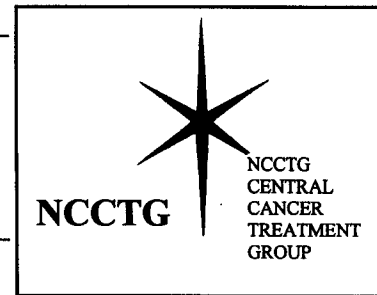

Operations Office

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_200239

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



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

13 Mar 2003

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

RE: Serious Adverse Event from Investigator Sponsored Trial
Tarceva™ (erlotinib hydrochloride)
Initial report
MCN 200239

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 fatty liver 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,

A handwritten signature in black ink, appearing to read "R Mass".

Robert Mass, MD
Medical Monitor

Enclosure

200239

MEDWATCH

THE U.S. MEDICAL PRODUCTS SAFETY PROGRAM

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

Form Approved OMB No. 0910-0045
 Do Not Write (Penalty)
 Report and
 Signature

Page ___ of ___

A. Patient information

1. Patient identifier: PA 04 #1
 2. Age at time of event: A-C
 3. Sex: female male
 4. Weight: _____ lbs
 Date of birth: 8/3/39

B. Adverse event or product problem

1. Adverse event and/or Product problem (e.g., defect/malfunction)
 2. Outcomes attributed to adverse event (check all that apply):
 death disability
 life-threatening congenital anomaly
 hospitalization - initial or prolonged required intervention to prevent permanent impairment/damage
 other: **Notable event**
 3. Date of event: 2/18/03
 4. Date of this report: 3/03/03

5. Describe event or problem:
 Pt had Plu Abd CT post chemo RT on 2/14/03 shows, new for patient diffuse fatty infiltration of liver.
 Pt went for end of study blood work in addition to monitoring her bile. Bili came back as a 6.9 - Gr 3. Bili. Pt also intermittent dark urine otherwise no complaints pruritis, No Δ in mental status. Skin quite icteric.
 Serial biweekly shows at end of 2 wk monitoring a Gr 4 Bili of 14.1
 Hepatic other: fatty infiltration severe Gr 3

6. Relevant test/laboratory data, including dates:
 2/14/03 Abd CT & Repeat CT on 2/28/03
 ↳ See attached reports.
 No biliary duct dilatation or obstruction
 2-18- to 2/26 Labs - attached.
 2/24/03: RUQ US No biliary Dilatation/Fat

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, PMS/Chemo dysfunction, etc.):
 Pt finished Chemo IV 1/20/03 & RT on 1/28/03. Toxicities felt not to be Chemo/RT.
 Gr 4 Bili / Gr 3 Hepatic Tox per attending felt to be possibly RT Tarceva

C. Suspect medication(s)

1. Name (give tablet strength & ml/container, if known):
 #1 **Genzar** #3 **Tarceva** Allergic React. Did not get
 #2 **Tarceva**
 2. Dose, frequency & route used:
 #1 75mg/m² IV QW x 6 #12/17/02 → 1/29/03
 #2 50mg/d po x 9 wks #12/18/02 → 4/1/03
 3. Therapy dates (if unknown, give duration):
 4. Diagnosis for use (indication):
 #1 Loc. adv Pancreatic CA
 #2 _____
 5. Lot # (if known): #1 _____ #2 _____
 6. Exp. date (if known): #1 _____ #2 _____
 7. NDC # for product problems only:
 8. Concomitant medical products & therapy dates (exclude treatment of event):

8. Event abated after use stopped or dose reduced:
 #1 Yes No doesn't apply
 #2 Yes No doesn't apply
 9. Event recurred after reintroduction:
 #1 Yes No doesn't apply
 #2 Yes No doesn't apply

D. Suspect medical device

1. Brand name:
 2. Type of device:
 3. Manufacturer name & address:
 4. Operator of device:
 health professional
 lay user/patient
 other:
 5. Expiration date (month/year):
 6. If implanted, give date (month/year):
 7. If explanted, give date (month/year):
 8. If explanted, give date (month/year):
 9. Device available for evaluation? (Do not send to FDA)
 yes no returned to manufacturer on _____
 10. Concomitant medical products and therapy dates (exclude treatment of event):

liver

E. Reporter (see confidentiality section on back)

Name, address & phone #:
 CAUSALITY: possibly
 3-3-03

11. Health professional? yes no
 12. Occupation:
 13. Also reported to:
 manufacturer

MED WATCH	A.1. Patient Identifier AC (#1)	G.9. Mfr. report number 200239	Addendum
------------------	--	---------------------------------------	----------

IND SAFETY REPORT: FATTY LIVER**CASE SUMMARY**

This IND safety report of Fatty Liver refers to a 63-year-old female enrolled in study OSI2580s, an investigator-sponsored Phase I study of erlotinib, gemcitabine, paclitaxel and radiation therapy for locally advanced pancreatic cancer. On 30 Oct 2002, the subject presented with obstructive jaundice, pancreatic cancer was diagnosed, and she underwent gastrojejunostomy and choledochoduodenostomy. She had no history of diabetes mellitus, steroid medication, or alcohol use. Past medical history included a 30-pound weight loss over the 2 months preceding the diagnosis of pancreatic carcinoma, but no recent weight loss. Past medical history also included cholecystectomy as well as hypertension treated with diltiazem and enalapril.

On 17 Dec 2002, the subject received her first dose of gemcitabine (75 mg/m² IV QW) followed by paclitaxel (dose not reported). The subject experienced an allergic reaction to paclitaxel, which was then permanently discontinued. On 18 Dec 2002, she received her first dose of erlotinib (50 mg PO QD). On 20 Jan 2003, the final gemcitabine dose was administered. On 28 Jan 2003, the final radiotherapy dose was administered.

On 14 Feb 2003, an abdominal CT was performed to "assess pancreatic mass" and revealed a mass at the head of the pancreas associated with pancreatic ductal dilatation and no interval increase in the 5 x 3 cm necrotic peripancreatic lymphadenopathy. On 18 Feb 2003, serum bilirubin was 6.9 mg/dL and increased over the ensuing 2 weeks to 14.1 mg/dL. On 20 Feb 2003, the last dose of erlotinib was administered.

On 24 Feb 2003, an abdominal ultrasound was performed to "evaluate for biliary obstruction, jaundice" and demonstrated poor visualization of the intrahepatic structures consistent with severe fatty infiltration, a lobulated hypoechoic mass inferior to the pancreatic head measuring 5.2 x 2.7 cm, and no intra- or extrahepatic biliary dilatation. On 27 Feb 2003, an abdominal CT was performed for "worsening jaundice and question hepatic vein thrombosis" and revealed (1) known pancreatic mass and adjacent lymphadenopathy, (2) fatty liver, (3) no biliary duct dilatation, and (4) attenuated hepatic veins without definite thrombus. Liver biopsy was not performed.

The investigator assessed the fatty liver and hyperbilirubinemia as possibly related to erlotinib.

ANALYSIS OF SIMILAR EVENTS

The Roche, OSIP and Genentech Safety Databases for erlotinib were searched for all serious events with the primary or linking preferred term of Fatty Liver. No similar events were identified.

ASSESSMENT OF RELATIONSHIP

In the index case of fatty liver, blind loop syndrome with bacterial overgrowth is a potential confounder given the history of intestinal surgery. A potential contribution of erlotinib to the event of fatty liver cannot be excluded. Of note, the protocol-defined dose of 50 mg erlotinib is lower than the 150 mg dose that has been used in combination with weekly gemcitabine in other pancreatic cancer trials.

Based on the review of the available data, the sponsor cannot establish or exclude the possibility of a cause and effect relationship between administration of erlotinib and the occurrence of fatty liver. Ongoing randomized controlled trials, such as the current Phase III trial of OSI2298g, will allow a comparison of the rates of such events in erlotinib treatment arms to those in the chemotherapy alone treatment arms.

After review of the clinical details and investigator's 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. However, Genentech, Inc. intends the submission of this IND Safety Report of Fatty Liver to represent a safety amendment to the OSI-774 (erlotinib; Tarceva) Investigator Brochure.