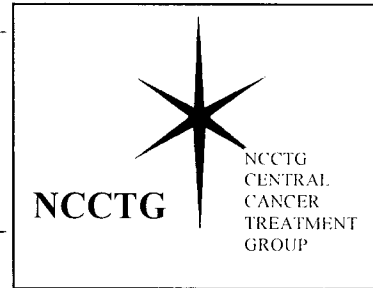


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**Operations Office**

Telephone (507) 266-3549

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**Date:** May 7, 2004

**To:** NCCTG Primary Clinical Research Associates

**From:** Lori Kelly

**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\_1087236\_F1

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 Kelly at 507-266-3549.

lk  
enclosure



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health  
National Cancer Institute

**DATE:** April 16, 2004  
**FROM:** Janet Dancey, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
**SUBJECT:** OSI-774 IND Safety Report, **Follow-Up #1, AE# 1087236**  
**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 53-year-old female with ovarian cancer experienced a grade 4 allergic reaction/hypersensitivity after being treated with OSI-774 in combination with carboplatin. Approximately 2 years prior to OSI-774 therapy, the patient was diagnosed with ovarian cancer and underwent surgical resection. She then received 5 cycles of carboplatin/paclitaxel. She did well for 1.5 years, but then presented with recurrent disease, and was treated with topotecan until a month prior to OSI-774 therapy. Approximately 23-24 hours after the carboplatin infusion and approximately 24-25 hours after taking OSI-774, the patient presented to the Emergency Room with swelling of the lips and tongue, dysphagia, laryngospasm, and moderate angioedema. Her vital signs upon arrival included a pulse of 120/minute, blood pressure of 159/92 mm Hg and a pulse oximetry reading of 83% on room air. Her physical examination did not reveal any rashes or urticaria; however, there was wheezing noted throughout the lung fields. The patient was treated with epinephrine, diphenhydramine HCl, albuterol, budesonide inhalation powder, ranitidine HCl, and hydrocortisone sodium succinate. The patient recovered within a few hours and was discharged to home with diphenhydramine HCl. Per the site, the patient returned to the clinic 6 days later and underwent carboplatin skin testing, which was negative. She was then re-challenged with the OSI-774 and tolerated it well.

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**Follow-up information was received 1 month later, which stated the patient had subsequently been re-challenged with both agents and is tolerating them well.**

There have been three other incidences of allergic reaction/hypersensitivity reported to the NCI as serious adverse events under this IND, all occurring on this trial. None of the incidences were attributed to the OSI-774; all were felt to be probably/definitely related to the carboplatin. There have been 753 patients enrolled in NCI-sponsored clinical trials under this IND.

**This report has been amended to reflect additional information.**

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## ADVERSE EVENTS ASSESSMENT

IND 63383 NSC 718781 OSI-774	ADVERSE EXPERIENCE REPORT NO. 6 IND Safety Report: Follow-Up #1 Event: Gr. 4: Allergic reaction/hypersensitivity
AE: 1087236	Protocol: NCIC-149

The patient is a 53-year-old female with ovarian cancer who suffered an allergic reaction while on a phase 2 trial using the investigational agent OSI-774. She began her first course of treatment on February 17, 2004 receiving OSI-774 150 mg orally daily and carboplatin AUC=5 intravenously over 30 minutes on day 1, every 21 days. She only received treatment on Day 1 (February 17, 2004).

The patient was initially diagnosed with ovarian cancer in April 2002 and underwent surgical resection. She then received 5 cycles of carboplatin/paclitaxel therapy beginning in May 2002; a sixth cycle was not given due to persistent cytopenias. She did well until September 2003, when she presented with recurrent disease, and was treated with topotecan HCL until January 2, 2004. She received her first doses of carboplatin and OSI-774 on February 17, 2004. Approximately 23-24 hours after the carboplatin infusion and approximately 24-25 hours after taking OSI-774, the patient presented to the Emergency Room with swelling of the lips and tongue, dysphagia, laryngospasm, and moderate angioedema. Upon arrival, her vital signs included a pulse of 120/minute, blood pressure of 159/92 mm Hg and a pulse oximetry reading of 83% on room air. Her physical examination did not reveal any rashes or urticaria; however, there was wheezing noted throughout the lung fields. A chest X-ray demonstrated a previously known right pleural effusion. The patient was treated with epinephrine, diphenhydramine HCl, albuterol, budesonide inhalation powder, ranitidine HCl, and hydrocortisone sodium succinate. The patient recovered within a few hours and was discharged to home with diphenhydramine HCl. The patient was not taking any new medications prior to this incident. The patient denied any food allergies; however, a friend brought a food dish of which the patient was unsure of the contents. Per the site, the patient returned to the clinic on February 24, 2004 and underwent carboplatin skin testing, which was negative. She was then re-challenged with the OSI-774 and tolerated it well.

**Follow-up information was received on March 24, 2004. Following re-challenge, the event has not recurred, and therapy with the protocol agents is ongoing.**

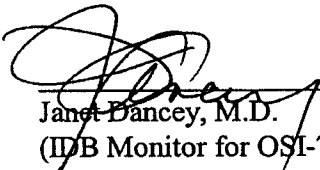
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The patient's past medical history is significant for pernicious anemia. Medications at the time of the event included monthly vitamin B12 injections, lorazepam, ranitidine bismuth citrate, sennasides, and docusate sodium. Her anti-emetic regimen, post-chemotherapy, included dexamethasone, prochlorperazine, and dolasetron.

There have been three other incidences of allergic reaction/hypersensitivity reported to the NCI as serious adverse events under this IND, all occurring on this trial. None of the incidences were attributed to the OSI-774; all were felt to be probably/definitely related to the carboplatin. **In this particular case, the Senior Investigator at the NCI initially felt that the carboplatin and OSI-774 probably/possibly caused the allergic reaction. However, upon re-challenge with both agents, the allergic reaction has not occurred. It is now felt that the reaction is possibly related to the food or the dolasetron and is unlikely related to the protocol agents.** There have been 753 patients enrolled in NCI-sponsored clinical trials under this IND.

	<u>Allergic reaction/hypersensitivity</u>
<u>Carboplatin</u>	<u>Unlikely</u>
<u>OSI-774</u>	<u>Unlikely</u>
<u>Dolasetron</u>	<u>Possible</u>
<u>Food allergy</u>	<u>Possible</u>

Date: 4/16/04

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

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

**This report has been amended to reflect additional information and include changes in the assessment. The probable attribution to carboplatin and the possible attribution to OSI-774 have both been changed to unlikely, while dolasetron and a food allergy have been added to the attributions. The new information is bolded. If this report is changed further, we will notify your office.**

cc: Christine Boisclair  
OSI Pharmaceuticals, Inc.

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