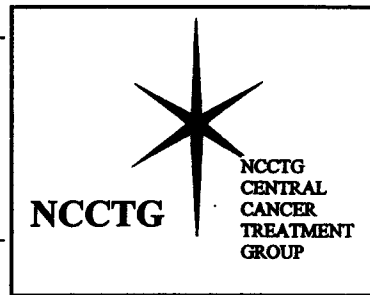

Operations Office

Telephone (507) 266-3853



Date: September 12, 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_342672

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

Medical Affairs
Genentech
1 August 2003

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

RE: F. Hoffmann-La Roche, Ltd. MCN 342672
Genentech MCN 201736
Tarceva™ (erlotinib hydrochloride)
OSI2661s

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 a study conducted by F. Hoffmann-La Roche, Ltd. Please review this case report and promptly submit this information to your Institutional Review Board or Independent Ethics Committee. Also, append this report 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.

Genentech, Inc. intends the submission of this IND Safety Report to represent a safety amendment to the Tarceva Investigator Brochure.

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

7. DESCRIBE REACTIONS INCLUDING RELEVANT TESTS/LAB DATA - continued

NINE DAYS AFTER TREATMENT WITH ERLOTINIB BEGAN THE PATIENT EXPERIENCED AN ACNEIFORM RASH, WORSE ON HER FACE AND ALSO INVOLVING THE SCALP AND TRUNK (POSTERIORLY AND ANTERIORLY). TREATMENT WITH PIRITON 4 MG VIA AN UNSPECIFIED ROUTE WAS INITIATED. ERLOTINIB WAS WITHHELD AND AT THE TIME OF REPORTING WAS SUBJECT TO REVIEW PENDING RE-INTRODUCTION. ON THE DAY AFTER DISCONTINUATION THE PATIENT EXPERIENCED CANDIDAL OESOPHAGITIS. TREATMENT WITH ORAMORPH AND FLUCONAZOLE WAS STARTED. AT THE TIME OF REPORTING, SKIN RASH AND CANDIDAL OESOPHAGITIS WERE PERSISTING AND ALL THREE STUDY DRUGS WERE SUBJECT TO REVIEW. THE INVESTIGATOR CONSIDERED THE CAUSAL RELATIONSHIP OF ERLOTINIB TO SKIN RASH RELATED AND OF CARBOPLATIN AND DOCETAXEL TO SKIN RASH UNRELATED. HE CONSIDERED CARBOPLATIN AND TAXOTERE AS HAVING BEEN MORE LIKELY TO HAVE CAUSED CANDIDAL OESOPHAGITIS THAN ERLOTINIB.

UPDATE INFORMATION WAS RECEIVED 01 AUG 2003. THE FOLLOWING INFORMATION WAS ADDED: DOSING AMOUNT, START DATE AND CAUSAL RELATIONSHIP OPINION (SKIN RASH) OF CARBOPLATIN AND DOCETAXEL.

ADVERSE EVENT TERM(S):

CANDIDAL OESOPHAGITIS/CANDIDAL OESOPHAGITIS/MEDDRA 6.0 +++
SKIN RASH/SKIN RASH/MEDDRA 6.0

(+++ denotes adverse event that generated submission)

14-19. SUSPECT DRUGS - continued

Suspect Drug: DOCETAXEL
Generic Name: DOCETAXEL
Daily Dose(s)/Strength: 136 MG 1 X per 3 WEEK /
Route: INTRAVENOUS
Indication: OVARIAN/FALLOPIAN TUBE/PERITONEAL CANCER/FEMALE
REPRODUCTIVE NEOPLASM NOS/MEDDRA 6.0
Therapy From Date: 16-JUL-2003
Therapy To Date: CONTINUING
Therapy Duration:

Suspect Drug: CARBOPLATIN
Generic Name: CARBOPLATIN
Daily Dose(s)/Strength: 710 MG 1 X per 3 WEEK /
Route: INTRAVENOUS
Indication: OVARIAN/FALLOPIAN TUBE/PERITONEAL CANCER/FEMALE
REPRODUCTIVE NEOPLASM NOS/MEDDRA 6.0
Therapy From Date: 16-JUL-2003
Therapy To Date: CONTINUING
Therapy Duration:

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION - continued

DOMPERIDONE
(DOMPERIDONE)
17-JUL-2003 / CONTINUING

LOPERAMIDE
(LOPERAMIDE HYDROCHLORIDE)
18-JUL-2003 / CONTINUING

DOTHIPIPIN
(DOTHIPIPIN HYDROCHLORIDE)
/ CONTINUING

NORETHISTERONE
(NORETHINDRONE)
/ CONTINUING

CIOMS TEXT

SKIN RASH IS LISTED IN THE IB FOR ERLOTINIB, CANDIDAL OESOPHAGITIS IS NOT. BASED ON THE INFORMATION RECEIVED FOR THIS CASE, A CAUSAL RELATIONSHIP BETWEEN THE REPORTED EVENT AND TREATMENT WITH TARCEVA IS ASSESSED AS POSSIBLE. COMPANY CAUSALITY WAS ASSESSED BASED ON THE NARANJO ALGORITHM.
HOWEVER, CONFOUNDING FACTORS IN BOTH EVENTS INCLUDE CONCOMITANT CHEMOTHERAPY.

REPORTER INFORMATION

Reporter: 1
 Name: GORDON RUSTIN
 Organisation: MOUNT VERNON HOSPITAL
 Address 1: RICKMANSWORTH ROAD
 Address 2:
 Address 3:
 Address 4:
 City: NORTHWOOD, MIDDX HA6 2RN
 Country: UNITED KINGDOM
 Address Phone:
 Address Fax:
 Representative Phone:
 Representative Fax:
 Reporter Type: HEALTH PROFESSIONAL
 Occupation: DOCTOR OF MEDICINE

Reporter: 2
 Name:
 Organisation: AVENTIS PHARMA
 Address 1:
 Address 2:
 Address 3:
 Address 4:
 City:
 Country: UNITED KINGDOM
 Address Phone:
 Address Fax: 01732 584081
 Representative Phone:
 Representative Fax:
 Reporter Type: PHARMACEUTICAL COMPANY
 Occupation:

CLINICAL TRIAL INFORMATION

Clin. Study Id: SCOTROC
 Clin. CRTN
 Design and Phase: OPEN I
 Clin. Patient Id: 303
 Clin. Investigator Id: 18188

DRUG-EVENT INFORMATION

Event: CANDIDAL OESOPHAGITIS/CANDIDAL OESOPHAGITIS/MEDDRA 6.0
 SOC: INFECTIONS AND INFESTATIONS
 Outcome: PERSISTING
 Severity:
 Seriousness: NEW/PROLONGED HOSPITAL
 Onset Date: 22 JUL 2003
 Resolved Date:
 Duration Reported:

Relation To: ERLOTINIB
 Drug Continued: THERAPY ALREADY COMPLETED
 AE Abated: NOT APPLICABLE
 AE Reappeared: NOT APPLICABLE
 Labeled US: NOT APPLICABLE
 Labeled Local: NOT APPLICABLE - GB
 Labeled IB: NO
 Labeled SPC: NOT APPLICABLE
 Labeled Core: NOT APPLICABLE
 Drug Related(Comp): YES
 Drug Related(Rept): YES
 Latency Reported: (First Dose)
 Latency Reported (Last Dose):

Relation To: DOCETAXEL
 Drug Continued: INSUFFICIENT INFO
 AE Abated: NOT APPLICABLE
 AE Reappeared: NOT APPLICABLE
 Labeled US: NOT APPLICABLE
 Labeled Local: NOT APPLICABLE - GB
 Labeled IB: NOT APPLICABLE
 Labeled SPC: NOT APPLICABLE
 Labeled Core: NOT APPLICABLE

Drug Related(Comp): YES
 Drug Related(Rept): YES
 Latency Reported: (First Dose)
 Latency Reported (Last Dose):

Relation To: CARBOPLATIN
 Drug Continued: INSUFFICIENT INFO
 AE Abated: NOT APPLICABLE
 AE Reappeared: NOT APPLICABLE
 Labeled US: NOT APPLICABLE
 Labeled Local: NOT APPLICABLE - GB
 Labeled IB: NOT APPLICABLE
 Labeled SPC: NOT APPLICABLE
 Labeled Core: NOT APPLICABLE
 Drug Related(Comp): YES
 Drug Related(Rept): YES
 Latency Reported: (First Dose)
 Latency Reported (Last Dose):

Event: SKIN RASH/SKIN RASH/MEDDRA 6.0
 SOC: SKIN AND SUBCUTANEOUS TISSUE DISORDERS
 Outcome: PERSISTING
 Severity:
 Seriousness: MEDICALLY SIGNIFICANT
 Onset Date: 18 JUL 2003
 Resolved Date:
 Duration Reported:

Relation To: ERLOTINIB
 Drug Continued: DISCONTINUED
 AE Abated: NO - EVENT DID NOT ABATE
 AE Reappeared: NOT APPLICABLE
 Labeled US: NOT APPLICABLE
 Labeled Local: NOT APPLICABLE - GB
 Labeled IB: YES
 Labeled SPC: NOT APPLICABLE
 Labeled Core: NOT APPLICABLE
 Drug Related(Comp): YES
 Drug Related(Rept): YES
 Latency Reported: (First Dose)
 Latency Reported (Last Dose):

Relation To: DOCETAXEL
 Drug Continued: INSUFFICIENT INFO
 AE Abated: NOT APPLICABLE
 AE Reappeared: NOT APPLICABLE
 Labeled US: NOT APPLICABLE
 Labeled Local: NOT APPLICABLE - GB
 Labeled IB: NOT APPLICABLE
 Labeled SPC: NOT APPLICABLE
 Labeled Core: NOT APPLICABLE
 Drug Related(Comp): NO
 Drug Related(Rept): NO
 Latency Reported: (First Dose)
 Latency Reported (Last Dose):

Relation To: CARBOPLATIN
 Drug Continued: INSUFFICIENT INFO
 AE Abated: NOT APPLICABLE
 AE Reappeared: NOT APPLICABLE
 Labeled US: NOT APPLICABLE
 Labeled Local: NOT APPLICABLE - GB
 Labeled IB: NOT APPLICABLE
 Labeled SPC: NOT APPLICABLE
 Labeled Core: NOT APPLICABLE
 Drug Related(Comp): NO
 Drug Related(Rept): NO
 Latency Reported: (First Dose)
 Latency Reported (Last Dose):



ANALYSIS OF SIMILAR EVENTS

Author: Marc Morris MD

Department: Pharma Development Medical Science, Drug Safety Risk Management, F. Hoffmann-La Roche Ltd, 4070 Basel, Switzerland

MCN # / Report: 342672

Report Origin: CLINICAL TRIAL

Country of Origin: United Kingdom

Drug Preferred Name(s): Tarceva® (erlotinib)

ADR: Candidal Oesophagitis

MedDRA SOC: Gastrointestinal Disorders

Date Roche first notified: 22 July 2003

Date ASIME written: 29 July 2003

1. GENERAL INFORMATION

Protocol no./Title: SCOTROC

A phase Ib study of erlotinib plus docetaxel and carboplatin in the treatment of newly diagnosed epithelial ovarian cancer, Fallopian tube cancer and primary peritoneal cancer.

Investigator: Dr Rustin, United Kingdom

Patient No.: 303

2. SUMMARY OF THE CASE

LAM, a 54 year old female patient, started oral erlotinib 100 mg daily, and 1 week later commenced docetaxel 75mg/m² IV and carboplatin (target AUC = 5) IV. Two days after starting the chemotherapy, she experienced an erlotinib-related rash, on her face, scalp and trunk. Erlotinib was withheld. The following day, she experienced candidal oesophagitis, and was treated with oramorph and fluconazole. Both events were persisting at the time of the report, and the investigator considered the chemotherapy agents as the more likely explanation.

3. ANALYSIS OF SIMILAR EVENTS

The erlotinib clinical trial safety database (Hoffmann-La Roche) was searched for all similar case reports. No similar cases were found.

4. CONCLUSION

It is most unlikely that the candidal oesophagitis was related to erlotinib; chemotherapy is the most likely explanation. No changes are needed to the conduct of any erlotinib trials, and this report constitutes an addendum to the clinical investigators' brochure.