



DATE: DEC 08 2010
FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: OSI-774 (erlotinib; Tarceva™) NCI IND Safety Report, AE# 1531241
TO: Investigators Using Erlotinib (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 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.

A 78-year-old female with metastatic adenocarcinoma of the pancreas experienced grade 3 pneumonitis, grade 4 pericardial effusion, and grade 5 Adult Respiratory Distress Syndrome (ARDS) while on a phase 1/2 trial using the investigational agent erlotinib in combination with gemcitabine.

ADVERSE EVENTS ASSESSMENT

IND 63383 NSC 718781 OSI-774 (erlotinib; Tarceva™)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 5: Adult Respiratory Distress Syndrome (ARDS) Gr. 4: Pericardial effusion Gr. 3: Pneumonitis Protocol: S0727
AE: 1531241	

The patient was a 78-year-old female with metastatic adenocarcinoma of the pancreas who experienced pneumonitis, pericardial effusion and died of Adult Respiratory Distress Syndrome (ARDS) while on a phase 1/2 trial using the investigational agent erlotinib in combination with gemcitabine. She began the investigational treatment on December 9, 2009, receiving erlotinib 100 mg PO daily and gemcitabine 1000 mg/m²/dose IV over 30 minutes on Days 1, 8, and 15, every 28 days. She received her last dose of erlotinib on July 6, 2010 (Cycle 8, Day 14), and her last dose of gemcitabine on June 30, 2010 (Cycle 8, Day 8).

The patient was diagnosed with metastatic adenocarcinoma of the pancreas in November 2009. She began the investigational treatment on December 9, 2009.

On July 19, 2010 (Cycle 8, Day 27), the patient had a CT scan to evaluate her disease status. She complained of severe headache shortly after receiving the IV contrast, and despite being attended to immediately, was found unresponsive within the CT scanner. The patient was cyanotic, pale, diaphoretic, and was spitting up pinkish frothy sputum on arrival to the emergency room. Her Glasgow Coma Scale was 3. Her arterial blood gas (ABG) prior to intubation showed a pH of 7.01 (reference range: 7.35-7.45), pCO₂ of 64 mmHg (reference range: 35-45 mm Hg), pO₂ of 88 mmHg (reference range: 80-105 mm Hg), and a bicarbonate of 15.8 mEq/L (reference range: 18-23 mEq/L). The patient was intubated and placed on mechanical ventilation.

A non-contrast CT scan of the head was negative for acute hemorrhage or infarct. A portable chest X-ray revealed bilateral diffuse airspace opacities, which were concerning for acute pulmonary interstitial edema versus ARDS, pulmonary hemorrhage/edema, or diffuse multifocal pneumonia. She had an oxygen saturation in the mid 90s post intubation, and her post intubation ABG revealed a pH of 7.16, pCO₂ of 54.6 mmHg, pO₂ of 85 mmHg, and a bicarbonate of 18.8 mEq/L. The patient was started on nitroglycerin, Lasix®, morphine, Ativan®, and Zemuron®.

The patient had a prior chest CT scan on May 24, 2010, which showed decrease in the size of the pancreatic lesion and stable pulmonary nodules, and interval development of bilateral interstitial infiltrate. At the last clinical visit on July 13, 2010, the patient appeared fragile but did not complain of dyspnea; a chest X-ray revealed persistent interstitial changes and new left pleural and moderate pericardial effusion. A transthoracic echocardiogram (TTE) on July 13, 2010, had revealed normal systolic function with an ejection fraction of 60-65% as well as moderate pericardial effusion over the right ventricle. However, a TTE on July 20, 2010, showed a left ventricular ejection fraction of 35%, moderate circumferential pericardial effusion with mid-apical septum and entire apical akinesia, which was concerning for pericardial tamponade. The CT scans on July 19, 2010 (on abdomen and pelvis) demonstrated interval development of bilateral pleural effusions with associated bibasilar atelectasis, mosaic attenuation of the visualized lung parenchyma likely associated with small airways disease, interval development of a moderate pericardial effusion, and an increase in size of the pancreatic head lesion consistent with progressive disease. On July 21, 2010 (Cycle 8, Day 29), a successful pericardiocentesis was done which yielded 450cc of straw-colored fluid; a pericardial drain was left in-situ. The pericardial fluid cytology showed reactive mesothelial cells and histiocytes in a predominantly acute inflammatory background. It was negative for malignant cells. Later that day, the patient also underwent a diagnostic and therapeutic thoracentesis, which yielded 500cc of clear yellow fluid, which was also negative for malignant cells.

Initially, the patient's pulmonary edema was thought to be secondary to a cardiac etiology given her depressed ejection fraction and pericardial tamponade. However, the pulmonologist felt that she most likely had ARDS considering her chest X-ray report, her PaO₂:FiO₂ of < 300 (reference range: 300-400), a pulmonary capillary wedge pressure of 8 (reference range: 8-10 mmHg), and euvolemia with persistent pulmonary edema. The possibilities of reaction to IV contrast, aspiration pneumonia, metastasis leading to lymphatic obstruction, and an infectious process were also considered. The patient was started on IV cefepime and IV vancomycin empirically. Her sputum cultures initially grew *Staphylococcus aureus*, which were later positive for Methicillin Sensitive *Staphylococcus aureus* (MSSA), and the antibiotics were switched to Ceftriaxone[®].

On July 27, 2010 (Cycle 8, Day 35), the patient self-extubated and was made Do-Not-Resuscitate (DNR) based on her family's decision. She expired that day. An autopsy was not performed.

The patient's past medical/surgical history was significant for bilateral deep venous thrombophlebitis, urinary incontinence, and basal cell carcinoma. Medications taken at the time of the event included Fragmin[®], oxycodone, Zofran[®], mirtazapine, promethazine, Colace[®], Citrucel[®], promethazine, magnesium oxide, Bisac-evac[®] suppository, senna, metronidazole cream, and megestrol acetate.

There have been 5 other cases of ARDS and 4 other cases of pericardial effusion reported to the NCI as serious adverse events under the erlotinib NSC and/or IND as shown in the table below. Pneumonitis is a known event for erlotinib.

Adverse Event	Grade	Attribution
ARDS (n = 5)	5	1 Unrelated, 3 Unlikely
	4	1 Unlikely
Pericardial effusion (n-4)	4	1 Unrelated, 1 Unlikely
	3	1 Unrelated

There have been 3,357 patients enrolled in NCI-sponsored trials under the erlotinib IND and/or NSC.

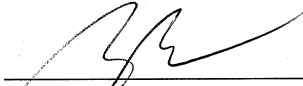
In this case, the pneumonitis discovered prior to the SAE is likely related to erlotinib or gemcitabine. The etiology of pericardial effusion is probably related to the underlying malignancy although attribution to the study drugs cannot be excluded. The acute development of pulmonary edema and respiratory failure could be multifactorial, due to pericardial tamponade, allergy to IV contrast or worsening interstitial pulmonary changes.

	ARDS	Pneumonitis	Pericardial effusion
Erlotinib	Unlikely	Possible	Possible
Gemcitabine	Unlikely	Possible	Possible
Adenocarcinoma of the pancreas	Possible	Possible	Probable
100 mL Optiray 350 IV contrast	Possible	N/A	Unlikely
Possible aspiration	Possible	Unrelated	N/A
Pericardial effusion	Possible	Unrelated	N/A

Date:

12/7/10

Signature:



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

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

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OSI Pharmaceuticals, Incorporated
Does it need to go to ImClone since the trial is under IMC-A12 IND?