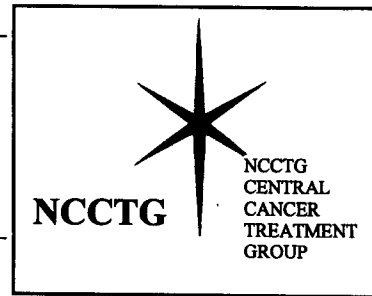

Operations Office

Telephone (507) 266-3853



Date: April 18, 2003

To: NCCTG Primary Clinical Research Associates

From: Linda S. Long

Re: N0177, Pilot and Phase II Trial of OSI-774 and Radiation in Glioblastoma Multiforme Patients

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_1496446

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 Linda S. Long at 507-266-3853.

lsl
enclosure



DATE: April 9, 2003

FROM: Janet Dancey, M.D., Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: OSI-774 IND Safety Report, AE# 1496446

TO: Investigators Using OSI-774, IND 63,383

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 (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 event is attached:

A 49-year-old male with metastatic carcinoma of the oropharynx experienced grade 3 creatinine after being treated with OSI-774 in combination with cisplatin. The patient's baseline creatinine level was 99 $\mu\text{mol/L}$. Prior to receiving cisplatin, his creatinine level was 325 $\mu\text{mol/L}$, and cisplatin was withheld. The patient was hospitalized and also complained of nausea and vomiting. He was treated with intravenous fluids. Despite treatment, his creatinine level did not improve for 2 days. It was subsequently noted that the patient had continued OSI-774 while he was hospitalized. The agent was discontinued, and he was continued on fluids. An abdominal ultrasound showed no evidence of hydronephrosis. At the time of his discharge, his creatinine level was 233 $\mu\text{mol/L}$. Subsequent laboratory results showed his creatinine level improved to 129 $\mu\text{mol/L}$. The patient has been removed from the study.

There have been four other cases of elevated creatinine reported to the NCI as serious adverse events under this IND, one with a possible attribution to the investigational agent and three with an unlikely attribution. There have been a total of 353 patients enrolled in NCI-sponsored clinical trials under this IND.

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ADVERSE EVENTS ASSESSMENT

IND 63383 NSC 718781 OSI-774	ADVERSE EXPERIENCE REPORT NO. 5 IND Safety Report: Event: Gr. 3: Creatinine
AE 1496446	Protocol: 5380

The patient is a 49-year-old male with metastatic carcinoma of the oropharynx who was admitted to the hospital with an elevated creatinine level while being treated with OSI-774. He is participating in a phase 1/2 study of OSI-774 in combination with cisplatin in patients with recurrent or metastatic squamous cell cancer of the head and neck. The patient started cycle 1 of therapy on March 10, 2003 taking OSI-774 100 mg orally every day. The patient's last dose of study drug was on March 19, 2003.

The patient was initially diagnosed in July 2002 and had a normal baseline creatinine of 78 $\mu\text{mol/L}$. At that time, he received radiation therapy and cisplatin chemotherapy, completing the therapy with cisplatin in August 2002. Of note, the patient's creatinine level on August 26, 2002 was 116 $\mu\text{mol/L}$. He developed lung metastases in early 2003 and initiated protocol treatment with OSI-774 on March 10, 2003. In this protocol, patients commence with one week of OSI-774 100 mg daily with cisplatin administered on the eighth day of OSI-774 administration. At the time of study entry, the patient's baseline creatinine level was normal at 99 $\mu\text{mol/L}$. The patient returned to the clinic on March 17, 2003 for administration of cisplatin, but was found to have a creatinine level of 325 $\mu\text{mol/L}$. The cisplatin dose was withheld, and the patient was admitted to the hospital for evaluation. At the time of admission, the patient was also experiencing nausea and vomiting (categorized as grade 1 by the investigator) without reported history of diarrhea. The patient was treated with intravenous fluids. His creatinine level did not improve for the first 2 days of the hospitalization despite hydration, suggesting that elevated creatinine was not due to dehydration from vomiting. It was subsequently noted that the patient was inadvertently taking the OSI-774 until March 19, 2003. An abdominal ultrasound performed on March 21, 2003 showed no evidence of hydronephrosis, but did show evidence of a medical cause for the elevated creatinine. After cessation of the study drug and continued hydration, the patient's creatinine level started to drop, and at the time of discharge on March 21, 2003, his creatinine level was 233 $\mu\text{mol/L}$. The latest values revealed a creatinine level of 190 $\mu\text{mol/L}$ on March 24, 2003 and a level of 129 $\mu\text{mol/L}$ on

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March 31, 2003. Also of note, the patient had a grade 2 skin rash, which improved after discontinuation of the study drug. It was decided that the patient would not be rechallenged with the agent, and he was removed from the protocol on March 24, 2003.

His past medical history is significant for a cerebrovascular accident in 2000, which resulted in short term memory loss. His medications at the time of the event included Codeine, Zopiclone, Dimenhydrinate, and intravenous Clodranate on March 11, 2003.

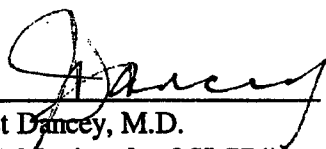
There have been four other incidences of elevated creatinine reported to the NCI as serious adverse events under this IND, one with a possible attribution to the study drug and three with an unlikely attribution. It is considered unlikely that the patient's underlying cancer contributed to this event; however, a possible attribution to the agent cannot be excluded. There have been 353 patients enrolled in NCI-sponsored clinical trials under this IND.

	Creatinine		
OSI-774	Possible		
Oral neoplasm	Unlikely		

Date:

April 10 / 03

Signature:


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

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

cc: Brian Watson
OSI Pharmaceuticals, Inc.