



National Institutes of Health  
National Cancer Institute  
Bethesda, Maryland 20892

**DATE:** February 2, 2010  
**FROM:** Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
**SUBJECT:** OSI-774 (erlotinib; Tarceva™) and Cetuximab (Erbix®) NCI IND Safety Report, AE# 1670060  
**TO:** Investigators Using Erlotinib (NSC 718781) and Cetuximab (NSC 714692)

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. Please find attached a copy of an IND Safety Report recently submitted to the FDA for the CTEP-sponsored investigational agent erlotinib.

The following must be completed by all investigators using erlotinib under NCI IND 63383:

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

If your study is not covered under IND 63383, it is strongly recommended that you follow the instructions above.

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

Based on CTEP's assessment of the current information in light of previous experience with erlotinib, there does not appear to be a change in the risk-benefit ratio for erlotinib studies; therefore, CTEP is not requiring a protocol amendment at this time.

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

The attached Adverse Events Assessment describes the adverse event(s) (synopsis provided below), relevant previous experience under this IND and/or NSC, and the total number of patients enrolled in trials under this IND and/or NSC.

The patient is a 56-year-old male with metastatic adenocarcinoma of the rectum experienced grade 3 asteatotic eczema while on a phase 1/2 trial utilizing the investigational agent erlotinib in combination with cetuximab.

## ADVERSE EVENTS ASSESSMENT

IND 63383		ADVERSE EXPERIENCE REPORT NO.
NSC 718781	714692	IND Safety Report: # 1
OSI-774 (erlotinib; Tarceva™)	Cetuximab (Erbix™)	Event: Gr. 3 Dermatology/skin- Asteatotic eczema
AE: 1670060		Protocol: 6980

The patient is a 56-year-old male with metastatic adenocarcinoma of the rectum who experienced asteatotic eczema while on a phase 1/2 trial using the investigational agent erlotinib in combination with cetuximab. He began the investigational treatment on April 17, 2009, receiving erlotinib 100 mg PO daily on Days 8-21 of cycle 1, then on Days 1-21 of all subsequent cycles, and cetuximab 250 mg/m<sup>2</sup> IV over 60-120 min weekly, every 21 days. He received his last dose of erlotinib on July 2, 2009 (Cycle 4, Day 14) and the last dose of cetuximab on June 19, 2009 (Cycle 4, Day 1).

The patient was initially diagnosed with adenocarcinoma of the rectum in April 2005 and is status post colon resection, chemotherapy, and radiation. He began the study on April 17, 2009.

On July 2, 2009 (Cycle 4, Day 14), the patient presented to the clinic complaining of severe, painful bilateral lower extremity edema associated with small, scattered, cracked, weeping lesions, and pustular lesions on the face, chest and arms for which he was admitted to the hospital. He had a history of intermittent edema since February 2009 with the most recent episode beginning 3 days prior for which he received Lasix<sup>®</sup> and minocycline. He also had a fever of 101<sup>0</sup> F. Examination revealed non-blanching papules and pustules on the abdomen, arms and chest; lower extremity non-blanching, palpable erythema in a vascular-like pattern extending from ankle to knee; extremely tender 3+ edema extending from foot to toe; oozing of serous discharge above left medial malleolus; and small papules on the right lower extremity. The investigational therapy was held. The dermatologist felt that the lesions on the patient's lower extremities were consistent with asteatotic eczema due to severe edema and that the lesions on his face, chest and arm were an acneiform drug reaction from erlotinib. Minocycline and Lasix<sup>®</sup> were continued, and the patient was started on clobetasol cream and Eucerin<sup>®</sup>. Vancomycin was started for possible superinfection.

On July 3, 2009, urine cultures grew coagulase-negative *Staphylococcus aureus* sensitive to doxycycline, so the vancomycin was stopped and the patient continued minocycline for both the skin eruptions and a urinary tract infection. He was discharged on July 6, 2009, on Lovenox<sup>®</sup>, minocycline, Lasix<sup>®</sup>, and topical steroids. At a July 16, 2009 (Cycle 4, Day 28) visit, both the asteatotic eczema and edema had improved, and the both agents were resumed. On July 31, 2009, the rash was completely resolved, and the edema had returned to baseline.

The patient's past medical/surgical history is significant for colorectal resection, femoral-popliteal bypass surgery in left lower extremity (2003), carpal tunnel surgery, abdominoperineal resection (2008), DVT (2003 and 2009), hypertension, diabetes, coronary artery disease status post myocardial infarctions × 2 and PTCA, peripheral arterial disease, and hypercholesterolemia.


Although rash/desquamation is a known event for erlotinib, there have been no other cases specifically of asteatotic eczema reported to the NCI as serious adverse events under this NSC and/or IND.

There have been 2927 patients enrolled in NCI-sponsored trials under this IND and/or NSC.

In this case, it is felt that a possible relationship exists between the asteatotic eczema and erlotinib treatment.

	<b>Asteatotic eczema</b>
<b>Erlotinib</b>	Possible
<b>Cetuximab</b>	Possible
<b>Adenocarcinoma of rectum</b>	Unrelated

Date: 2/1/2010

Signature:   
Helen Chen, M.D.  
(IDB Monitor for erlotinib)

If this assessment is changed, we will notify your office.

cc: Christine Boisclair  
Brian Watson  
Safetygroup@osip.com  
OSI Pharmaceuticals, Incorporated