

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_1471353

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: September 2, 2005
FROM: Janet Dancey, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: OSI-774 (erlotinib; Tarceva®)IND Safety Report, AE# 1471353
TO: Investigators Using OSI-774, IND 63,383

APM
Janet 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 63,383.

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 76-year-old female with non-small cell lung cancer experienced grade 4 renal failure 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®)

ADVERSE EXPERIENCE REPORT NO. 10
 IND Safety Report:
 Event: Gr. 4: Renal failure

AE: 1471353

Protocol: S0341

The patient is a 76-year-old female with non-small cell lung cancer (NSCLC) who experienced renal failure while on a phase 2 trial using the investigational agent OSI-774. She began her first course of treatment on June 28, 2005 receiving OSI-774 150 mg PO daily on days 1-21, every 21 days. She received her last dose on July 26, 2005 (Cycle 2, Day 8).

The patient was initially diagnosed with NSCLC in June 2005 and started on OSI-779 therapy on June 28, 2005. In mid-July, the patient complained of increasing dyspnea, lethargy, fatigue, and some left lower quadrant abdominal pain. A urinalysis was performed on June 22, 2005, which was suggestive of a mild urinary tract infection; however, her symptoms appeared more consistent with mild diverticulitis, for which she had a past history. She was treated with both Cipro® and Flagyl® for a presumed urinary tract infection/diverticulitis. On July 27, 2005, her Flagyl® was discontinued, she was given 500 mL of fluid for presumed dehydration, and a CBC was performed, which was essentially normal. Of note, a basic metabolic profile was not performed.

On July 28, 2005, the patient presented for her scheduled talc pleurodesis. However, pre-operative laboratory values were abnormal as shown in the table below:

	7/28/2005 (Course 2, Day 8)	7/31/2005 (Course 2, Day 11)	8/03/2005 (Course 2, Day 14)	8/11/2005 (Course 2, Day 22)
Creatinine (mg/dL) (reference range: 0.6-1.0 mg/dL)	6.3	8.9	4.4	1.8
BUN (mg/dL) (reference range: 7-20 mg/dL)	33	44	18	27
Albumin (g/dL) (reference range: 3.4-5.0 g/dL)	3.0	2.4	-	-

Her CBC was essentially normal. A urinalysis showed 10-20 red blood cells, 3+ protein, trace of leukocyte esterase, and nitrite negative. The patient was extremely fatigued and lethargic, as well as dyspneic. Of note, the patient admitted that she had a significant decrease in her urinary frequency over the past 1 to 2 weeks. She was admitted to the hospital for acute renal failure. The pleurodesis procedure was put on hold, and she was started on IV fluids. While a renal sonogram on July 29, 2005 showed no evidence of hydronephrosis, a complex cystic mass in the left mid-kidney was observed. A pelvic CT scan on July 30, 2005 revealed some mild hydronephrosis of the left kidney. Her creatinine and BUN levels continued to rise, peaking on July 31, 2005, and she was started on dialysis. The patient had a diuretic renal scan on August 1 2005, which showed bilateral changes consistent with possible acute tubular necrosis. She tolerated the dialysis well, and her creatinine level started improving slowly. On August 3, 2005, her dialysis catheter was removed. Her creatinine level continued to decrease without further dialysis, and as of August 11, 2005, it was 1.8 mg/dL. The patient was removed from the protocol.

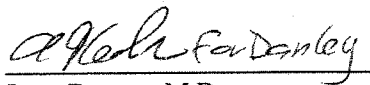
The patient's medical/surgical history is significant for hepatitis, angina, myocardial infraction, diabetes, alcoholism, mild hypertension, GERD, peptic ulcer disease, tonsillectomy, eye surgery, knee surgery, vagotomy for duodenal ulcer, appendectomy, cholecystectomy, rotator cuff repair, cataract surgery, and right breast biopsy (benign). Medications at the time of the event included Prilosec®, Cipro®, Flagyl®, and vitamins.

There have been five other incidences of renal failure (four considered unlikely related and one considered possibly related) reported to the NCI as serious adverse events under IND 63383 (OSI-774).

In this case, the renal failure cannot be explained by dehydration alone, and a possible relationship between the event and the antibiotics and/or the OSI-774 cannot be excluded. There have been 1348 patients enrolled in NCI-sponsored clinical trials under IND 63383 (OSI-774).

	Renal failure
OSI-774	Possible
Non-small cell lung cancer	Unlikely
Dehydration	Possible
Cipro[®]	Possible
Flagyl[®]	Possible

Date: 9/6/05

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
Safetygroup@osip.com
OSI Pharmaceuticals, Incorporated