

# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**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\_221015

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<sup>®</sup>NCOLOGY

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

January 19, 2006

Ravi Rao, MD  
Mayo Clinic  
Gonda-Desk 10 South  
Medical Oncology  
200 First Street SW  
Rochester, MN 55905  
507-284-8964

RE: IND Safety Report  
Molecule: erlotinib  
MCN: 221015 INITIAL

Dear Dr. Rao:

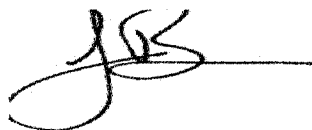
A sponsor conducting a study under an investigational new drug application (IND) is required to inform all participating investigators, in writing, of any IND study occurrence of a serious and unexpected adverse drug reaction (ADR). An unexpected ADR is an adverse event that is judged by either an investigator 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 exposed to erlotinib. 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 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 erlotinib contributed to the adverse event.

If questions arise, please contact the undersigned.

Sincerely,



Jeffrey Bloss, MD  
*Group Medical Monitor*

FINAL  
Version: 1.0  
1/20/2006

# MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

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

Mfr report #	221015
UF/Importer Report #	
FDA Use Only	

### A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event: 61 Years or Date of Birth:	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 123.9 lbs or 56.2 kgs
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### 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 (mo/day/yr)  Disability

Life-threatening (mo/day/yr)  Congenital Anomaly

Hospitalization - initial or prolonged  Required Intervention to Prevent Permanent Impairment/Damage

Other: \_\_\_\_\_

3. Date of Event (mo/day/year) 12/27/2005

4. Date of This Report (mo/day/year) 01/19/2006

5. Describe Event or Problem  
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)  
esophagobronchial fistula[OESOPHAGOBRONCHIAL FISTULA]

Case Description:  
IND SAFETY REPORT

This case, manufacturer control number 221015, is a report from the United States referring to a 61 year old male subject. An Investigator reported this from study 5411, a phase I study of OSI-774 based multimodality therapy for inoperable stage III non-small cell lung cancer sponsored by OSI Pharmaceuticals.

Medical conditions present at the time of the report include gastroesophageal reflux disease and multiple thromboses at multiple sites. No allergies were reported. The subject was diagnosed with non-small cell lung cancer in Jul 05. continued in additional info section...

6. Relevant Tests/Laboratory Data, Including Dates

#1 12/29/2005 Ultrasound (continued)

#2 12/27/2000 Ultrasound (continued)

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

#1 UNK, Current Condition, THROMBOSIS (Multiple thrombosis in multiple locations)

#2 UNK, Current Condition, GASTROESOPHAGEAL REFLUX DISEASE

### C. SUSPECT MEDICATION(S)

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

#1. Erlotinib(Erlotinib) Tablet

#2. CARBOPLATIN(CARBOPLATIN)

2. Dose, Frequency & Route Used

#1. 150 mg, qd, days (continued)

#2. day 1, 22., Intravenous

3. Therapy Dates (if unknown, give duration) from/to (or best estimate)

#1. 09/14/2005 to 12/02/2005

#2. 09/14/2005 to 11/30/2005

4. Diagnosis for Use (Indication)

#1. NON-SMALL CELL LUNG CANCER

#2. NON-SMALL CELL LUNG CANCER

6. Lot # (if known) 7. Exp. Date (if known)

#1. unknown #1. UNK

#2. unknown #2. UNK

9. NDC# (For product problems only)

5. Event Abated After Stopped or Dose Reduced?

#1.  Yes  No  Doesn't Apply UNK

#2.  Yes  No  Doesn't Apply UNK

8. Event Reappeared After Reintroduction?

#1.  Yes  No  Doesn't Apply UNK

#2.  Yes  No  Doesn't Apply UNK

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

LOVENOX (ENOXAPARIN SODIUM) UNK to UNK

WARFARIN (WARFARIN SODIUM) UNK to UNK

### 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) 01/03/2006

5. (A)NDA #

IND # 61,874

PLA #

Pre-1938  Yes

OTC Product  Yes

6. If IND, Give Protocol # 5411

7. Type of Report (Check all that apply)

5-day  15-day

10-day  Periodic

Initial  Follow-up # \_\_\_\_\_

8. Adverse Event Term(s) OESOPHAGOBRONCHIAL FISTULA

9. Manufacturer Report Number 221015

### E. INITIAL REPORTER

1. Name and Address Phone #

2. Health Professional?  Yes  No

3. Occupation Physician

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.

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

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

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C. SUSPECT MEDICATION(S)	
<b>1. Name (Give labeled strength &amp; mfr/labeler, if known) (Regimens Continued)</b> #3. PACLITAXEL(PACLITAXEL) #4.	
<b>2. Dose, Frequency &amp; Route Used</b> #3. day 1, 22, Intravenous #4.	<b>3. Therapy Dates (if unknown, give duration) from/to (or best estimate)</b> #3. 09/14/2005 to 11/30/2005 #4.
<b>4. Diagnosis for Use (Indication)</b> #3. NON-SMALL CELL LUNG CANCER #4.	<b>5. Event Abated After Use Stopped or Dose Reduced?</b> #3. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply UNK #4. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
<b>6. Lot # (if known)</b> <b>7. Exp. Date (if known)</b> #3. unknown      #3. UNK #4.      #4.	<b>8. Event Reappeared After Reintroduction?</b> #3. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply UNK #4. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
<b>9. NDC# (For product problems only)</b> NA	
<b>10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)</b> NA	

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

Concomitant medications included enoxaparin sodium and warfarin sodium. The subject had received no prior therapy for his disease.

Protocol induction therapy consisted of carboplatin 6 AUC IV and paclitaxel 200mg/m<sup>2</sup> IV both given on day one and 22 for two cycles (cycle length 21 days). Additional therapy continued with paclitaxel 50mg/m<sup>2</sup> and carboplatin 2 AUC given on days 43, 50, 57, 64, 71, 78 and 85. The last known administration of carboplatin and paclitaxel were given on 30 Nov 05 (lot numbers were unknown).

On study day 43 (14 Sep 05) the subject commenced therapy with erlotinib 150mg QD PO, to be continued until study day 91. The last known administration of erlotinib was given on 02 Dec 05 (lot number unknown). Additionally on study day 43 the subject also commenced radiation therapy consisting of 6600cGY as five fractions per week for seven weeks.

On 02 Dec 05 the subject was removed from the study as the investigator considered that further radiation therapy would damage the subjects left ventricle.

On 27 Dec 05 the subject presented to the emergency department with complaints of dyspnea, pain and edema in the left lower leg. The subject was admitted for observation.

Two days later on 29 Dec 05 a fistula between the esophagus and left mainstem bronchus was noted on esophagram. A venous ultrasound also noted a thrombosis; however the investigator noted that this was a continuation from a previous clot. The subject would continue with his enoxaparin and warfarin therapy. Treatment for the fistula was not reported.

At the time of this report, the outcome of the esophagobronchial fistula was not reported.

The investigator assessed the event esophagobronchial fistula as possibly related to erlotinib, possibly related to carboplatin and paclitaxel and probably related to radiation and the subject's underlying non-small cell lung cancer.

No further information is available.

**Pharmacovigilance:**

After review of the clinical details and investigator comments pertaining to this adverse event and based upon the experience of erlotinib to date, the sponsor does not believe that changes to the conduct of this clinical trial are warranted.

**B6. LABORATORY DATA**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	12/29/2005	Ultrasound  Esophagram confirmed fistula between esophagus and left mainstem bronchus		
2	12/27/2000	Ultrasound  Venous ultrasound confirmed thrombosis.		

**C2. Dose, frequency & route used (cont.)**

Suspect Medication #1: 150 mg, qd, days 43-91, Ophthalmic

**Block C - Additional Dosage Regimens**

Suspect Product	2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)	6. Lot # (if known)	7. Exp. date (if known)
#2 CARBOPLATIN Regimen # 2	day 43, 50, 57, 64, 71, 78, 85, Intravenous	UNK	UNK	UNK
#3 PACLITAXEL Regimen # 2	day 43, 50, 57, 64, 71, 78, 85, Intravenous	UNK	UNK	UNK

**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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