

NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: April 7, 2006
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_2006000539

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




DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

DATE: March 29, 2006

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

SUBJECT: OSI-774 (Erlotinib, Tarceva™) Investigator Notification: **Dactylitis and Palmar Plantar-Like Syndrome**
OSI Pharmaceuticals Report # 2006000539

TO: Investigators of CTEP-sponsored Trials Using OSI-774 (NSC 718781)

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 dactylitis and palmar plantar-like syndrome in a patient participating in an OSI Pharmaceuticals-sponsored clinical study utilizing the investigational agent OSI-774 (NSC 718781), was recently distributed to investigators.

The following must be completed by all investigators using OSI-774 under NCI IND 63383:

- 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 Dear Investigator Letter and MedWatch Report that describe the following adverse events are attached:

A 66-year-old patient of unknown gender with non-small cell lung cancer developed grade 2 dactylitis and palmar plantar-like syndrome while participating in an expanded access program utilizing the investigational agent OSI-774.

There has been one incidence of rash: hand-foot skin reaction (grade 3, considered definitely related to the investigational agent) reported to the NCI as a serious adverse event under OSI-774 NSC 718781.

There have been 1794 patients enrolled in NCI-sponsored clinical trials using the investigational agent, OSI-774 (NSC 718781).

CONFIDENTIAL

00001

(OSI) pharmaceuticals

Drug Safety Department

Tarceva® (erlotinib, OSI-774)

Serious Adverse Event Report – 15 Day Investigator Notification

Report # 2006000539

Preferred Term: Dactylitis and palmar-plantar erythrodysesthesia

18-Mar-2006

Re: MO18109 A Roche expanded access program of Tarceva (erlotinib) in patients 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 experienced dactylitis and palmar plantar-like syndrome that was considered medically significant and possibly related to erlotinib therapy. This patient was treated in Roche study MO18109. This report, from Ireland, was received at OSI Pharmaceuticals on 03-Mar-2006. Please include a copy of this letter with your study records and forward a copy to your Institutional Review Board/Ethics Committee as required by local regulations.

Event Narrative

A 66-year-old patient of unknown gender, developed dactylitis and palmar plantar-like syndrome, during participation in the above study. The patient's medical history was significant for hypothyroidism, obesity and arthritis. The patient was taking multiple concomitant medications. On 22-Dec-2005, oral erlotinib (150 mg once per day) was started. On 14-Feb-2006, the patient developed dactylitis and palmar plantar-like syndrome to feet and hands (grade II). It was reported that three days later, the patient had attended for week five to eight review, where physical exam had confirmed the event. The patient had been referred to a dermatologist. On 23-Feb-2006, the patient received treatment for the event in the form of topical betamethasone dipropionate/ salicylic acid (Diprosalic), topical metronidazole (Narobic), and clarithromycin (Klacid). Five days later, clarithromycin treatment had been discontinued. At the time of the report, erlotinib therapy was ongoing. The outcome of the event was reported as persisting.

No further information was available.

Company Medical Assessment

The investigator related causality of the event to erlotinib therapy and to non-small cell lung cancer. The investigator considered the event to be medically significant.

Similar Events:

The OSI and Roche erlotinib clinical safety databases were searched for all reports with the preferred term of palmar-plantar erythrodysesthesia. The search found 2 reports of Palmar-plantar erythrodysesthesia. Both of these reports of palmar-plantar erythrodysesthesia were considered at least possibly related to erlotinib by the investigator.

The first case involved a 58-year-old female patient, with advanced stage IIIB/IV non-small cell lung cancer was on oral erlotinib, 150 mg once daily. Three months later she presented

OSI Confidential Information

OSI Pharmaceuticals, Inc.
2860 Wilderness Pl. • Boulder CO 80301 • 303-546-7600
Headquarters: 41 Pinelawn Rd. • Melville, NY 11747 • www.osip.com

• 00002

(osi) pharmaceuticals

Drug Safety Department

with dactylitis and a palmar-plantar like syndrome of her feet and hands at her visit. The patient was otherwise well, and her symptoms were not causing any pain or discomfort.

The second case involved a 65-year-old male subject enrolled in a phase II trial of erlotinib and capecitabine for patients with previously untreated metastatic colorectal cancer. The subject's past medical history included carcinoma of vocal cords, colitis, liver cirrhosis (elevated PSA), alcohol abuse and tobacco abuse. Concomitant medications included aspirin, tamsulosin, spironolactone and furosemide. The patient started erlotinib, 150 mg PO QD, and capecitabine, 1000mg/m² PO. Approximately 16 days later, he presented with grade 2 or 3 desquamation of palms and soles. Physical exam revealed grade I/II acneiform rash with desquamation of palms and soles with weeping. It was noted that these toxicities were a possible interaction between Xeloda and erlotinib. No relevant diagnostic tests were reported.

Conclusion

After review of the clinical details and investigator 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.

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

" 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]

OSI Confidential Information

OSI Pharmaceuticals, Inc.
2860 Wilderness Pl. • Boulder CO 80301 • 303-546-7600
Headquarters: 41 Pinelawn Rd. • Melville, NY 11747 • www.osip.com

00003

MED WATCH

THE 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 09/25/95 (Clinvarium)

Mfr report # 2006000539
UPD/Ret report #
FDA Use Only

A. Patient information			
1. Patient identifier Unk	2. Age at time of event: or Date of birth: 66 Years Unk	3. Sex <input type="checkbox"/> female <input checked="" type="checkbox"/> UNK <input type="checkbox"/> male	4. Weight Unk lbs or Unk 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 type="checkbox"/> death (m/d/y)	<input type="checkbox"/> disability	<input type="checkbox"/> congenital anomaly	
<input type="checkbox"/> life-threatening	<input type="checkbox"/> required intervention to prevent permanent impairment/damage		
<input type="checkbox"/> hospitalization - initial or prolonged	<input checked="" type="checkbox"/> other: <u>Medica-Cont.</u>		
3. Date of event (m/d/y) 02/14/06	4. Date of this report (m/d/y) 03/16/06		
5. Describe event or problem			
PALMAR-PLANTAR ERYTHRODYSAESTHESIA (Dactylitis and palmar-plantar-like syndrome)			
MO18109 An expanded access program of Tarceva (erlotinib) in patients with advanced stage IIIB/IV nonsmall cell lung cancer.			
The patient's medical history was significant for hypothyroidism, obesity and arthritis. The patient was taking multiple concomitant medications.			
A 66-year-old patient of unknown gender, developed dactylitis and palmar plantar-like syndrome to feet and hands, during participation in the above study.			
On 22-Dec-2005, oral erlotinib (150 mg once per day) was started. On 14-Feb-2006, the patient developed dactylitis and palmar plantar-like syndrome to feet and hands (grade II). It was reported that three days later, the patient had attended for week five to eight review, where physical exam had confirmed the event. The patient had 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.)			
Concurrent Disease: HYPOTHYROIDISM OBESITY ARTHRITIS			

C. Suspect medication(s)			
1. Name (give labeled strength & mfr/labeler, if known) #1 Erlotinib (Tablet) (Erlotinib HCl)			
#2			
2. Dose, frequency & route used #1 150 mg (QD), Oral		3. Therapy dates (if unknown, give duration) (m/d/y or best estimate) #1 12/22/05 - Unk	
#2		#2	
4. Diagnosis for use (indication) #1 NON-SMALL CELL LUNG CANCER		5. Event abated after use stopped or dose reduced	
#2		#1 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply	
#2		#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply	
6. Lot # (if known) #1 Unk		7. Exp. date (if known) #1 Unk	
#2		#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	
4. Date received by manufacturer (m/d/y) 03/03/06		3. Report source (check all that apply)	
6. If IND, protocol # MO18109		<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:	
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 #		5. (A)NDA # IND # 53,728 PLA # pre-1938 <input type="checkbox"/> yes OTC product <input type="checkbox"/> yes	
9. Mfr. report number 2006000539		8. Adverse event term(s) 1) DACTYLITIS AND PALMAR PLANTAR-LIKE SYNDROME (Palmar-plantar erythrodyseaesthesia syndrome)	
E. Initial reporter			
1. Name & address Dr. Seamus O'Reilly Cork University Hospital Wilton Cork, IRELAND		phone #	
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 checked="" 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 contributed to the event.

3500A Facsimile

00004

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

Continuation Sheet for FDA-3500A Form

Page 2 of 2

Mfr. report # : 2006000539

Date of this report : 03/16/06

B. Adverse event or product problem

B.2 Outcome attributed to adverse event (Cont...)

Other : Medically significant

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

been referred to a dermatologist. On 23-Feb-2006, the patient received treatment for the event in the form of topical betamethasone dipropionate/ salicylic acid (Diprosalic), topical metronidazole (Narobic), and clarithromycin (Klacid). Five days later, clarithromycin treatment had been discontinued.

At the time of the report, erlotinib therapy was ongoing. The outcome of the event was reported as persisting.

The investigator related causality of the event to erlotinib therapy and to non small cell lung cancer. The investigator considered the event to be medically significant.

No further information was available.

C. Suspect medication (Cont...)

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

* 00005