



DATE: May 27, 2009

FROM: Helen Chen, M.D., Associate Branch Chief, Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: OSI-774 (erlotinib; Tarceva™) NCI IND Safety Report, AE# 1225018

TO: Investigators Using OSI-774 (erlotinib; Tarceva™) (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. Please find attached a copy of an IND Safety Report recently submitted to the FDA for the CTEP-sponsored investigational agent OSI-774.

The following must be completed by all investigators using OSI-774 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 OSI-774, there does not appear to be a change in the risk-benefit ratio for OSI-774 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.

A 69-year-old female with metastatic non-small cell lung cancer experienced renal failure and subsequently died while on a phase 2 trial utilizing the investigational agent OSI-774 in combination with paclitaxel and carboplatin.

ADVERSE EVENTS ASSESSMENT

IND 63383 NSC 718781 OSI-774 (erlotinib; Tarceva™) AE: 1225018	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 5: Renal Failure Gr. 4: Diarrhea Protocol: CALGB-30406
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The patient was a 69-year-old female with metastatic non-small cell lung cancer (NSCLC) who developed renal failure and subsequently died while on a phase 2 trial using the investigational agent OSI-774 in combination with paclitaxel and carboplatin. She began investigational treatment on January 22, 2009, receiving erlotinib 150 mg PO daily, paclitaxel 200 mg/m² IV over 3 hours on Cycle 1, Day 1, and over 1-3 hours on Day 1 of subsequent cycles, for 6 cycles, and carboplatin AUC 6 IV over 15-30 minutes on Day 1 for 6 cycles. She received her last doses of paclitaxel and carboplatin on January 22, 2009 (Cycle 1, Day 1) and the last dose of OSI-774 on January 27, 2009 (Cycle 1, Day 6).

The patient was diagnosed with biopsy-proven, poorly-differentiated adenocarcinoma of the lung occurring in a non-smoker in January 2009 and had not received any prior therapy before starting the investigational treatment on January 22, 2009.

On January 27, 2009 (Cycle 1, Day 6), the patient presented to the clinic reporting increased shortness of breath, rash, and a 3-day history of vomiting and profuse watery diarrhea. Prior to developing the diarrhea she had a 5-day history of constipation for which she took Senokot® and stool softeners. She was admitted to the hospital to receive intravenous hydration, antibiotics, and antiemetics. Upon examination, the patient had lost 3.5 pounds in one week, she was afebrile, her blood pressure was 109/64 mmHg, her heart rate was 117 bpm and regular, and her lungs were clear. Significant laboratory findings included an increased potassium of 6.1 mmol/L (reference range: 4.0-5.5 mmol/L), sodium of 130 mmol/L (reference range: 137-143 mmol/L), bicarbonate of 18 mmol/L (reference range: 23-30 mmol/L), BUN of 52 mg/dL (reference range: 6-19 mg/dL), and creatinine of 1.2 mg/dL (reference range: 0.5-1.0 mg/dL). The CBC was: hemoglobin (Hgb) 9.4 g/dL (reference range: 11.5-15.5 g/dL), hematocrit 30.1% (reference range: 36-45%), WBC 4.2 × 10³/μL (reference range: 4-10 × 10³/μL), and platelets 480 × 10³/μL (reference range: 150-400 × 10³/μL). The BUN and creatinine initially improved to 17 mg/dL and 0.9 mg/dL respectively after she received hydration. Investigational treatment was held. However, her diarrhea persisted despite treatment with loperamide. Stool cultures were negative for enteropathogens and *Clostridium difficile*.

On February 1, 2009 (Cycle 1, Day 11), the patient had an episode of hypotension (reading blood pressure was not provided), and developed acute renal failure with non-anion gap metabolic acidosis (bicarbonate was 5 mmol/L), and tachypnea; she was transferred to the intensive care unit for overall deterioration of her status. Her Hgb was 10.6 g/dL, and the platelet count was 292 × 10³/μL. It was thought that the patient's acidosis stemmed from the bicarbonate losses in her stool and that the combination of volume loss and possible sepsis caused the acute renal failure. However, all blood cultures were negative. Although she was initially neutropenic, her white blood cell count increased to 14.2 × 10³/μL (reference range: 4.0-10.0 × 10³/μL). Additional antibiotics, fluid, and sodium bicarbonate were administered. The patient elected to be placed on "do not resuscitate" status. By February 5, 2009 (Cycle 1, Day 15), the patient remained oliguric with between 300 and 600 mL of urine output per day, and her creatinine level increased to 3.5 mg/dL. At this point the renal failure was deemed secondary to acute tubular necrosis. Her status continued to decline, and she was placed on comfort care on February 13, 2009. She expired on February 17, 2009.

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Pertinent laboratory values are shown in the table below.

	1/13/09 Pre-study	1/27/09 Admission	1/30/09 C1, D9	2/1/09 C1, D11	2/7/09 C1, D 17	2/11/09 C1, D21
BUN (reference range: 6-19 mg/dL)	22	52	17	41	60	75
Creatinine (reference range: 0.5-1.0 mg/dL)	0.8	1.2	0.9	2.1	3.6	4.3
CO2 (reference range: 23-30 mmol/L)	23	18	*	5	23	19
Potassium (reference range: 4.0-5.5 mmol/L)	5.2	6.1	*	*	*	*
Anion gap	*	*	*	19	11	18
Hgb (reference range: 11.5-15.5 g/dL)	10.6	9.4	10.1	10.5		9.1
Platelets (reference range: 150-400 × 103/μL)	710	480	242	300	*	228
Total bilirubin (reference range: 0-1.0 mg/dL)	0.6	1.9	*	*	*	*

*not provided

The patient's past medical/surgical history is significant for COPD or asthma, hypertension, cataract surgery, total abdominal hysterectomy, and bilateral salpingo-oophorectomy. Medications taken at the time of the event included Singulair®, Protonix®, Zofran®, enalapril, Advair®, and megestrol.

Diarrhea is a known event for erlotinib, and there have been 11 other incidences of renal failure reported to the NCI as serious adverse events under this NSC and/or IND. The incidences are shown in the table below.

Adverse Event	Grade	Attribution
Renal failure (n = 11)	4 3	2 Possible, 1 Unlikely 3 Unrelated, 4 Unlikely, 1 Probable

There have been 2,787 patients enrolled in NCI-sponsored trials under the erlotinib IND and/or NSC.

In this case, it is felt that the etiology of renal failure may have been multifactorial, with possible attribution to carboplatin, the diarrhea resulting from erlotinib and chemotherapy and possible sepsis although infection has not been identified.

	Diarrhea	Renal Failure
Erlotinib	Probable	Possible
Paclitaxel	Possible	Unlikely
Carboplatin	Possible	Possible
NSCLC	Unrelated	Unlikely
Diarrhea	NA	Probable
Possible sepsis	NA	Possible

Date: _____

5/27/09

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