

# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** January 28, 2005  
**To:** NCCTG Primary Clinical Research Associates  
**From:** Lori Kelly  
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\_1834844\_1063758\_1038780\_1972775\_1249502

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.

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enclosure



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health  
National Cancer Institute

**DATE:** January 7, 2005

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

**SUBJECT:** OSI-774 IND Safety Report, AE# 1834844, 1063758, 1038780, 1972775, 1249502

**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 events is attached:

A 68-year-old male with non-small cell lung cancer (NSCLC) experienced grade 3 gastric ulcer and grade 3 melena/GI bleeding while on a phase 2 study of the investigational agent OSI-774 in combination with high dose celecoxib 400 mg bid (AE #1834844). Of note, the patient was on therapeutic doses of Coumadin (warfarin) for a known pulmonary embolus at the time of the events.

A 73-year-old male with NSCLC experienced grade 3 melena/GI bleeding while on the same phase 2 study of OSI-774 in combination with celecoxib (AE #1063758). Of note, the patient was on warfarin for a history of atrial fibrillation at the time of the event.

A 69-year-old male with NSCLC experienced grade 3 melena/GI bleeding while on the phase 2 study of OSI-774 in combination with celecoxib (AE #1038780).

A 62-year-old male with NSCLC experienced grade 3 gastric ulcer and grade 3 melena/GI bleeding while on the phase 2 study of OSI-774 in combination with celecoxib (AE #1972775). Of note, the patient was receiving Fragmin for a blood clot in his neck at the time of the events.

A 69-year-old female with NSCLC experienced grade 3 gastric ulcer and grade 3 melena/GI bleeding

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while on the phase 2 study of OSI-774 in combination with celecoxib (AE #1249502). Of note, the patient had a past medical history significant for a stomach ulcer 6 years earlier.

In reviewing these cases, three (3) patients had upper GI ulcers documented and an additional two (2) patients had GI bleeding without documented ulcers. It is felt that the combination of the EGFR inhibitor OSI-774 and the COX-2 inhibitor celecoxib given at a high dose of 400 mg bid may increase the risk of GI ulcers. At this time, there is no indication of an increased frequency of ulcers/bleeding in patients receiving OSI-774 and recommended doses of non-steroidal anti-inflammatory drugs used to treat pain. Moreover, OSI-774 is an inhibitor of CYP3A4 and, therefore, may interfere with warfarin metabolism leading to elevated levels of warfarin, which subsequently led to increases in INR with associated increase risk of bleed in the cases described above. Thus, there is the potential for a drug interaction in those patients who were receiving concomitant warfarin.

There have been a total of eight (8) incidences of ulcer (gastric and duodenal) reported to the NCI as serious adverse events under this IND, of which three cases (AE #1834844, 1249502, and 1972775) occurred on protocol 5416 and are described above. There have been a total of 18 incidences of melena/gastrointestinal bleeding/hematemesis reported to the NCI as serious adverse events under this IND, of which five cases (AE #1834844, 1063758, 1038780, 1972775, 1249502) occurred on protocol 5416 and are described above.

<b>Ulcer (gastric, duodenal) (n=8)</b>	2 possible, 6 unlikely/unrelated
<b>Melena/GI bleeding/Hematemesis (n=22)</b>	5 possible, 17 unlikely/unrelated

There have been 1163 patients enrolled in NCI-sponsored clinical trials under this IND, 26 of whom are enrolled on protocol 5416.

## ADVERSE EVENTS ASSESSMENT

IND 63383 NSC 718781 OSI-774	ADVERSE EXPERIENCE REPORT NO. 8 IND Safety Report: Event: Gr. 3: Gastric Ulcer Gr. 3: Melena/GI bleeding
AE: 1834844, 1063758, 1038780, 1972775, 1249502	Protocol: 5416

This report summarizes the experiences of five (5) patients who participated in protocol 5416, the phase 2 study of OSI-774 in combination with celecoxib as second-line therapy for advanced non-small cell lung cancer. All patients were treated with OSI-774 150 mg orally every day and celecoxib 400 mg orally twice daily, with a cycle equal to 28 days. All patients developed gastrointestinal bleeding, and 3 patients had ulcers noted on esophageal gastroduodenoscopy (EGD). Accrual to the study has been suspended as of December 3, 2004 and closed to accrual December 23, 2004.

**AE #1834844:** The first patient is a 68-year-old male who presented to the hospital on November 21, 2004 (cycle 2, day 25) with nausea, brown-colored emesis, diarrhea, and severe dehydration. Laboratory results at the time of admission revealed nonoliguric acute renal failure, with a creatinine level of 4.7 mg/dL, a BUN level of 109 mg/dL, and a potassium level of 6.5 mmol/L. Other significant laboratory values included a total white blood cell count of 16,000/mm<sup>3</sup>, with a minimal left shift; an INR of 16; and hemoglobin of 7.6 mg/dL, with a normal platelet count. Of note, the patient was on therapeutic doses of Coumadin (warfarin) for a known pulmonary embolus. The patient was treated aggressively in the ICU with antibiotics, vasopressors and packed red blood cell transfusions. An EGD on November 23, 2004 revealed multiple benign ulcers. On November 26, 2004, the patient was found to have bilateral DVTs on Doppler exam, and an inferior vena cava filter was placed that day. Further information has been requested regarding the outcome of this event. His past medical history is significant for hypertension and hypercholesterolemia. Medications at the time of event included warfarin, Norvasc, Lipitor, Atarax, Vicodin as needed, and Lotensin.

**AE #1063758:** The second patient is a 73-year-old male who presented to the clinic on March 12, 2004 (cycle 1, day 18) with anemia, dehydration, and complaints of numbness and tingling, with no decrease in sensation; his neurological exam was unremarkable. He was admitted for a work-up of the vague neurologic symptoms. A CT scan of the head was negative. His PT value was greater than 100 seconds, and he was given fresh frozen plasma (FFP). Of note, the patient was on warfarin for a

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history of atrial fibrillation. He also began to experience melena, which was thought likely secondary to a gastro-intestinal lesion bleeding in the presence of an elevated INR. The patient refused to have an EGD and colonoscopy. His celecoxib and warfarin were discontinued, along with the OSI-774. He was stable for discharge on March 15, 2004. His past medical history is significant for diabetes, hypertension, atrial fibrillation, and peripheral vascular disease. Medications at the time of the event included warfarin, Micronase, hydrochlorothiazide, Tenormin, and Zoloft.

**AE #1972775:** The third patient is a 62-year old male who presented to the hospital on May 4, 2004 (cycle 1, day 22) with a 3-day history of vomiting and melanic stools. In the emergency room, the patient had episodes of emesis of coffee ground material, with bright red blood. Of note, this patient was receiving Fragmin for a blood clot in his neck. Significant laboratory results on admission included a hemoglobin level of 6.6 mg/dL, a normal INR, a platelet count of 142,000/mm<sup>3</sup>, and a normal white blood cell count. The patient was transfused with packed red blood cells. An EGD performed on May 5, 2004 revealed ulcers, with bleeding at the junction of the duodenal bulb and the second portion of the stomach; this area was cauterized. A repeat EGD was performed on May 10, 2004, which revealed a healing duodenal ulcer, with no evidence of active bleeding. His past medical history is significant for hypertension and the previously mentioned thrombus in the neck. Medications at the time of the event included Fragmin and Toprol.

**AE #1249502:** The fourth patient is a 69-year old female who presented to the hospital on May 4, 2004 (cycle 5, day 2), with a 5-day history of black liquid stools. Her hemoglobin on admission was 10.5 mg/dl, but the patient refused a transfusion; she was given iron supplementation instead. Her platelet count and white blood cell count were normal. She underwent an EGD on May 5, 2004, which revealed a large ulcer in the pylorus, which was cauterized. The remainder of the hospitalization was uneventful, and the patient was discharged on May 7, 2004. Her past medical history is significant for a stomach ulcer 6 years earlier and hypertension. Medications at the time of the event included Lotensin.

**AE #1038780:** The fifth patient with gastro-intestinal bleeding is a 69-year old male who received two cycles of therapy and went off protocol on June 16, 2004 for progressive disease. He was admitted to the hospital on July 5, 2004 with a 3-day history of bright red blood per rectum

associated with diarrhea. On admission, he was febrile to 101.4° F, with a normal white blood cell count. Other significant laboratory values included a hemoglobin level of 9.9 mg/dL, a normal platelet count, and a normal coagulation profile. The patient was treated with blood product transfusions and underwent a flexible sigmoidoscopy, which demonstrated an anal fissure, internal hemorrhoids, and sigmoid diverticulosis. The patient was treated empirically with antibiotics for *C. difficile* colitis; a source for the fever was never identified. The patient's fever subsided, and he was discharged to a nursing home in stable condition on July 9, 2004. His past medical history is significant for hypertension. Medications at the time of the event included Norvasc, Diovan, aspirin, and multivitamins.

In reviewing these cases, it is felt that the combination of the EGFR inhibitor OSI-774 and the COX-2 inhibitor celecoxib at the dose of 400 mg po bid may increase the risk of GI ulcers. Moreover, OSI-774 is an inhibitor of CYP3A4 and, therefore, may interfere in warfarin metabolism leading to elevated levels of warfarin, which subsequently led to increases in INRs and bleeding in the cases described above. Thus, there is the potential for a drug interaction in those patients who were receiving concomitant warfarin.

There have been a total of eight (8) incidences of ulcer (gastric and duodenal) reported to the NCI as serious adverse events under this IND, of which three cases (AE #1834844, 1249502, and 1972775) occurred on protocol 5416 and are described above. There have been a total of 18 incidences of melena/gastrointestinal bleeding/hematemesis reported to the NCI as serious adverse events under this IND, of which five cases (AE #1834844, 1063758, 1038780, 1972775, 1249502) occurred on protocol 5416 and are described above.

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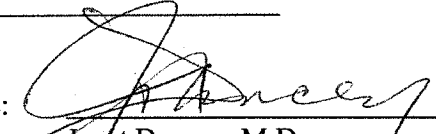
There have been 1163 patients enrolled in NCI-sponsored clinical trials under this IND, 26 of whom are enrolled on protocol 5416.

	<b>Gastric ulcer</b>	<b>Melena/GI bleeding</b>
<b>OSI-774</b>	Possible	Possible
<b>Celecoxib</b>	Possible	Possible
<b>Non small cell lung cancer</b>		

Date:

Jan 7/05

Signature:

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

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

cc: Christine Boisclair  
OSI Pharmaceuticals, Inc.

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