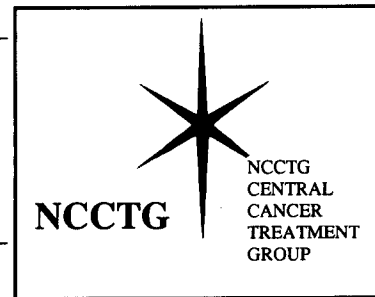

Operations Office

Telephone (507) 266-3853



Date: March 7, 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_1583811

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

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

DATE: February 19, 2003

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

SUBJECT: OSI-774 IND Safety Report, AE# 1583811

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 71-year-old male with metastatic mandibular squamous cell cancer died due to gram-negative sepsis pneumonia after being treated with OSI-774. The patient complained of dyspnea, weakness, chills, rapid heart rate, and palpitations. In the emergency room, the patient was noted to be tachycardic with an irregular rhythm and hypoxemic. He was treated with a Cardizem drip and intubated. The patient was transferred to the intensive care unit due to respiratory failure and septic shock. His white blood cell count was $0.4 \times 10^9/L$ with an absolute neutrophil count of $0.3 \times 10^9/L$; however, he was afebrile. His platelet count dropped to $28 \times 10^9/L$ although it was within normal range at admission. A chest X-ray was consistent with a post-obstructive pneumonia in the right lobe. Cultures from a bronchoscopy were positive for *Klebsiella pneumoniae*, *Candida albicans*, and alpha hemolytic *Streptococcus*. Blood cultures were also positive for *Klebsiella pneumoniae*. Despite aggressive measures, the patient's condition deteriorated, and he expired due to complications of gram-negative sepsis and pneumonia. No autopsy was performed.

There has been one other case of infection with neutropenia with an unlikely attribution to the investigational agent reported to the NCI as a serious adverse event under this IND. There have been a total of 243 patients enrolled in NCI-sponsored clinical trials under this IND.

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**NOTIFICATION TO INVESTIGATORS OF EXPEDITED
ADVERSE EVENTS REPORTED TO THE FDA**

The Food and Drug Administration (FDA) regulations [21 CFR 312.32(c)] require sponsors of clinical studies conducted under an IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. In compliance with these FDA regulations, CTEP will notify its investigators by the following methods:

- **IND Safety Report** - The investigators are sent a copy of the expedited adverse event sent to the FDA by CTEP. The investigators are requested to file a copy with their protocol file and to send a copy to their IRB according to the local IRB's policies and procedures. CTEP does not require a revision to the protocol and/or informed consent document.
- **IND AE Action Letter** - These letters are issued by CTEP for those serious adverse events, which warrant a change in the informed consent form and/or protocol. The investigators are sent a copy of the expedited adverse event sent to the FDA by CTEP with the requirement that the informed consent form and/or protocol be amended to include the new event. The investigators are provided a time frame for which to submit the amendment to the CTEP Protocol and Information Office. The letter will specify if accrual to the protocol is to be suspended until the revision is made and whether patients already on study require reconsenting.

Updates to the ASAEL do not require notification of the investigators. The ASAEL will be available on the CTSU web site, which requires a username and password.

Both the IND Safety Report and IND AE Action Letter will include the number of similar events reported for the agent as well as the number of patients treated to date under the CTEP IND for the agent. Using the following guidelines, the frequency of the event can be categorized: Common event - 20 to 100%, Occasional event - 5 to 20%; and Rare event - < 5%.

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ADVERSE EVENTS ASSESSMENT

IND 63383 NSC 718781 OSI-774	ADVERSE EXPERIENCE REPORT NO. 4 IND Safety Report: Event: Gr. 5: Infection with grade 3 or 4 neutropenia
AE 1583811	Protocol: 5393

The patient was a 71-year-old male with metastatic mandibular squamous cell cancer who died of sepsis while participating in a phase 1/2 study of OSI-774 in combination with docetaxel in squamous cell cancer of the head and neck (HNSCC). He began his first course of therapy on December 19, 2002 receiving OSI-774 100 mg orally every day, every 28 days. He also received docetaxel 35 mg/m² intravenously over 60 minutes on days 8, 15, and 22, every 28 days. Cycle 2 commenced on January 16, 2003. The patient received a total of 16 days of OSI-774 and 2 doses of docetaxel during this course of therapy.

The patient was originally diagnosed with mandibular squamous cell cancer in 1999 and subsequently underwent surgery and radiation. At the time of study entry, the patient had known lung metastases in the apices and pleural thickening on the left side. He also had a recurrence of tumor in the right mandibular region with bleeding noted from the lesion. On February 1, 2003, the patient sought medical attention for symptoms of dyspnea, weakness, chills, rapid heart rate, and palpitations. Of note, the patient had chronic atrial fibrillation for which he was taking Sotalol, Cardizem, and Digoxin. In the emergency room, the patient was noted to be tachycardic with an irregular rhythm and was treated with a Cardizem intravenous infusion. He was also found to be hypoxemic and was intubated. He was then transferred to the intensive care unit because of respiratory failure and septic shock. His admission laboratory results revealed a white blood cell count of $0.4 \times 10^9/L$ and an absolute neutrophil count of $0.3 \times 10^9/L$. The chest X-ray was consistent with a post-obstructive pneumonia in the right lobe. An emergent bronchoscopy was performed and cultures from this were positive for *Klebsiella pneumoniae*, *Candida albicans*, and alpha hemolytic *Streptococcus*. Blood cultures were also positive for *Klebsiella pneumoniae*. Despite aggressive measures, the patient's condition continued to deteriorate, and he died due to complications of gram-negative sepsis and pneumonia on February 2, 2003. No autopsy was performed.

His past medical history is significant for chronic atrial fibrillation, benign prostatic hypertrophy, and a history of pneumonia. His medications at the time of event included Sotalol, Cardizem, Digoxin, and Ambien, and Decadron with the chemotherapy.

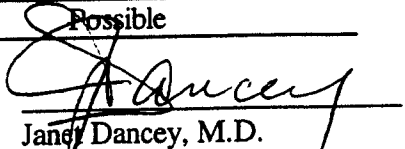
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There has been one other incidence of infection with grade 3 or 4 neutropenia with an unlikely attribution reported to the NCI as a serious adverse event under this IND. The patient's death was due to gram-negative sepsis and pneumonia, in the setting of docetaxel-induced neutropenia; however, the contribution of OSI-774 cannot be excluded. The radiology reports are consistent with obstructive pneumonia in the right lung rather than a drug-induced pneumonitis. There have been 243 patients enrolled in NCI-sponsored clinical trials under this IND.

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	Grade 5 Infection with grade 3 or 4 neutropenia
Docetaxel	Probable
OSI-774	Possible
HNSCC	Possible

Date: Feb 20/03

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
OSI Pharmaceuticals, Inc.