

NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: November 18, 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_1556104

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: October 31, 2005
FROM: Janet Dancey, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: OSI-774 (Erlotinib; Tarceva®)IND Safety Report, AE# 1556104
TO: Investigators Using OSI-774, IND 63383



for J. Dancey

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 under IND 63383.

Please complete the following:

- 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.

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 Adverse Events Assessment that describes the following adverse events, previous experience under this IND, and the total number of patients enrolled in trials under this IND is attached:

A 73-year-old male with metastatic papillary renal cell carcinoma died from pneumonitis/pulmonary infiltrates while on a phase 2 trial using the investigational agent OSI-774.

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ADVERSE EVENTS ASSESSMENT

IND 63383 NSC 718781 OSI-774 (erlotinib; Tarceva™) AE: 1556104	ADVERSE EXPERIENCE REPORT NO. 12 IND Safety Report: Initial Event: Gr: 5 Pneumonitis/pulmonary infiltrates Protocol: S0317
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The patient was a 73-year-old male with metastatic papillary renal cell carcinoma who died from pneumonitis/pulmonary infiltrates while on a phase 2 trial using the investigational agent OSI-774. He began his first course of treatment with OSI-774 on April 22, 2005 receiving OSI-774 150 mg PO daily, every 28 days. He received the last dose of OSI-774 on July 28, 2005 (Cycle 4, Day 14).

The patient was initially diagnosed with papillary renal cell carcinoma in June 1991 and was status post left nephrectomy and lobectomy. He began the investigational therapy on April 22, 2005 and completed three cycles with complaints of only acneiform rash and diarrhea reported. On July 28, 2005 (Cycle 4, Day 14), he presented to the clinic with a 3- to 4-day history of progressive shortness of breath, fatigue, decreased appetite, and a dry cough. Upon physical examination, the patient demonstrated respiratory distress with tachypnea, decreased tidal volume, diffuse dry crackles bilaterally, and oxygen saturation of 91% on 7 liters oxygen by face mask. A chest X-ray indicated interstitial markings, as well as nodules, and a pleural effusion seen in March 2005 was no longer evident. Of note, the patient had a history of interstitial lung disease. He was admitted to the hospital for further evaluation, and was removed from the protocol on July 28, 2005. A CT scan of the thorax that day demonstrated multiple bilateral pulmonary nodules, all less than 1.5 cm in size, as well as an interval dramatic increase in inter- and intra-lobular septal thickening associated with architectural distortion and consistent with rapid progression of pulmonary fibrosis. In addition, there was interval development of superimposed ground glass opacities involving all lobes of the lung. Multiple lesions in the liver and mediastinal lymph nodes were also seen. The patient was initially started on steroids, Atrovent® nebulizers every 6 hours, and oxygen by face mask at a flow rate of 7 liters per minute without improvement; consequently, he was transitioned to BiPAP. After 2 days, his respiratory status appeared to improve, and he was transitioned from BiPAP to 100% face mask. A chest X-ray done on August 1, 2005 indicated diffuse patchy opacification consistent with underlying interstitial pulmonary fibrosis, interval decrease of prominent apical vascular markings, and stable decreased inflation of lungs bilaterally. Because the patient's carbon dioxide content rose to 40 mEq/L (reference range: 23-30 mEq/L), he was treated with acetazolamide starting on August 5, 2005, with an almost immediate decrease in his carbon dioxide content to 30-31 mEq/L. The patient's status improved, and after being stable for several days, he was discharged on prednisone, acetazolamide, Atrovent®, and home oxygen to home hospice care on August 10, 2005. He died at home on August 15, 2005.

The patient's past medical history is significant for hypertension and interstitial lung disease. Medications taken at the time of the event included verapamil, aspirin, simvastatin, and vitamin B6.

There have been 19 other incidences of pneumonitis/pulmonary infiltrates reported to the NCI as serious adverse events under this IND, including 3 other grade 5 events. These are summarized in the table below.

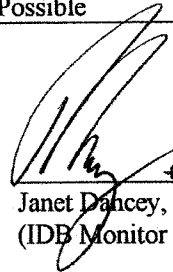
Grade 5 (n=3)	2 Possible, 1 Unlikely
Grade 4 (n=0)	None reported
Grade 3 (n=14)	3 Possible, 8 Unlikely, 3 Unrelated
Grade 2 (n=2)	2 Unlikely

In this case, it is felt that a possible causal relationship between the patient's death due to pneumonitis/pulmonary infiltrates and OSI-774 cannot be excluded. There have been 1464 patients enrolled in NCI sponsored clinical trials under this IND.

	Pneumonitis/Pulmonary infiltrates
OSI-774	Possible
Papillary renal cell carcinoma	Possible
Pulmonary fibrosis	Possible

Date: 11.01.05

Signature:

 for J. Dancy
Janet Dancy, M.D.
(IDB Monitor for OSI-774)

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

cc: Christine Boisclair
Brian Watson
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OSI Pharmaceuticals, Incorporated