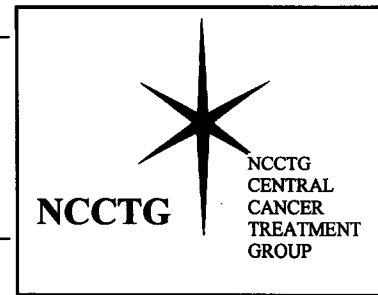

Operations Office

Telephone (507) 266-3853



Date: April 11, 2003

To: NCCTG Primary Clinical Research Associates

From: Linda S. Long

Re: N0177, Pilot and Phase II Trial of OSI-774 and Radiation in Glioblastoma Multiforme Patients

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_200156

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 Linda S. Long at 507-266-3853.

lsl
enclosure

Genentech[®]

BIO ONCOLOGY

Genentech, Inc.

1 DNA Way, MS 59
South San Francisco, CA 94080
Fax (650) 225-5862

PEREZ, Edith, MD
Mayo Clinic Jacksonville
Division of Hematology/Oncology
4500 San Pablo Road
Jacksonville, FL 32224

14 March 2003

RE: Serious Adverse Event from Investigator Sponsored Trial
Tarceva[™] (erlotinib hydrochloride)
Initial report
MCN 200156

Dear Dr. Perez:

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 an initial case summary and analysis of similar events of a serious and unexpected ADR that occurred in a subject exposed to Tarceva previously submitted to the Food and Drug Administration by an investigator conducting a clinical trial for Tarceva under another IND. Please review this case report and promptly submit this information to your Institutional Review Board or Independent Ethics Committee. Also amend this report of death unknown cause to your Tarceva Investigator Brochure.

Although this adverse event has been documented and reported to the appropriate regulatory agencies, this does not reflect a conclusion by Genentech or the regulatory agencies that Tarceva contributed to the adverse event.

If questions arise, please contact the undersigned.

Sincerely,



Robert Mass, MD
Medical Monitor

Enclosure

MED WATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting
by health professionals of adverse events
and product problems

Form Approved: OMB No. 0910-0281 Expires: 12/31/94
See OMB statement on reverse

FDA Use Only (MB)

Triage unit sequence # 200156

Page 1 of 1

A. Patient Information			
1. Patient Identifier 045 <small>In confidence 881464</small>	2. Age at time of event: 55 or Date of birth: 02/09/1948	3. Sex <input checked="" type="checkbox"/> female <input type="checkbox"/> male	4. Weight 164 lbs or ___ kgs
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 checked="" type="checkbox"/> death, date of death: 3/1/03 <input type="checkbox"/> disability <input type="checkbox"/> life-threatening <input type="checkbox"/> congenital anomaly hospitalization - initial or prolonged <input type="checkbox"/> other: <input type="checkbox"/> required intervention to prevent permanent impairment/damage			
3. Date of event: 03/01/2003		4. Date of this report: 03/03/2003	
5. Describe event or problem: 55yo female s/p resection of the right upper and right lower lobe in 8/7/1998 for a T1N2M0 stage IIIA tumor. Pathology report revealed 90% bronchioalveolar carcinoma (BAC) and 5-10% showed invasive moderately differentiated carcinoma. Finished mediastinal radiation therapy 10/28/1998. On 11/29/2002 a CT scan of chest revealed multiple tiny new nodules in the lungs and lytic lesion of T9. She underwent vertebroplasty and radiation therapy to the spine, completed in January 2003. 2/18/2003 chest CT revealed innumerable ill defined tiny nodular densities within the left lung, and new right large right pleural fluid. Patient chose to start clinical trial on 2/21/2003 with Tarceva alone in BAC. She was seen in clinic on 2/28/2003, relating some symptom improvement. On 3/1/2003, while patient was home she experienced severe coughing episode and then suddenly became unresponsive. EMS responded, initiated CPR, transported patient to the emergency room, however, patient was unable to be resuscitated. Autopsy not done; unable to determine if this event is directly caused by study drug.			
6. Relevant test/laboratory data, including dates: 2/28/2003 Complete blood count with differential, and comprehensive metabolic panel were all was unremarkable.			
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Non smoker Hx of hypertension since 1993			

C. Suspect Medication(s)		
1. Name (give labeled strength & mfr/labeled, if known) OSI -774 (erlotinib) 150 mg		
2. Dose, frequency & route used 150 MG PO QD	3. Therapy dates (if unknown, give duration) 2/21/2003-3/1/2003	
4. Diagnosis for use (indication) #1 Bronchioalveolar carcinoma	5. Event abated after use stopped or dose reduced #1 <input type="checkbox"/> Yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply #2 <input type="checkbox"/> Yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply	
6. Lot # (if known) #1 #2	7. Exp. date (if known) #1 #2	8. Event reappeared after reintroduction #1 <input type="checkbox"/> Yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply #2 <input type="checkbox"/> Yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply
9. NDC # (for product problems only)		
10. Concomitant medical products and therapy dates (exclude treatment or event) Abivan 0.5 mg l po pm anxiety started 2/14/2003; Altace 10 mg po QD; Inderal 20mg po QD; Premarin/Provera .625mg l po QD; ibuprofen 200mg l po pm pain		

D. Suspect Medical Device			
1. Brand name.			
2. Type of device			
3. Manufacturer name & address:		4. Operator of device <input type="checkbox"/> health professional <input type="checkbox"/> lay user/patient	
5. Model #	6. Exp. date / /	7. If implanted, give date / /	
8. Catalog #	8. If explanted, give date / /		
9. Serial #	9. If explanted, give date / /		
10. Lot #	10. If explanted, give date / /		
11. Other #	11. If explanted, give date / /		
12. Device available for evaluation: (Do not send to FDA) <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Returned to manufacturer on / /			
13. Concomitant medical products and therapy dates (exclude treatment or event)			

E. Reporter (see confidentiality section on back)			
1. Name, address & phone no. Ben Garcia 481 Preston Blvd 2200Pierce Ave Nashville, Tn 37232 Phone 615 936-1074			
2. Health Professional? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	3. Occupation RN	4. Also reported to <input checked="" type="checkbox"/> manufacturer <input type="checkbox"/> user facility <input type="checkbox"/> distributor	
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box. <input type="checkbox"/>			

FDA

Mail to:

MedWatch
8490 Fishers Lane
Rockville, MD 20852-9787

or FAX to:

1-800-FDA-0178

MED WATCH	A.1. Patient Identifier CRD (ID #45)	G.9. Mfr. report number 200156	Addendum
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IND SAFETY REPORT

DEATH UNKNOWN CAUSE

This 55-year old female patient was enrolled in protocol OSI2542s, phase II study to determine the response rate of OSI-774 in patients with unresectable or metastatic bronchioloalveolar cell variant of non-small cell lung cancer. Protocol therapy with oral erlotinib 150 mg daily was initiated on 21 Feb 2003.

The patient was diagnosed with bronchioloalveolar carcinoma and underwent resection of the right upper and right lower lobe on 7 Aug 1998. Initial treatment included mediastinal radiation therapy, completed on 28 Oct 1998. On 29 Nov 2002, a CT scan of the chest revealed multiple new nodules in the lungs and a lytic lesion of T9. Treatment included vertebroplasty and radiation therapy to the spine, completed in January 2003. On 18 Feb 2003, a chest CT revealed nodular densities within the left lung.

On 1 Mar 2003, while at home, the patient experienced a severe coughing episode and suddenly became unresponsive. Resuscitation attempts were unsuccessful. No autopsy was performed.

The investigator assessed the event as possibly related to erlotinib.

Company Medical Assessment

Since no suspected or actual cause of death was provided, an assessment of relationship to study medication cannot be made.

Similar Events

The global safety database for erlotinib was searched for all reports with the primary or linking term of death unexplained, sudden death, or death NOS. There are currently four other case reports of events of unexplained death, irrespective of relationship to the study medication. The relevant cases are presented in the table below. Thus, to date a total of five cases of death unexplained/NOS, regardless of relationship to study drug, have been reported to the study sponsor.

In addition, there were seven previously-reported cases of death unexplained/NOS in which the reported event was later changed: three cases (Roche MCN 301507, 304232, and 304719) were changed to pulmonary embolism, one case (Roche MCN 313432) was changed to probable myocardial infarction, one case (Roche MCN 269646) was later deemed to be due to respiratory distress related to pneumonia, and two cases (Roche MCN 301945 and 330174) were later deemed to be related to disease progression.

ASSESSMENT OF RELATIONSHIP

In the absence of a documented cause of death, no causal relationship can be established between the event and treatment with erlotinib. In this therapeutic investigation, the cause of death is assumed to be disease progression or its complications, until there is contradictory evidence. The sponsor does not believe that changes to the conduct of the clinical trial are warranted in response to this case report. Though this safety report will represent an addendum to the current Investigators' Brochure, further reports of death unexplained will continue to be reported expeditiously.

Cases of Unexplained Death as of 10 March 2003

Roche MCN STUDY	AGE SEX	STUDY DRUG(S)	PAST HISTORY/ CONCOMITANT MEDICATION	VERBATIM TERM	REPORTER CAUSALITY	LATENCY	COMMENT
						From study/ onset	
328260 OSI-P Ph III NSCLC	44 M	Erlotinib	ConMed: buprenorphine	DEATH UNEXPLAINED	Unassessable	87 Days 2 Days	Died at home, protocol therapy cont until date of death
325160 OSI-P Ph III NSCLC	71 F	Erlotinib	ConMed: diclofenac, amlodipine, pantoprazole	SUDDEN DEATH	Not Provided	17 Days 2 Days	Died at home, had 2 day history of grade 2 diarrhea. Death possibly due to pulmonary embolism. No autopsy performed.
320118 Roche Ph III NSCLC	71 M	Erlotinib Cisplatin Gemcitabine	ConMed: furosemide, glucose, laevulose, mannitol, metoclopramide, potassium chloride, tropisetron, acetaminophen,	DEATH UNEXPLAINED	Related	37 Days 2 Days	Hospitalized 14 days after starting therapy for grade 4 thrombocyto-penia and neutropenia. Events resolved 4 days later, study tx was resumed, pt expired 19 days later.
311693 OSI-P Ph IB Advanced Malignancies	63 M	Erlotinib Capecitabine	HTN, aortic insufficiency, prosthetic valve, rectal bleeding ConMed : warfarin, furosemide, metoprolol, thyroxine	DEATH UNEXPLAINED	Related	23 Days 9 Days	Febrile neutropenia, increased PT and abscess. Discharged to hospice 3 days prior to death

NSCLC : Non-small cell lung cancer
PT: Prothrombin Time

HTN : Hypertension
ConMed : Concomitant medication