



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: September 30, 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_1650647

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: September 16, 2005
FROM: Janet Dancey, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: OSI-774 (erlotinib; Tarceva®)IND Safety Report, AE# 1650647
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.

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 64-year-old female with high-grade glioblastoma multiforme experienced grade 4 neutropenia, grade 4 thrombocytopenia, and grade 3 dyspnea while on a phase 2 trial using the investigational agent OSI-774 in combination with temozolomide and radiation therapy.

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ADVERSE EVENTS ASSESSMENT

IND 63383	ADVERSE EXPERIENCE REPORT NO.
NSC 718781	IND Safety Report:
OSI-774 (erlotinib; Tarceva™)	Event: Gr. 4: Neutrophils/granulocytes (ANC/AGC)
	Gr. 4: Platelets
	Gr. 3: Dyspnea (shortness of breath)
AE: 1650647	Protocol: N0177

The patient is a 64-year-old female with high-grade glioblastoma multiforme who experienced neutropenia, thrombocytopenia, and dyspnea while on a phase 2 trial using the investigational agent OSI-774 in combination with temozolomide (TMZ) and radiation therapy. She began her first course of treatment on June 22, 2005 and was to receive OSI-774 150 mg PO daily for 1 week; then OSI-774 150 mg PO daily along with TMZ 75 mg/m² PO daily, and radiation 6000 cGy total over 5 days each week, for 6 weeks; then OSI-774 150 mg daily for 4 weeks, then TMZ 200 mg/m² PO on days 1-5, every 28 days, with OSI-774 150 mg PO daily, for six cycles. The last doses of OSI-774 and radiation therapy were administered on August 10, 2005, and the last dose of TMZ was administered on August 3, 2005.

The patient was initially diagnosed with high-grade glioblastoma multiforme in June 2005 and underwent a debulking craniotomy on June 5, 2005. She started on OSI-774 trial on June 22, 2005 receiving her first dose of OSI-774. The first doses of radiation and TMZ started on June 29, 2005. She tolerated treatment well until July 27, 2005 when she became thrombocytopenic with a platelet count of 68,000/ μ L (reference range: 140,000-440,000/ μ L). Her TMZ dose was reduced by 25%. However, her platelet count continued to decrease and was 4,000/ μ L on August 3, 2005. She was transfused with platelets, and her TMZ treatment was discontinued. OSI-774 and radiation treatment were continued until completion on August 10, 2005. At that time, her platelet count was 3,000/ μ L and her absolute neutrophil count (ANC) had decreased to 100/ μ L from 1500/ μ L on August 3, 2005 (reference range: 1500-8000/ μ L). She was placed on Neupogen[®] at that time. Several days later, she was also placed on oral Levaquin[®] for a low grade fever. Despite treatment, her fever continued, which was frequently associated with shaking chills. On August 17, 2005, she started having increasing shortness of breath and presented to the clinic. She had a fever of 101°F, an ANC of 1600/ μ L, a platelet count of 17,000/ μ L, and an oxygen saturation of 85% on exercise. She was admitted to the hospital for evaluation and removed from the protocol that same day. A chest X-ray performed that day revealed diffuse infiltrates. A chest CT scan revealed dense infiltrates in the left and right upper lobes, no evidence of pulmonary emboli, pleural effusion, or metastatic disease. She underwent a bronchoscopy on August 23, 2005, with no abnormalities noted. Cultures were negative for *Pneumocystis*, fungi, and other infectious agents. In addition, blood and urine cultures were negative. It was felt that she had developed an acute interstitial lung disease, likely secondary to OSI-774 treatment. Of note, the patient did not have any history of lung disease. She was started on cortico steroids and improved dramatically. A chest X-ray performed on August 29, 2005 showed almost complete resolution of the infiltrates in the left upper lung and significant reduction of the infiltrates in the right upper lung. The patient was discharged home on August 31, 2005, with instructions to follow-up daily with the clinic to monitor her blood counts. She was discharged on albuterol and prednisone, and her aspirin was discontinued due to her thrombocytopenia. As of September 7, 2005, her platelet count was 25000/ μ L and her ANC was 3800/ μ L.

The patient's medical history is significant for uterine cancer in 1987 for which she had a hysterectomy, and bilateral salpingo-oophorectomy, neuromas, and hyperlipidemia. Her surgical history includes an appendectomy, tonsillectomy, and adenoidectomy. Medications at the time of the event included Decadron[®], doxycycline, Neupogen[®], Levaquin[®], aspirin, and fluconazole.

There have been 18 other incidences of neutrophils/granulocytes, 17 other incidences of platelets, and 58 other incidences of dyspnea reported to the NCI as serious adverse events under IND 63383 (OSI-774). These events are summarized in the table below:

Neutrophils/granulocytes (n=18)	18 unlikely
Platelets (n=17)	2 unrelated, 15 unlikely
Dyspnea (n=58)	23 unrelated, 34 unlikely, 1 possible

Although myelosuppression is a known adverse effect of temozolomide, delayed and worsening myelosuppression as experienced by this patient after discontinuing the drug is unusual. In this case, the OSI-774 was considered probably related to the neutrophils/granulocytes and platelets and possibly related to the dyspnea by inducing a possible pneumonitis. There have been 1364 patients enrolled in NCI-sponsored clinical trials under IND 63383 (OSI-774).

	Neutrophils	Platelets	Dyspnea
OSI-774	Probable	Probable	Possible
Temozolomide	Probable	Probable	Unrelated
High-grade Astrocytoma	Unrelated	Unrelated	Unrelated
Radiation	Unrelated	Possible	Possible
Decadron	Unrelated	Unrelated	Unrelated
Doxycycline	Unrelated	Unrelated	Unrelated
Infection	Unrelated	Unrelated	Possible
Drug-related pneumonitis	Unrelated	Unrelated	Possible

Date:

Sept 20/05

Signature:

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

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

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

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