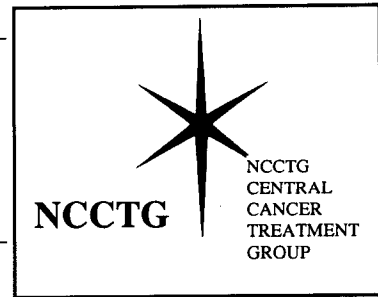


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**Operations Office**

Telephone (507) 266-3853

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**Date:** January 31, 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\_1898327

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



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health  
National Cancer Institute

**DATE:** January 27, 2003  
**FROM:** Janet Dancey, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
**SUBJECT:** OSI-774 IND Safety Report, AE# 1898327  
**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 68-year-old female with gastric cancer metastatic to the liver experienced a grade 5 CNS cerebrovascular ischemia after being treated with OSI-774. The patient received 2 days of the study drug and woke up somewhat confused and unable to move the right side of her body. There was associated pain/discomfort. Her symptoms were consistent with a stroke. Her condition deteriorated, and she was placed in hospice care. The patient subsequently expired, and no autopsy was performed.

There have been no other cases of CNS cerebrovascular ischemia reported to the NCI as a serious adverse event under this IND. There have been a total of 178 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. † IND Safety Report: Event: Gr. 5: CNS cerebrovascular ischemia
AE 1898327	Protocol: S0127

The patient is a 68-year-old female with gastric cancer who apparently suffered a stroke while on a phase 2 trial using the investigational agent OSI-774 in unresectable or metastatic adenocarcinoma of the stomach and gastroesophageal junction. She began her first course of treatment on December 13, 2002 taking OSI-774 150 mg orally (PO) every day, with a cycle being 28 days.

During the patient's initial consultation on December 6, 2002, the patient's physical examination was unremarkable. The cardiovascular examination was within normal limits. The neurologic examination was symmetric. The patient's performance status was 100%. The endoscopy that was performed confirmed the malignant gastric mass, demonstrating an invasive adenocarcinoma. The pre-study computerized tomography (CT) scan of the abdomen and pelvis demonstrated multiple hepatic metastases. The baseline complete blood count with differential revealed a white blood cell count of  $14.9 \times 10^3/\mu\text{l}$  (upper limit of normal is  $10.0 \times 10^3/\mu\text{l}$ ), with values for hemoglobin and platelets falling within the normal range. The renal function studies and liver function studies were all within normal limits. The prothrombin time (PT) was slightly elevated at 15.6 seconds (upper limit of normal is 13.9 seconds).

The patient had only received 2 days of the study drug when she awoke on the morning of December 15, 2002, somewhat confused, and unable to move the right side of her body. There was associated pain/discomfort with this event. The clinical syndrome was consistent with a cerebral vascular event but no investigations were conducted. The patient's status continued to decline following this event, and she was placed in hospice care. The patient died on December 20, 2002. No autopsy was performed.

The patient's past medical history is significant for the underlying gastric cancer metastatic to the liver. Prior to enrollment on study there was no history or clinical evidence of brain metastases. The patient had no history nor known risk factors for cardiovascular or cerebral vascular disease other than age and malignancy. She had no prior surgical history. The patient's medications at the time of the event was Oxycontin.

There have been no other incidences of CNS cerebrovascular ischemia reported to the NCI as a serious adverse event under this IND. It should be noted that the absence of investigations in to the patient's

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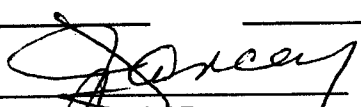
hemiparesis renders a diagnosis and attribution for this event difficult. It is possible that the patient hemorrhaged into an unsuspected brain metastasis. It is also possible that the patient experienced a cerebral vascular accident due to thrombosis/embolism as she is at risk of cerebral vascular disease (CVD) due to her age; however, she had no document history of CVD or risk factors. In addition, there is a known risk of both venous and arterial thrombosis and embolism with malignancy; however, a possible causal relationship between the investigational agent cannot be excluded. There have been 178 patients enrolled in NCI-sponsored clinical trials under this IND.

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	<b>CNS</b>		
	<b>cerebrovascular</b>		
	<b>ischemia</b>		
<u>OSI-774</u>	<u>Possible</u>	<u>                    </u>	<u>                    </u>
<u>Gastric cancer</u>	<u>Possible</u>	<u>                    </u>	<u>                    </u>

Date: Jan 24/03

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.

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