To: NCCTG Primary Clinical Research Associates

From: Alicia Elsing
Protocol Development Coordinator

Re: N0821, A Phase II First-Line Study of a Combination of Pemetrexed, Carboplatin and Bevacizumab in Advanced Nonsquamous NSCLC Evaluating Efficacy and Tolerability in Elderly Patients (Age \geq 70 yrs) with Good Performance Status (PS $<$ 2)

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 Alicia Elsing at Elsing.alicia@mayo.edu or 507-538-3893.

AE/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 |
| 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: _____ <input checked="" type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening (mm/dd/yyyy) <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) 10/21/2008 | |
| 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 | 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) | |
| #1. nsclc (NSCLC) | |
| #2. nsclc (NSCLC) | |
| 5. Event Abated After Use Stopped or Dose Reduced? | 8. Event Reappeared After Reintroduction? |
| #1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply | #1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply |
| #2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply | #2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" 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) 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) | |
| <input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> 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) |
| | <input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input checked="" type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input type="checkbox"/> Follow-up # _____ |
| 8. Adverse Event Term(s) MEMORY IMPAIRMENT | 9. Manufacturer Report Number 269963 |

| E. INITIAL REPORTER | | |
|---|---------------|--|
| 1. Name and Address | | Phone # |
| | | |
| 2. Health Professional? | 3. Occupation | 4. Initial Reporter Also Sent Report to FDA |
| <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No | | <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)

| | |
|----------------------|--------------|
| Mir Report # | 269963 |
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| | FDA Use Only |

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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.