



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: September 9, 2005
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_2005001356

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



National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

DATE: August 9, 2005

FROM: Janet Dancey, M.D., Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: OSI-774 (OSI-774-01 (hydrochloride salt), CP-358,774, Tarveca™, erlotinib)
OSI Pharmaceuticals Investigator Notification: Skin necrosis

TO: Investigators of CTEP-sponsored trials Using OSI-774 (IND 63383)

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. An investigator notification, which describes necrotic ulceration of the skin in a patient participating in an OSI Pharmaceuticals-sponsored clinical study utilizing the investigational agent OSI-774 (IND 63383), was recently distributed to investigators.

Please complete the following:

- Send a copy of this letter to your Institutional Review Board (IRB) according to your local IRB's policies and procedures.
- File a copy of this letter in your protocol file.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

CTEP's evaluation of this IND Safety Report in light of previous experience with OSI-774 does not require a change in the clinical protocols for this agent at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The MedWatch Report that describes the following adverse event is attached:

A 68-year-old male with non-small cell lung cancer developed multiple necrotic ulcerations on both feet, his right femur, and right forearm while participating in an expanded access program using the investigational agent OSI-774. Both the investigator and sponsor considered the necrotic ulceration at least possibly related to OSI-774 treatment.

There have been no incidences of skin necrosis or necrotic ulceration reported to the NCI as serious adverse events under IND 63383.

There have been 1338 patients enrolled in NCI-sponsored clinical trials using the investigational agent, OSI-774.

MED WATCH

HE FDA MEDICAL PRODUCTS REPORTING PROGRAM

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

Page 1 of 2

FDA Facsimile Approval 89/2595 (Clinarium)

Mfr report # 2005001356
UF/Dist report #
FDA Use Only

A. Patient information

1. Patient identifier HHE	2. Age at time of event: or Date of birth: <u>03/07/1937</u>	3. Sex <input type="checkbox"/> female <input checked="" type="checkbox"/> male	4. Weight Unk lbs or Unk kgs
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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 type="checkbox"/> death (mo/day/yr)	<input type="checkbox"/> disability
<input type="checkbox"/> life-threatening	<input type="checkbox"/> congenital anomaly
<input checked="" type="checkbox"/> hospitalization - initial or prolonged	<input type="checkbox"/> required intervention to prevent permanent impairment/damage
<input type="checkbox"/> other: _____	
3. Date of event (mo/day/yr) <u>07/02/05</u>	4. Date of this report (mo/day/yr) <u>07/27/05</u>

5. Describe event or problem
SKIN NECROSIS (Necrotic ulceration [skin])

MO18109
AN EXPANDED ACCESS PROGRAM OF TARCEVA (ERLOTINIB) IN PATIENT'S WITH ADVANCED STAGE IIIB/IV NON-SMALL CELL LUNG CANCER

A 68-year-old male patient developed necrotic ulceration whilst participating in the above trial.

The patient started oral erlotinib (150 mg once daily) on 1 April 2005. Approximately three months later, on 2 July 2005, the patient showed the first signs of a rash (CTC II). Ten days later he was hospitalised due to deterioration, multiple necrotic ulcerations on both feet, his right femur and right forearm. The patient was also experiencing massive pain and was treated with metamizole sodium (Novalgine, 90 drops per day), dexamethasone (5 mg), tramadol (Tramal, 60 drops) and morphine (25 mg). The necrotic ulceration was treated with sulfadiazine silver (Flammazine). On this day erlotinib therapy was discontinued. The following day the patient was given an
Cont

6. Relevant tests/laboratory data, including dates
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Unk

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known) #1 Erlotinib HCl (Tablet) (Erlotinib HCl) #2	
2. Dose, frequency & route used #1 150 mg (QD), Oral #2	3. Therapy dates (if unknown, give duration) from/to (or best estimate) #1 04/01/05 - 07/12/05 #2
4. Diagnosis for use (indication) #1 NON SMALL CELL LUNG CANCER NOS #2	5. Event abated after use stopped or dose reduced #1 <input type="checkbox"/> yes <input checked="" 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 Unk #2	7. Exp. date (if known) #1 Unk #2
8. Event reappeared after reintroduction #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 type="checkbox"/> doesn't apply	
9. NDC # - for product problems only (if known)	

10. Concomitant medical products and therapy dates (exclude treatment of event)
None Reported

G. All manufacturers

1. Contact office - name/address (& mfring site for devices) OSI Pharmaceuticals Boulder Safety 2860 Wilderness Place Boulder, CO 80301 USA (Initial Unit)	2. Phone number 303-546-7600
3. Report source (check all that apply)	
<input checked="" type="checkbox"/> foreign	
<input checked="" type="checkbox"/> study	
<input type="checkbox"/> literature	
<input type="checkbox"/> consumer	
<input checked="" type="checkbox"/> health professional	
<input type="checkbox"/> user facility	
<input type="checkbox"/> company representative	
<input type="checkbox"/> distributor	
<input type="checkbox"/> other: _____	
4. Date received by manufacturer (mo/day/yr) 07/19/05	5. (A)NDA # IND # <u>53,728</u> PLA # _____ pre-1938 <input type="checkbox"/> yes OTC product <input type="checkbox"/> yes
6. If IND, protocol # MO18109	8. Adverse event term(s) 1) NECROTIC ULCERATION (SKIN) (Skin necrosis)
7. Type of report (check all that apply) <input type="checkbox"/> 5-day <input checked="" type="checkbox"/> 15-day <input type="checkbox"/> 10-day <input type="checkbox"/> periodic <input checked="" type="checkbox"/> Initial <input type="checkbox"/> follow-up # _____	
9. Mfr. report number 2005001356	

E. Initial reporter

1. Name & address M Karhaus Evangelisches Kraukenhaus Schifalescher Str. 101 Bielefeld, 3360 GERMANY	phone #
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2. Health professional? <input checked="" type="checkbox"/> yes <input type="checkbox"/> no	3. Occupation Study Investigator	4. Initial reporter also sent report to FDA <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unk
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Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

OSI Pharmaceuticals
Boulder Safety
2860 Wilderness Place
Boulder, CO 80301
JSA

Continuation Sheet for FDA-3500A Form

Page 2 of 2

Mfr. report #: 2005001356

Date of this report: 07/27/05

B. Adverse event or product problem

B.5 Describe event or problem (Cont...)

increased dose of dexamethasone (10 mg daily).

At the time of the report the necrotic ulceration was reported to be persisting.

In the opinion of the investigator there was a causal relationship between the necrotic ulceration and erlotinib.

No further information was available.

C. Suspect medication (Cont...)

Seq No.	: 1
C.I Suspect medication	: Erlotinib HCl (Tablet) (Erlotinib HCl)
Approval information	
IND #	: 53,728

000003

(osi) pharmaceuticals

Drug Safety Department

Tarceva® (erlotinib, OSI-774)

Serious Adverse Event Report – 15 Day Investigator Notification

Report # 2005001356

Preferred Term: Skin Necrosis

03-Aug-2005

Re: MO18109 An Expanded Access Program of Tarceva (Erlotinib) in Patient's with Advanced Stage IIIB/IV Non-Small Cell Lung Cancer.

Dear Investigator:

This letter is to advise you that we have submitted a report to local regulatory authorities regarding a patient who developed skin necrosis, which was considered at least possibly related to erlotinib therapy. This patient was treated in Roche sponsored study MO18109. The report, which originated in Germany, was received at OSI Pharmaceuticals on 19-Jul-2005.

Attached please find the similar events analysis and CIOMS I form from Roche regarding this serious adverse event. Please include a copy of this correspondence as a supplement to the Investigator's Brochure for Tarceva® (erlotinib, OSI-774), and forward a copy to your Institutional Review Board/Ethics Committee as required by local regulations.

Please feel free to contact the OSI Drug Safety Department or your local clinical contact with any questions or concerns you may have in this regard. We appreciate your continuing efforts and cooperation in the conduct of our clinical trials.

Sincerely,

Drug Safety Department
OSI Pharmaceuticals, Inc.
Telephone: (303) 546-7869
e-mail: safetygroup@osip.com

Attached: Copy of Roche Investigator Letter and CIOMS I form for Roche Report 410547

" A safety report or other information submitted by a sponsor under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse experience. A sponsor need not admit, and may deny, that the drug caused or contributed to an adverse experience." [CFR 312.32]

Confidential Information

OSI Pharmaceuticals, Inc.
58 South Service Rd. • Melville, NY USA • 631-962-2000

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ANALYSIS OF SIMILAR EVENTS

Pharma Development Medical Science, Safety Risk Management

P

Pharmaceuticals

INN Generic/Trade Name: Erlotinib (Tarceva)

Preferred Term: Necrotic ulceration

MCN # / Report: 410547

1 CASE SUMMARY

See summary of case report as in enclosed regulatory form (CIOMS/Medwatch)

2 INVESTIGATORS OPINION

The investigator assessed the causal relationship between the reported event of erlotinib and necrotic ulceration as related.

3 ANALYSIS OF SIMILAR EVENTS

Up to the cut off date of 5th July 05, there was one case of decubitus ulcer reported to the erlotinib database. This was assessed as being unrelated to erlotinib.

4 CONCLUSION

Following review of all the data pertaining to the case, the sponsor cannot rule out a causal association between the event and treatment with erlotinib.

This safety report will not be an addendum to the Investigators' Brochure.

Author: Indira Hara

Date: 27/July /05

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

SUSPECT ADVERSE EVENT REPORT

EVENT INFORMATION

PAGE 1 OF 3

1. PATIENT INITIALS (FIRST, LAST) (IN CONFIDENCE) RHE 1	1A. COUNTRY D	2. DATE OF BIRTH <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">DA</td> <td style="width: 33%;">MO</td> <td style="width: 33%;">YR</td> </tr> <tr> <td style="text-align: center;">7</td> <td style="text-align: center;">MAR</td> <td style="text-align: center;">1937</td> </tr> </table>	DA	MO	YR	7	MAR	1937	2A. AGE (YRS) 68 YR	3. SEX M	4-6. EVENT ONSET <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">DA</td> <td style="width: 33%;">MO</td> <td style="width: 33%;">YR</td> </tr> <tr> <td style="text-align: center;">2</td> <td style="text-align: center;">JUL</td> <td style="text-align: center;">2005</td> </tr> </table>	DA	MO	YR	2	JUL	2005	8-12. CHECK ALL APPROPRIATE <input type="checkbox"/> PATIENT DIED <input checked="" type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION <input type="checkbox"/> INVOLVED SIGNIFICANT DISABILITY OR INCAPACITY? <input type="checkbox"/> LIFE THREATENING
DA	MO	YR																
7	MAR	1937																
DA	MO	YR																
2	JUL	2005																
7. DESCRIBE REACTIONS INCLUDING RELEVANT TESTS/LAB DATA 2004-000564-28. M018109 AN EXPANDED ACCESS PROGRAM OF TARCEVA (ERLOTINIB) IN PATIENT'S WITH ADVANCED STAGE IIIB/IV NON-SMALL CELL LUNG CANCER A 68 YEAR OLD MALE PATIENT DEVELOPED NECROTIC ULCERATION WHILST PARTICIPATING IN THE ABOVE TRIAL. THE PATIENT STARTED ORAL ERLOTINIB (150 MG ONCE DAILY) ON 1 APRIL 2005. APPROXIMATELY THREE MONTHS LATER, ON 2 JULY 2005, THE PATIENT SHOWED THE FIRST SIGNS OF A RASH (CTC II). TEN DAYS LATER HE WAS HOSPITALISED DUE TO DETERIORATION, MULTIPLE NECROTIC ULCERATIONS ON BOTH FEET, HIS RIGHT FEMUR AND RIGHT FOREARM. THE PATIENT WAS ALSO EXPERIENCING MASSIVE PAIN AND WAS TREATED WITH METAMIZOLE SODIUM (NOVALGIN, 90 DROPS PER DAY), DEXAMETHASONE (5 MG), TRAMADOL (TRAMAL, 60 DROPS) AND MORPHINE (25 MG). THE NECROTIC ULCERATION WAS TREATED WITH SULFADIAZINE SILVER (FLAMMACINE). ON THIS DAY CONTINUED																		

SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUGS (INCLUDE GENERIC NAME) ERLOTINIB (ERLOTINIB)	20. DID EVENT ABATE AFTER STOPPING DRUGS? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> NA
15. DAILY DOSE(S) / STRENGTH 150 MG 1 X per DAY /	16. ROUTE(S) OF ADMINISTRATION ORAL
17. INDICATION(S) FOR USE NON-SMALL CELL LUNG CANCER/NON-SMALL CELL LUNG CANCER/MEDDRA 8.0	21. DID EVENT REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
18. THERAPY DATES (FROM/TO) FROM 01-APR-2005 TO 12-JUL-2005	19. THERAPY DURATION 103 DAYS

CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (EXCLUDE THOSE USED TO TREAT EVENT)
23. OTHER RELEVANT HISTORY (E.G. DIAGNOSES, ALLERGIES, PREGNANCY, WITH LMP, ETC.) MEDICAL HISTORY TERM(S): NON-SMALL CELL LUNG CANCER/NON-SMALL CELL LUNG CANCER/MEDDRA 8.0

MANUFACTURER INFORMATION

24. NAME AND ADDRESS OF MANUFACTURER 24b. MFR. CONTROL NO. 410547	GERMANY CIOMS
24c. DATE RECEIVED BY MANUFACTURER 13-JUL-2005	
24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL	
25a. REPORT TYPE <input type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP	

Where MedDRA is used the following format applies: Reported term/ MedDRA LL.T/version number

000006

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

ERLOTINIB THERAPY WAS DISCONTINUED. THE FOLLOWING DAY THE PATIENT WAS GIVEN AN INCREASED DOSE OF DEXAMETHASONE (10 MG DAILY). AT THE TIME OF THE REPORT THE NECROTIC ULCERATION WAS REPORTED TO BE PERSISTING. IN THE OPINION OF THE INVESTIGATOR THERE WAS A CAUSAL RELATIONSHIP BETWEEN THE NECROTIC ULCERATION AND ERLOTINIB.
NO FURTHER INFORMATION WAS AVAILABLE.

ADVERSE EVENT TERM(S):
NECROTIC ULCERATION (SKIN)/ULCERO-NECROTIC SKIN LESION/MEDDRA 8.0 +++

(+++ denotes adverse event that generated submission)

000007

CIOMS TEXT

NECROTIC ULCERATION IS NOT LISTED IN THE COMPANY REFERENCE DOCUMENT (IB) FOR ERLOTINIB. BASED ON THE INFORMATION RECEIVED FOR THIS CASE, A CAUSAL RELATIONSHIP BETWEEN THE REPORTED EVENT AND TREATMENT WITH ERLOTINIB IS ASSESSED AS POSSIBLE. COMPANY CAUSALITY WAS ASSESSED BASED ON THE NARANJO ALGORITHM.

000008

REPORTER INFORMATION

Reporter: 1
Name: M KARTHAUS
Organisation: EVANGELISCHES KRAUKENHAUS
Address 1: SCHIFALESCHER STR. 101
Address 2:
Address 3:
Address 4:
City: BIELEFELD 3360
Country: GERMANY
Address Phone:
Address Fax:
Representative Phone:
Representative Fax:
Reporter Type: HEALTH PROFESSIONAL
Occupation: DOCTOR OF MEDICINE

CLINICAL TRIAL INFORMATION

Clin. Study Id: MO18109
Clin. CRTN 48403
Design and Phase: OPEN IV
Clin. Patient Id: 1
Clin. Investigator Id: 221486

DRUG-EVENT INFORMATION

Event: NECROTIC ULCERATION (SKIN)/ULCERO-NECROTIC SKIN
LESION/MEDDRA 8.0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS
SOC: PERSISTING
Outcome: PERSISTING
Severity:
Seriousness: NEW/PROLONGED HOSPITAL
Onset Date: 2 JUL 2005
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 - D
Labeled IB: NO
Labeled SPC: NOT APPLICABLE
Labeled Core: NO
Drug Related(Comp): YES
Drug Related(Rept): YES
Latency Reported: (First Dose)
Latency Reported (Last Dose):

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