

NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: January 27, 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_1265259

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.

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enclosure



DATE: January 17, 2006
FROM: Janet Dancey, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: OSI-774 (erlotinib; Tarceva®)IND Safety Report, AE# 1265259
TO: Investigators Using OSI-774, IND 63383

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.

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.

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 61-year-old male with inoperable Stage III non-small cell lung cancer developed an esophageal fistula while on a phase 1 trial using the investigational agent OSI-774 in combination with paclitaxel, carboplatin and radiotherapy.

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ADVERSE EVENTS ASSESSMENT

IND 63383 NSC 718781 OSI-774 (erlotinib; Tarceva™) AE: 1265259	ADVERSE EXPERIENCE REPORT NO. 16 IND Safety Report: Initial Event: Gr. 3 Fistula-esophageal Protocol: 5411
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The patient is a 61-year-old male with inoperable Stage III non-small cell lung cancer (NSCLC) who developed an esophageal fistula while on a phase 1 trial using the investigational agent OSI-774 in combination with paclitaxel, carboplatin and radiotherapy. He began induction chemotherapy on September 14, 2005, receiving paclitaxel 200 mg/m² IV over 1 hour and carboplatin AUC 6 IV over 30 minutes on days 1 and 22. The patient began concomitant chemoradiotherapy on October 26, 2005 receiving OSI-774 150 mg PO daily × 7 weeks (days 43-91), paclitaxel 50 mg/m² IV over 1 hour and carboplatin AUC 2 IV on days 43, 50, 57, 64, 71, 78, and 85, and chest radiotherapy 6600 cGy total given as 5 fractions/week × 7 weeks beginning on day 43. He received his last doses of paclitaxel, carboplatin, and radiotherapy on November 30, 2005 (Day 78) and his last dose of OSI-774 on December 2, 2005 (Day 80).

The patient was initially diagnosed with NSCLC in July 2005 and had not received any prior therapy. He began induction chemotherapy on September 14, 2005. Treatment was complicated by frequent deep venous thromboses (DVTs); as a result, the patient received Lovenox® and Coumadin® throughout his treatment. His radiotherapy was terminated on November 30, 2005 (Day 78) because it was felt that further radiation would damage the patient's left ventricle. Additionally, all chemotherapy was terminated as of December 2, 2005 (Day 80) since these agents were administered for radiosensitization.

On December 27, 2005, the patient presented to the Emergency Room with a 1-day history of dysphagia, as well as a 2-day history of pain and edema in the left lower leg. He denied chest pain, nausea, vomiting, diarrhea, black or bloody stools. A venous ultrasound performed at that time confirmed a DVT, which was a continuation from a previous DVT. The patient was admitted to the hospital for observation and treatment. An esophagram on December 29, 2005 revealed a short segment stricture of the mid-esophagus that was irregular and somewhat lobulated (possibly metastatic disease), as well as a fistula at the stricture site between the esophagus and the left mainstem bronchus. On January 5, 2006, an esophageal stent was placed across the stricture site. An esophagram on January 6, 2006 showed rapid passage of swallowed barium through the area of the stent and into the stomach. Additional information is pending.

The patient's past medical history is significant for possible exposure to Agent Orange while serving in Vietnam, arthritis, mild gastroesophageal reflux disease, migraines, hepatitis A in 1976, benign prostatic hypertrophy, hyperlipidemia, an irregular heart rhythm, possible phlebitis, a cervical fracture, depression, and anxiety. His past surgical history is significant for a left thoracotomy with left lower lobectomy for a large bleb approximately 12 years ago and three inguinal hernia repairs. Medications at the time of the event included Darvocet-N®, lorazepam, ciprofloxacin, Coumadin®, prochlorperazine, Zofran®, Lovenox®, Correctol®, and oxycodone.

There have been two other incidences of fistula reported to the NCI as serious adverse events under this IND. Both incidences were unlikely related to the investigational agent.

In this case, it is felt that a possible relationship between the esophageal fistula and OSI-774 treatment cannot be excluded. There have been 1621 patients enrolled in NCI-sponsored trials under this IND.

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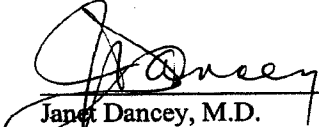
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	Esophageal Fistula
OSI-774	Possible
Paclitaxel	Possible
Carboplatin	Possible
Radiation	Probable
NSCLC	Probable
History of Multiple Thromboses at Multiple Sites	Unlikely

Date: 6/17/06

Signature: _____


Janet Dancey, 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