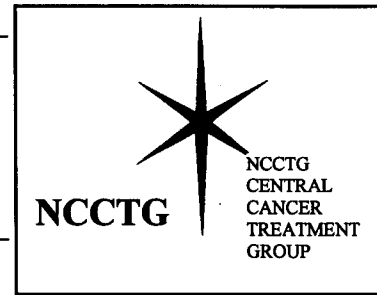

Operations Office

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_105417_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 Linda S. Long at 507-266-3853.

lsl
enclosure



Genentech, Inc.

1 DNA Way, MS 59
South San Francisco, CA 94080
Fax (650) 225-5862
07 March 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)
MCN 105417

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 a case summary and analysis of similar events of a serious and unexpected ADR that occurred in a subject exposed to Tarceva while participating in an investigator-sponsored clinical trial 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 hypertension 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 "RM", with a horizontal line extending to the right.

Robert Mass, MD
Medical Monitor

Enclosure

RED WATCH

Safety Information and
Event Reporting Program

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

105417

ME, 000

My report #
UPRISIS report #
FDA Use Only

Patient information			
1. Patient identifier ME, 0008	2. Age at time of event: or <u>70 years old</u> Date of birth: <u>06/09/1932</u>	3. Sex <input checked="" type="checkbox"/> female <input type="checkbox"/> male	4. Weight <u>127</u> lbs or ____ kg

Adverse event or product problem

<input checked="" type="checkbox"/> Adverse event and/or	<input type="checkbox"/> Product problem (e.g., defects/malfunctions)
Contributing factors attributed to adverse event (check all that apply)	
<input checked="" type="checkbox"/> death <input type="checkbox"/> life-threatening <input checked="" type="checkbox"/> hospitalization - initial or prolonged	<input type="checkbox"/> disability <input type="checkbox"/> congenital anomaly <input type="checkbox"/> required intervention to prevent permanent impairment/damage <input type="checkbox"/> other: _____

3. Date of event <u>12/21/02</u>	4. Date of this report <u>02/19/03</u>
-------------------------------------	---

Describe event or problem

A 70-year-old female was enrolled on a phase I/II study for metastatic breast cancer. Treatment with weekly Herceptin 114mg IV started on 09/17/02 and investigational OSI-774 (Tarceva) 100mg PO daily started on 09/18/02. The patient received 18 weeks of this regimen as of 12/21/02. She was brought to ER for 3 episodes of headache and blood pressure of 220/140 mmHg on 12/21/02. The patient received Clonidine 0.2, resulting in a blood pressure of 149/76mmHg in ER. Then she was admitted for further evaluation.

The patient was discharged with blood pressure of 124/62 mmHg on 12/22/02. Her ER physician, Anxiety may have contributed to the hypertension. The patient had stable blood pressure when she was seen on 12/23/02 for C4W3 Herceptin treatment. On 12/30/02, she was restarted on Clonidine daily for blood pressure of 173/90mmHg. Her hypertension was sometimes accompanied by headache.

The patient was off study on 01/06/03 due to progressive disease and the last dose of OSI-Herceptin was taken on 01/02/03. She started new treatment of weekly Nevelbine on 01/06/03 and continual weekly Herceptin. At the time of this report the patient has continual on Clonidine daily with stable blood pressure. Given that the patient was on beta blockers for palpitations not hypertension and given that the patient had no prior history of hypertension, the investigator considered the event of hypertension with headache as unknown etiology, and possibly related to the study drug.

Supportive tests/laboratory data, including dates

Venous Doppler Ultrasound showed no deep venous thrombosis on 12/22/02. The head CT revealed no intracranial pathology and the EKG revealed normal sinus rhythm on 12/21/02. The troponin I was less than 0.038 ng/mL and CPK was 58 U/L on 12/21/02.

Relevant history, including pre-existing medical conditions (e.g., allergies, diets, pregnancy, smoking and alcohol use; hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & multiplier, if known)		3. Therapy dates (if unknown, give duration) (provide for both #1 and #2)	
#1 Erlotinib (OSI-774, Tarceva)		#1 Started on 09/18/02	
#2 Trastuzumab (Herceptin)		#2 Started on 09/17/02	
2. Dose, frequency & route used		4. Diagnosis/for use (indication)	
#1 100mg daily, P.O.		#1 Metastatic Breast Cancer	
#2 114mg weekly IV		#2 Metastatic Breast Cancer	
5. Event abated after use stopped or dose reduced		8. Event reappeared after reintroduction	
#1 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply		#1 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply	
#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply		#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply	
6. Lot # (if known)		7. Exp. date (if known)	
#1 X10186		#1	
#2		#2	
9. NOC # - for product problems only (if known)			
NA			

10. Concomitant medical products and therapy dates (exclude treatment of event)

Propranolol, Paxil, Lorazepam, Vizodin, Allegra, Plevavid, Excedrin, Tylenol, Motrin

Suspect medical device

Brand name	N/A
Type of device	
Manufacturer name & address	
4. Operator of device	<input type="checkbox"/> health professional <input type="checkbox"/> lay user/patient <input type="checkbox"/> other: _____
5. Expiration date (month/year)	
7. If implanted, give date (month/year)	
8. If explanted, give date (month/year)	
Model #	
Catalog #	
Serial #	
Lot #	

Device available for evaluation? (Do not send to FDA)

yes no returned to manufacturer on _____ (month/year)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E

1. Name & Address	phone # <u>(310) 825-8195</u>
Carolyn Britton, M.D. 10945 Le Conte Avenue PVUB, Suite 3360 Los Angeles, CA 90095	

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
<input checked="" type="checkbox"/> yes <input type="checkbox"/> no	M. D.	<input checked="" type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unk



Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or

Medication and Device Experience Report

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

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

(continued)

Refer to guidelines for specific instructions

IND Safety

FDA Use Only

For use by user facility/distributor - devices only

1. Check one
 user facility NA distributor

2. UFR01at report number

3. User facility or distributor name/address

4. Contact person

5. Phone Number

6. Date user facility or distributor became aware of event (month/year)

7. Type of report
 initial
 follow-up # _____

8. Date of this report (month/year)

9. Approximate age of device

10. Event problem codes (refer to coding manual)
 patent code: _____ - _____ - _____
 device code: _____ - _____ - _____

11. Report sent to FDA?
 yes (month/year) _____
 no

12. Location where event occurred
 hospital outpatient diagnostic facility
 home ambulatory surgical facility
 nursing home
 outpatient treatment facility
 other: _____

13. Report sent to manufacturer?
 yes (month/year) _____
 no

14. Manufacturer name/address

H. Device manufacturers only

1. Type of reportable event
 death NA
 serious injury
 malfunction (see guidelines)
 other: _____

2. If follow-up, what type?
 correction
 additional information
 response to FDA request
 device evaluation

3. Device evaluated by mfr?
 not returned to mfr.
 yes evaluation summary attached
 no (attach page to explain why not) or provide code: _____

4. Device manufacture date (month)

5. Labeled for single use?
 yes no

6. Evaluation codes (refer to coding manual)
 method: _____ - _____ - _____ - _____
 results: _____ - _____ - _____ - _____
 conclusions: _____ - _____ - _____ - _____

7. If remedial action initiated, check type
 recall notification
 repair inspection
 replace patient monitoring
 relabeling modification/adjustment
 other: _____

8. Usage of device
 initial use of device
 reuse
 unknown

9. If action reported to FDA under 21 USC 360(f), list correction/removal reporting number: _____

10. Additional manufacturer narrative and/or 11. Corrected data

I. All manufacturers

1. Contact office - name/address (& mailing label for devices)

2. Phone number

3. Report source (check all that apply)
 foreign
 study
 literature
 consumer
 health professional
 user facility
 company representative
 distributor
 other: _____

4. Date received by manufacturer (month/year)

5. (A)NDA # _____
 IND # 62,727
 PLA # _____
 pre-1938 yes
 OTC product yes

6. If IND, protocol # _____

7. Type of report (check all that apply)
 5-day 15-day
 10-day periodic
 initial follow-up # 1

8. Adverse event term(s)

Mfr. report number

This public reporting burden for the collection of information has been estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DEHS Reports Clearance Office
Paperwork Reduction Project (0918-0231)
Rupert M. Harmanby Building, Room 531-H
200 Independence Avenue, S.W.
Washington, D.C. 20201

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this form to this address.

MED WATCH	A.1. Patient Identifier ME/008	G.9. Mfr. report number 105417	Addendum
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IND SAFETY REPORT**CASE SUMMARY: Genentech MCN 105417**

This IND safety report of HYPERTENSION from the United States refers to a 70-year-old female enrolled in OSI2365s, a phase I/II study of Herceptin combined with erlotinib in the first line treatment of metastatic breast cancer associated with HER2/neu overexpression. The subject was diagnosed with breast carcinoma in June 1997. Initial treatment included a right mastectomy and axillary lymph node dissection. In April 2000, axillary biopsy revealed invasive carcinoma compatible with HER2/neu positive, poorly differentiated invasive ductal carcinoma of the breast. A chest CT showed extensive bilateral pulmonary nodules and mediastinal adenopathy. Initial treatment included one dose of doxorubicin and cyclophosphamide followed by treatment with docetaxel, carboplatin, and Herceptin. Past medical history included hyperthyroidism, chronic goiter, palpitations, depression, headaches, and sinusitis. Concomitant medications included propranolol, fexofenadine, lansoprazole, paroxetine, lorazepam, acetaminophen/ hydrocodone, Excedrin, ibuprofen, and acetaminophen. Allergies included penicillin, tetracycline, and sulfa drugs.

On 17 Sep 2002, the subject received a scheduled dose of Herceptin (2 mg/kg IV). On 18 Sep 2002, she received her first dose of erlotinib (100 mg PO QD).

On 21 Dec 2002, the subject was evaluated in the emergency department for 3 reported episodes of severe hypertension and headache. Initial vital signs included blood pressure 220/140 mmHg, heart rate 86 BPM, respiratory rate 18. The subject had no neurological deficits. Treatment included clonidine (0.2 mg PO). At an unreported time, blood pressure was reported as 149/76 mmHg. Head CT revealed no intracranial pathology and electrocardiogram showed normal sinus rhythm. The treating emergency room physician reported, "anxiety may have contributed to the hypertension". The subject was admitted to the hospital, then discharged 22 Dec 2002 with a blood pressure of 124/62 mmHg.

On 30 Dec 2002, the subject underwent outpatient evaluation by an endocrinologist whose impression was subclinical hyperthyroidism secondary to toxic multinodular goiter and labile hypertension perhaps due to thyroid disorder and/or anxiety. Treatment included clonidine (0.1 mg PO QHS) and propylthiouracil (50 mg PO QD). At subsequent endocrinology visits, the dose of propylthiouracil was increased to 50 mg PO BID and then 50 mg PO TID.

On 2 Jan 2003, erlotinib was discontinued due to progression of malignancy. On 6 Jan 2003, the subject was removed from study and began treatment with vinorelbine and Herceptin. The investigator assessed the event of hypertension as possibly related to erlotinib.

MED WATCH	A.1. Patient Identifier	G.9. Mfr. report number	Addendum
	ME/008	105417	

ANALYSIS OF SIMILAR EVENTS

The global safety database for erlotinib was searched with the primary or linking term of hypertension.

Previous Reports of Hypertension

There were 4 previous reports of serious adverse events (SAEs) of hypertension; all were assessed as not related to erlotinib or erlotinib/placebo (Table 1).

Table 1

Roche ID Study Age/Sex	Indication/ Chemotherapy	Preferred Term	Causality	Outcome	Latency from start of study drug	Comments
331022 PA.3	Pancreatic CA Gemcitabine	Hypertension	Not related	Died due to CVA	30 days	History of HTN
330908 BR21	NSCLC	Hypertension	Not related	Ongoing	3 days	History of HTN
330096 BR21	NSCLC	Hypertension	Not related	Resolved	55 days	History of HTN, DM, arrhythmia, COPD
327743 BR21	NSCLC	Hypertension	Not related	Died due to progression of cancer	41 days	History of HTN

ASSESSMENT OF RELATIONSHIP

The 4 similar events of hypertension were confounded by a previous history of hypertension. In the index case, underlying hyperthyroidism is a confounder.

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

After review of the clinical details and investigators' 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 HYPERTENSION to represent a safety amendment to the OSI-774 (erlotinib; Tarceva™) Investigator Brochure.