



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: March 24, 2006
To: NCCTG Primary Clinical Research Associates
From: Lori Bratvold
Protocol Development Coordinator
Re: N0177, A Phase I/II Study of OSI-774 and Temozolomide in Combination with Radiation Therapy in Glioblastoma Multiforme

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with OSI-774 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_219146_F1

Please note that all risks currently cited in the NCCTG consent form can not 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 Lori Bratvold at 507-266-3549.

lb
enclosure

Genentech

BIO[®]NCOLOGY

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South San Francisco, CA 94080-4990
(650) 225-1000

January 25, 2006

Ravi Rao, MD
Mayo Clinic
Gonda-Desk 10 South
Medical Oncology
200 First Street SW
Rochester, MN 55905

RE: IND Safety Report
Molecules: Bevacizumab and Erlotinib
MCN:219146 FOLLOW UP 1

Dear Dr. Rao:

A sponsor conducting a study under an investigational new drug application (IND) is required to inform all participating investigators, in writing, of any IND study occurrence of a serious and unexpected adverse drug reaction (ADR). An unexpected ADR is an adverse event that is judged by either an investigator or the sponsor as having a reasonable suspected causal relationship to an investigational product, and that is not already identified as an ADR in the current product Investigator Brochure (IB) or in its amendments.

Attached is a case summary of a serious and unexpected ADR that occurred in a subject participating in a Genentech-sponsored clinical trial. Please review the case report and promptly submit this information to your Institutional Review Board or Independent Ethics Committee. Also, please physically append this report to your bevacizumab investigator brochure. If you are participating in a combination study with erlotinib and bevacizumab please also append this report to the erlotinib investigator brochure.

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,



Jeffrey Bloss, MD
Group Medical Monitor

FINAL
Version: 1.0
January 10, 2006

MEDWATCH

The FDA Safety Information and
Adverse Event Reporting Program

Mfr report #	219146
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event: 66 Years or Date of Birth:	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 151.0 lbs or 68.5 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 11/01/2005 (mo/day/yr)
 Life-threatening
 Hospitalization - initial or prolonged

Disability
 Congenital Anomaly
 Required Intervention to Prevent Permanent Impairment/Damage
 Other:

3. Date of Event (mo/day/year) 11/01/2005
4. Date of This Report (mo/day/year) 01/25/2006

5. Describe Event or Problem
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)
hemoptysis[HAEMOPTYSIS]

Case Description:
IND SAFETY REPORT

This case, manufacturer control number 219146, is a report from the United States referring to a 66 year old male subject. An Investigator reported this case from study OSI2950G a phase II, multicenter, randomized clinical trial to evaluate the efficacy and safety of Avastin (bevacizumab) in combination with docetaxel or Tarceva (Erlotinib hydrochloride) compared with docetaxel alone for treatment of recurrent or refractory non-small cell lung cancer sponsored by Genentech Inc.

Past medical history, concurrent conditions, allergies and concomitant medications were not reported.
continued in additional info section...

6. Relevant Tests/Laboratory Data, Including Dates
#1 07/02/2005 CT Scan (continued)
#2 Pathology (continued)
#3 blood culture Positive (continued)

7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)
#1 Historical Condition, HAEMOPTYSIS (continued)
#2 08/23/2005 to 08/23/2005 Procedure, (continued)
#3 05/26/2005, Procedure, RADIOTHERAPY (continued)
#4 UNK, Current Condition, ANAEMIA (continued)
continued in additional info section...

C. SUSPECT MEDICATION(S)

1. Name (Give labeled strength & mfr/labeler, if known)

#1. Erlotinib(Erlotinib) Tablet
#2. Avastin(BEVACIZUMAB) Pwdr & solvent,infusion soln, 100mg

2. Dose, Frequency & Route Used
#1. 150 mg, qd, Oral
#2. 1035 mg, Q3W, Intravenous

3. Therapy Dates (if unknown, give duration) from/to (or best estimate)
#1. 09/14/2005 to 10/--/2005
#2. 09/14/2005 to 10/05/2005

4. Diagnosis for Use (Indication)
#1. NON-SMALL CELL LUNG CANCER
#2. NON-SMALL CELL LUNG CANCER

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

6. Lot # (if known) #1. 1(continued) #2. not reported
7. Exp. Date (if known) #1. UNK #2. UNK

8. Event Reappeared After Reintroduction?
#1. Yes No Doesn't Apply
#2. Yes No Doesn't Apply

9. NDC# (For product problems only)

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)
ASA (ASPIRIN) UNK to UNK
LOVENOX (ENOXAPARIN SODIUM) UNK to UNK
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

3. Report Source (Check all that apply)
 Foreign
 Study
 Literature
 Consumer
 Health Professional
 User Facility
 Company Representative
 Distributor
 Other:

4. Date Received by Manufacturer (mo/day/yr) 01/11/2006

5. (A)NDA # IND # 61,874
PLA #
Pre-1938 Yes
OTC Product Yes

6. If IND, Give Protocol # OSI2950G-O

7. Type of Report (Check all that apply)
 5-day 15-day
 10-day Periodic
 Initial Follow-up #1

8. Adverse Event Term(s) HAEMOPTYSIS

9. Manufacturer Report Number 219146

E. INITIAL REPORTER

1. Name and Address Phone # UNK

2. Health Professional? Yes No

3. Occupation Investigator

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.

3500A Facsimile

**Medication and Device
Experience Report**
(continued)Submission of a report does not constitute
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ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (cont.)**

On 14 Sep 05 the subject commenced erlotinib 150 mg PO, QD (lot # 150359, 150357) and bevacizumab 1035 mg IV Q3W (lot # not reported). The last known administration of erlotinib was reported as Oct 05 (no day specified) and for bevacizumab 05 Oct 05.

During Oct 05, the subject was admitted to the hospital for dehydration (see MCN 218761). While still hospitalized, on 01 Nov 05 he developed a sudden onset of severe hemoptysis and arrested. Unspecified treatment medications were administered. Resuscitation was unsuccessful and the subject died the same day. The investigator reported that there was evidence of possible progression of underlying non-small cell lung cancer (not specified further). No laboratory data or other clinical information was available.

The investigator assessed the event of hemoptysis as not related to erlotinib, but related to bevacizumab. In the reporter's opinion, other possible etiological factors included the subject's underlying non-small cell lung cancer.

Additional information has been requested.

ADDITIONAL INFORMATION RECEIVED ON 11 JAN 06.

Concomitant medications included aspirin and enoxaparin for DVT prophylaxis; fluticasone/ salmeterol, albuterol, morphine sulphate, acetaminophen/ oxycodone, simethicone, polyethylene glycol and aspirin. The subject smoked one pack a day for 55 years, but quit in May 2005. The subject also used to drink heavily but has recently reduced this. The subject's father died from lung cancer at age 65 and his mother of stomach and GI cancer at age 77. Allergies included penicillin and streptomycin causing rash.

The subject's predominant histological type of cancer was noted as adenocarcinoma. CT scan on 02 Jul 05 describes a left upper lobe mass extending to right hilum excluding upper lobe pulmonary vein without occlusion. A thoracentesis was performed on 23 Aug 05. The subject received a total of 5500Gy of radiation therapy over 22 fractions to the gross chest domain.

The subject had experienced one episode of hemoptysis prior to treatment on this study.

On 05 Oct 05, during the scheduled visit for the second administration of bevacizumab, the investigator noted that the subject had streaky sputum per information detailed in the physicians notes (during the second administration of bevacizumab). The investigator noted this was a grade I event and no change to study dosing was made. It was reported that the subject had several episodes of hemoptysis but none that persisted. Again on 07 Oct 05 the subject reported coughing up blood but hospital notes indicate that the subject refused to attend the emergency room at the time. The subject was admitted to hospital on 12 Oct 05. The subject was reported to be weak and dehydrated, he had not been able to eat and could barely stand. On admission the subject did not have fever, chills or night sweats. He had a mild rash from the erlotinib. There was a mild sore throat but no dysphagia. No diplopia or blurred vision. The subject had dyspnea at rest and on exertion. The subject had occasional hemoptysis on coughing. There were decreased breath sounds at the bases. He had chest discomfort but no palpitations. There was nausea with occasional vomiting and anorexia. The subject denied diarrhea, constipation, hematochezia or melena. There was no epistaxis or gum bleeding. There was no evidence of cavitation noted until the chest x-ray taken on admission to hospital.

On 30 Oct 05 laboratory tests noted a sodium of 132, chloride 102, potassium 4.0, CO2 23, BUN 23, calcium 7.4 and creatinine 0.4. At 31 Oct 05 CBC was taken and noted WBC 11.8, hemoglobin 10.8, hematocrit 36.7 and platelets 560.

Following the episode of hemoptysis there was no bronchoscopy performed to evaluate the source of bleeding. Treatment included morphine and other unspecified medications for pain control. A pulmonary evaluation was performed. Blood cultures were positive for Gram positive bacteremia and later cultures coagulase negative staphylococcus. Vancomycin treatment was added. The subject also received a two unit blood transfusion for slight anemia.

The subject's continued to decline. He experienced episodes of tachycardia which required telemetry for several days. The subject received unspecified supportive care and his condition continued to decline. He experienced a respiratory arrest; despite advanced life support measures he died.

The death certificate was signed off as respiratory demise due to non-small cell lung cancer.

No additional information is expected.

REPORTS OF SIMILAR EVENTS

Genentech has previously filed the following IND safety reports of similar events from studies of bevacizumab (IND #7023) and Erlotinib

**Medication and Device
Experience Report**
(continued)

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service - Food and Drug Administration

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(61,874) for the indication of non-small cell lung cancer.

MCN 102204 Hemoptysis submitted on 22 April 2002. The event was considered related to bevacizumab.

MCN 103861 Hemoptysis submitted on 28 August 2002. The event was initially considered related to Erlotinib or placebo, but the investigator amended the opinion to unrelated to Erlotinib or placebo but related to disease progression.

MCN 214919 Hemoptysis submitted on 28 June 2005. The event was considered related to bevacizumab and unrelated to erlotinib.

SPONSOR ASSESSMENT

Based on review of available data, the Sponsor cannot establish or exclude the possibility of a cause-and-effect relationship between the administration of bevacizumab and the occurrence of hemoptysis.

At this time the Sponsor does not believe changes to the conduct of this clinical trial are warranted.

Pharmacovigilance:

This is a report of fatal hemoptysis in a 66 year-old male with non-small cell lung cancer. The temporal relationship between Avastin administration and event onset suggests that a causal association cannot be excluded. Possible contributing factors include the patient's underlying malignancy. Hemoptysis is expected per the erlotinib investigator's brochure; events of fatal or life-threatening hemoptysis are upgraded and considered unexpected per the bevacizumab investigator's brochure and Avastin US package insert.

B6. LABORATORY DATA

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	07/02/2005	CT Scan		
		Describes a left upper lobe mass extending to right hilum excluding upper lobe pulmonary vein without occlusion.		
2		Pathology		
		Histology of cancer was predominantly adenocarcinoma.		
3		blood culture Positive		
		Blood cultures were positive for Gram positive bacteremia and later cultures coagulase negative staphylococcus.		

B7. OTHER RELEVANT HISTORY

#	Start/Stop Date	Condition Type / Condition	Notes
1	UNK	Historical Condition HAEMOPTYSIS	One episode prior to starting study.
2	08/23/2005 08/23/2005	Procedure ASPIRATION PLEURAL CAVITY	5500Gy in 22 fractions to gross chest domain
3	05/26/2005 06/27/2005	Procedure RADIOTHERAPY	
4	UNK	Current Condition ANAEMIA	due to chemotherapy

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5	UNK	Current Condition THROMBOCYTHAEMIA	due to chemotherapy
6	UNK	Current Condition HAEMOPTYSIS	
7	UNK	Current Condition CHRONIC OBSTRUCTIVE PULMONARY DISEASE	
8	UNK	Historical Condition SMOKER	Smoker for 55 years and quit in May 2005.
9	UNK	Historical Condition ALCOHOL USE	Patient reportedly used to drink heavily but has now cut down.
10	UNK	Other NEOPLASM MALIGNANT	Mother died from stomach and GI cancer age 77
11	UNK	Other LUNG NEOPLASM MALIGNANT	Father died from lung cancer age 65
12	UNK	Allergy DRUG HYPERSENSITIVITY	Drug allergy to penicillin and streptomycin causing rash

C6. lot#(if known) (cont.)

Suspect Medication #1: 150359, 150357

C10. CONCOMITANT MEDICAL PRODUCTS

ADVAIR (FLUTICASONE PROPIONATE, SALMETEROL XINAFOATE) UNK to UNK
 ALBUTEROL INHALER (ALBUTEROL/ALBUTEROL SULFATE) UNK to UNK
 MS CONTIN (MORPHINE SULFATE) UNK to UNK
 PERCOCET (ACETAMINOPHEN, OXYCODONE HYDROCHLORIDE) UNK to UNK
 SIMETHICONE (SIMETHICONE) UNK to UNK
 MIRALAX (POLYETHYLENE GLYCOL) UNK to UNK
 ASPIRIN (ASPIRIN) UNK to UNK