



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: October 31, 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 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_266802_F1

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

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

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| | |
|----------------------|--------|
| Mfr Report # | 266802 |
| UF/Importer Report # | |
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| A. PATIENT INFORMATION | | | |
|--|--|---|--|
| 1. Patient Identifier | 2. Age at Time of Event: 55 Years or Date of Birth: | 3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male | 4. Weight 121.0 lbs or 54.9 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) 08/20/2008 | | 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) troponin leak [TROPONIN INCREASED] | | | |
| Case Description: IND SAFETY REPORT | | | |
| This case, manufacturer control number 266802, is a report from United States referring to a 55 year-old female subject (ID #). An Investigator reported this case from study AVF3744G, A phase II Non-small cell lung cancer/squamous cell study | | | |
| Past medical treatments included paclitaxel and carboplatin. Medical history included chronic obstructive pulmonary disease. Concomitant medications included acetaminophen, hydrocodone bitartrate, fluticasone propionate, salmeterol xinafoate, continued in additional info section... | | | |
| 6. Relevant Tests/Laboratory Data, Including Dates | | | |
| #1 08/22/2008 BLOOD CREATINE PHOS (continued) | | | |
| #2 08/22/2008 CARDIAC ENZYMES (continued) | | | |
| #3 08/25/2008 INVESTIGATION (continued) | | | |
| #4 08/23/2008 ECHOCARDIOGRAM (continued) | | | |
| #5 08/20/2008 ELECTROCARDIOGRAM (continued) | | | |
| #6 08/20/2008 TROPONIN I (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.) Race: Caucasian | | | |
| #1 Negative Med Cond, SMOKER | | | |
| #2 Negative Med Cond, DRUG ABUSE | | | |
| #3 Historical Condition, (Continued) continued in additional info section... | | | |

| C. SUSPECT PRODUCT(S) | | | |
|---|--------------|--|--|
| 1. Name (Give labeled strength & mfr/labeler) | | | |
| #1. Avastin (BEVACIZUMAB) Powder and solvent for solution (Continued) | | | |
| #2. | | | |
| 2. Dose, Frequency & Route Used | | 3. Therapy Dates (if unknown, give duration) from/to (or best estimate) | |
| #1. 880 mg, Q3W, Intravenous | | #1. 01/09/2008 to UNK | |
| #2. | | #2. | |
| 4. Diagnosis for Use (Indication) | | 5. Event Abated After Use Stopped or Dose Reduced? | |
| #1. NSCLC (NSCLC) | | #1. <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Doesn't Apply | |
| #2. | | #2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply | |
| 6. Lot # | 7. Exp. Date | 8. Event Reappeared After Reintroduction? | |
| #1. 703976 | #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 type="checkbox"/> Doesn't Apply | |
| 9. NDC# or Unique ID | | | |
| 10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event) | | | |
| #1. VICODIN (ACETAMINOPHEN, HYDROCODONE BITARTRATE) continued in additional info section... | | | |
| 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) | | | 3. Report Source (Check all that apply) |
| 08/28/2008 | | | |
| 6. If IND, Give Protocol # | | | |
| AVF3744G | | | |
| 7. Type of Report (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: |
| <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 type="checkbox"/> Initial | | | |
| <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up #1 | | | |
| 5. (A)NDA # | | IND # | |
| | | BB 7023 | |
| 6. PMA/ 510(k) # | | STN # | |
| | | | |
| Combination Product | | Pre-1938 | |
| <input type="checkbox"/> Yes | | <input type="checkbox"/> Yes | |
| OTC Product | | | |
| <input type="checkbox"/> Yes | | | |
| 9. Manufacturer Report Number | | 8. Adverse Event Term(s) | |
| 266802 | | TROPONIN INCREASED | |
| 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.

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

oxycodone hydrochloride, and tiotropium bromide. Allergies reported included drug hypersensitivity to codeine, sulfa, and methocarbamol.

On 09-JAN-2008, the subject received bevacizumab (880 mg, Q3W, Intravenous). The lot number was #703976. The last dose prior to the event was administered on 06-AUG-2008.

On an unknown date, the subject presented with weakness and shortness of breath. On 20-AUG-2008, the subject hospitalized with troponin leak (TROPONIN INCREASED). Relevant laboratory tests included troponin I of 1.125. On 21-AUG-2008, troponin I was 0.450. EKG revealed a sinus bradycardia left axis deviation poor R progression anterior lead, no ectopy or arrhythmia. Chest x-ray was negative. The treatment for the event included sodium chloride. Treatment with Bevacizumab was held.

At the time of the report, the event remained ongoing.

The Investigator assessed the event troponin increased as related to Bevacizumab. No other possible etiological factors were reported.

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

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

ADDITIONAL INFORMATION RECEIVED ON 28-AUG-2008:

On 22-AUG-2008, relevant laboratory tests included elevated CK 201 U/L (normal range 30-135), CKMB 8.8 ng/mL (normal range 0.1-3.2), troponin I ES 2.54 ng/mL (normal range 0.0-0.034). Relevant diagnostic tests included the following: echocardiogram done on 23-AUG-2008 that revealed an estimated ejection fraction 25-30%, moderate global hypokinesis of the left ventricle, and the mid-inferior, apical anterior, apical inferior, and apical wall segments were hypokinetic and a cardiac catheterization done on 25-AUG-2008 that revealed findings of normal coronaries with severely depressed left ventricular systolic function (LV ejection fraction 34%) probably secondary to chemotherapy.

No further information is available.

PREVIOUSLY FILED IND SAFETY REPORTS OF SIMILAR EVENTS

Genentech has not filed previous IND safety reports of troponin leak 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 troponin leak.

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 | 08/22/2008 | BLOOD CREATINE PHOSPHOKINASE INCREASED | 201 U/L | 135 30 |
| 2 | 08/22/2008 | CARDIAC ENZYMES | 8.8 ng/mL | 3.2 0.1 |
| 3 | 08/25/2008 | INVESTIGATION | see notes | |
| | | cardiac catheterization revealed an estimated ejection fraction 25-30%, moderate global hypokinesis of the left ventricle, and the mid-inferior, apical anterior, apical inferior, and apical wall segments were hypokinetic | | |
| 4 | 08/23/2008 | ECHOCARDIOGRAM | see notes | |
| | | revealed an estimated ejection fraction 25-30%, moderate global hypokinesis of the left ventricle, and | | |

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the mid-inferior, apical anterior, apical inferior, and apical wall segments were hypokinetic

| | | | | |
|---|------------|--|-------------|--------------|
| 5 | 08/20/2008 | ELECTROCARDIOGRAM | see notes | |
| sinuse bradycardia lt axis deviation poor r progression anterior lead no ectopy or arrythmia. | | | | |
| 6 | 08/20/2008 | TROPONIN I | 1.125 ng/mL | 0.034 0.0 |
| 7 | 08/21/2008 | TROPONIN I | 0.45 ng/mL | 0.034 0.0 |
| 8 | 08/22/2008 | TROPONIN I | 2.54 ng/mL | 0.034 0.0 |
| 9 | 08/20/2008 | X-RAY Negative no infiltrates, no pneumothorax, no hemothorax, no masses, no cardiomegaly, no CHF, no effusion, no free air. | see notes | |

B7. OTHER RELEVANT HISTORY

| # | Start/Stop Date | Condition Type / Condition | Notes |
|---|-----------------|--|----------------------------|
| 3 | | Historical Condition CHRONIC OBSTRUCTIVE PULMONARY DISEASE | |
| 4 | | Historical Drug PACLITAXEL; Drug Indication: DRUG USE FOR UNKNOWN INDICATION | |
| 5 | | Historical Drug CARBOPLATIN; Drug Indication: DRUG USE FOR UNKNOWN INDICATION | |
| 6 | | Allergy DRUG HYPERSENSITIVITY | Codeine and Methocarbamol. |
| 7 | | Allergy DRUG HYPERSENSITIVITY | |

C1. NAME (Continued)

Suspect Medication #1: Avastin(BEVACIZUMAB) Powder and solvent for solution for infusion, 100mg

C10. CONCOMITANT MEDICAL PRODUCTS (Continued)

- #2. ADVAIR DISKUS (FLUTICASONE PROPIONATE, SALMETEROL XINAFOATE)
- #3. OXYCONTIN (OXYCODONE HYDROCHLORIDE)
- #4. SPIRIVA (TIOTROPIUM BROMIDE)

| | |
|--|--|
| SUSPECT ADVERSE REACTION REPORT | |
| | |
| | |

I. REACTION INFORMATION

| | | | | | | | | | | | |
|---|-------------------------------------|------------------|-------|------|---------------------|---------------|---------------------|--------------------|-------|------|---|
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY UNITED STATES | 2. DATE OF BIRTH | | | 2a. AGE | 3. SEX | 3a. WEIGHT | 4-6 REACTION ONSET | | | 8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION |
| | | Day | Month | Year | 55 Years | Female | 54.88 kg | Day | Month | Year | |
| 7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) troponin leak [TROPONIN INCREASED] Case Description: IND SAFETY REPORT This case, manufacturer control number 266802, is a report from United States referring to a 55 year-old female subject (ID #). An Investigator reported this case from study AVF3744G, A phase II Non-small cell lung cancer/squamous cell study Past medical treatments included paclitaxel and carboplatin. | | | | | | | | | | | <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 |
| (Continued on Additional Information Page) | | | | | | | | | | | |

II. SUSPECT DRUG(S) INFORMATION

| | | |
|--|--|---|
| 14. SUSPECT DRUG(S) (include generic name) #1) Avastin (BEVACIZUMAB) Powder and solvent for solution for infusion, 100 mg [Lot # 703976] | | 20. DID REACTION ABATE AFTER STOPPING DRUG? |
| 15. DAILY DOSE(S) #1) 880 mg, Q3W | 16. ROUTE(S) OF ADMINISTRATION #1) Intravenous | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> NA |
| 17. INDICATION(S) FOR USE #1) NSCLC (NSCLC) | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? |
| 18. THERAPY DATES(from/to) #1) 09-JAN-2008 / Unknown | 19. THERAPY DURATION #1) Unknown | <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA |

III. CONCOMITANT DRUG(S) AND HISTORY

| | | |
|--|-------------------------|-------------------------|
| 22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1) VICODIN (ACETAMINOPHEN, HYDROCODONE BITARTRATE) ; Unknown #2) ADVAIR DISKUS (FLUTICASONE PROPIONATE, SALMETEROL XINAFOATE) ; Unknown #3) OXYCONTIN (OXYCODONE HYDROCHLORIDE) ; Unknown #4) SPIRIVA (TIOTROPIUM BROMIDE) ; Unknown | | |
| 23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) | | |
| From/To Dates | Type of History / Notes | Description |
| Unknown | Negative Med Cond | SMOKER (SMOKER) |
| Unknown | Negative Med Cond | DRUG ABUSE (DRUG ABUSE) |

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. 266802 | 25b. NAME AND ADDRESS OF REPORTER |
| 24c. DATE RECEIVED BY MANUFACTURER 28-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 type="checkbox"/> INITIAL <input checked="" type="checkbox"/> FOLLOWUP: 1 | |

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

Medical history included chronic obstructive pulmonary disease. Concomitant medications included acetaminophen, hydrocodone bitartrate, fluticasone propionate, salmeterol xinafoate, oxycodone hydrochloride, and tiotropium bromide. Allergies reported included drug hypersensitivity to codeine, sulfa, and methocarbamol.

On 09-JAN-2008, the subject received bevacizumab (880 mg, Q3W, Intravenous). The lot number was #703976. The last dose prior to the event was administered on 06-AUG-2008.

On an unknown date, the subject presented with weakness and shortness of breath. On 20-AUG-2008, the subject hospitalized with troponin leak (TROPONIN INCREASED). Relevant laboratory tests included troponin I of 1.125. On 21-AUG-2008, troponin I was 0.450. EKG revealed a sinus bradycardia left axis deviation poor R progression anterior lead, no ectopy or arrhythmia. Chest x-ray was negative. The treatment for the event included sodium chloride. Treatment with Bevacizumab was held.

At the time of the report, the event remained ongoing.

The Investigator assessed the event troponin increased as related to Bevacizumab. No other possible etiological factors were reported.

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No further information is available.

PREVIOUSLY FILED IND SAFETY REPORTS OF SIMILAR EVENTS

Genentech has not filed previous IND safety reports of troponin leak 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 troponin leak.

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 | 22-AUG-2008 | BLOOD CREATINE PHOSPHOKINASE INCREASED | 201 U/L | 135 30 |
| 2 | 22-AUG-2008 | CARDIAC ENZYMES | 8.8 ng/mL | 3.2 0.1 |
| 3 | 25-AUG-2008 | INVESTIGATION | see notes | |
| | | cardiac catheterization revealed an estimated ejection fraction 25-30%, moderate global hypokinesis of the left ventricle, and the mid-inferior, apical anterior, apical inferior, and apical wall segments were hypokinetic | | |
| 4 | 23-AUG-2008 | ECHOCARDIOGRAM | see notes | |
| | | revealed an estimated ejection fraction 25-30%, moderate global hypokinesis of the left ventricle, and the mid-inferior, apical anterior, apical inferior, and apical wall segments were hypokinetic | | |

ADDITIONAL INFORMATION**13. Lab Data**

| # | Date | Test / Assessment / Notes | Results | Normal High / Low |
|---|-------------|---|-------------|-------------------|
| 5 | 20-AUG-2008 | ELECTROCARDIOGRAM | see notes | |
| | | sinuse bradycardia lt axis deviation poor r progression anterior lead no ectopy or arrythmia. | | |
| 6 | 20-AUG-2008 | TROPONIN I | 1.125 ng/mL | 0.034 0.0 |
| 7 | 21-AUG-2008 | TROPONIN I | 0.45 ng/mL | 0.034 0.0 |
| 8 | 22-AUG-2008 | TROPONIN I | 2.54 ng/mL | 0.034 0.0 |
| 9 | 20-AUG-2008 | X-RAY Negative no infiltrates, no pneumothorax, no hemothorax, no masses, no cardiomegaly, no CHF, no effusion, no free air. | see notes | |

23. OTHER RELEVANT HISTORY continued

| From/To Dates | Type of History / Notes | Description |
|---------------|---------------------------------------|--|
| Unknown | Historical Condition | COPD (CHRONIC OBSTRUCTIVE PULMONARY DISEASE); |
| Unknown | Historical Drug | (PACLITAXEL); Drug Indication: DRUG USE FOR UNKNOWN INDICATION (DRUG USE FOR UNKNOWN INDICATION), Drug Reaction: () |
| Unknown | Historical Drug | (CARBOPLATIN); Drug Indication: DRUG USE FOR UNKNOWN INDICATION (DRUG USE FOR UNKNOWN INDICATION), Drug Reaction: () |
| Unknown | Allergy Codeine and Methocarbamol. | DRUG ALLERGY (DRUG HYPERSENSITIVITY); |
| Unknown | Allergy | SULFONAMIDE ALLERGY (DRUG HYPERSENSITIVITY); |