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**FROM:** L. Austin Doyle, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
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**SUBJECT:** MK-2206 and OSI-774 (erlotinib) NCI IND Safety Report, AE# 1964323

**TO:** Investigators Using MK-2206 (NSC 749607) and OSI-774 (NSC 718781)

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 agents MK-2206 and OSI-774.

The following must be completed by all investigators using MK-2206 under NCI IND 109493 and OSI-774 under NCI IND 63383:

- Send a copy of this letter to your Institutional Review Board (IRB) of record according to your policies and procedures.
- File a copy of this letter in your protocol file.

If your study is not covered under IND 109493 and 63383, it is strongly recommended that you follow the instructions above.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

Based on CTEP's assessment of the current information in light of previous experience with MK-2206 and OSI-774, there does not appear to be a change in the risk-benefit ratio for MK-2206 and OSI-774; therefore, CTEP is not requiring a protocol amendment at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The attached Adverse Events Assessment describes the adverse event(s) (synopsis provided below), relevant previous experience under these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 50-year-old female with non-small cell lung cancer experienced a grade 3 urinary tract infection while on a phase 2 trial utilizing the investigational agents MK-2206 and OSI-774.

## ADVERSE EVENTS ASSESSMENT

IND <b>109493</b> <b>63383</b> NSC <b>749607</b> <b>718781</b> MK-2206 <b>OSI-774</b> <b>(erlotinib,</b> <b>Tarceva®)</b>	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 <b>Gr. 3: Urinary tract infection</b>
AE: <b>1964323</b>	Protocol: <b>8698</b>

The patient is a 50-year-old female with metastatic non-small cell lung cancer who experienced a urinary tract infection while on a phase 2 trial utilizing the investigational agents MK-2206 and OSI-774. The planned protocol therapy the patient was assigned to is as follows:

Cycle = 28 days:  
 MK-2206: 45 mg PO QOD  
 OSI-774 (Erlotinib): 150 mg PO QD

The patient was diagnosed with non-small cell lung cancer in February 2010, metastatic to the brain liver, lymph and bone, and is status post radiation therapy and single-agent systemic chemotherapy. She began the first course of the investigational therapy on April 8, 2011 and received the last doses of MK-2206 and OSI-774 on May 14, 2011 (Cycle 2, Day 9).

On May 7, 2011 (Cycle 2, Day 2), the patient presented to the emergency room with aphasia and a fever of 103°F that improved after Tylenol® was administered. A CT scan of the head (without prior scans for comparison) showed a 6-mm hyperdensity in the frontal lobe possibly calcification or artifactual and no evidence of an acute intracranial abnormality. A chest X-ray revealed a left lower lobe infiltrate consistent with pneumonia. She had no symptoms of increasing cough, sputum production, or hemoptysis. Her urinalysis showed slightly hazy urine with 500 leukocytes (reference range: negative), 15 protein (reference range: negative), 25 blood (reference range: negative), 15-30 white blood cells, and a few bacteria. The urine culture showed >100,000 CFU/mL heavy mixed bacterial flora and scant to light *E. coli*. Her white blood cell (WBC) count was 11.6 K/mm<sup>3</sup> (reference range: 5-10 K/mm<sup>3</sup>), and she was started on IV Levaquin®, hydrated and monitored overnight. She was discharged on May 8, 2011, and laboratory findings at the time of discharge showed improvement in her WBC count back to within normal range. On May 14, 2011, the treating physician decided to hold the investigational agents for one week.

The patient's past medical/surgical history is significant for hypertension. Medications taken at the time of the event included an OTC allergy tablet, benzonatate, Cleocin T®, Fragmin®, minocycline and Pepcid®.

There have been no other cases of urinary tract infection reported to the NCI through AdEERS as serious adverse events for MK-2206 and 9 other cases of urinary tract infection reported to the NCI through AdEERS as serious adverse events for OSI-774, as summarized in the table below:

Adverse Event	Grade	Attribution
<b>OSI-774</b>		
Urinary tract infection (n=9)	5	1 Unrelated
	3	1 Unrelated, 5 Unlikely, 1 Probable
	2	1 Possible

To date, a total of 70 patients have been enrolled in NCI-sponsored clinical trials under the MK-2206 IND and/or NSC, and 3,537 patients have been enrolled in NCI-sponsored clinical trials under the OSI-774 IND and/or NSC.

In this case, it is felt that a possible causal relationship exists between the event and the investigational therapies MK-2206 and OSI-774.

	<u>Urinary tract infection</u>
<u>MK-2206</u>	<u>Possible</u>
<u>OSI-774</u>	<u>Possible</u>
<u>Non-small cell lung cancer</u>	<u>Unlikely</u>

Date: 7/26/11

Signature:

L. Austin Doyle M.D.  
L. Austin Doyle, M.D.  
(IDB Monitor for MK-2206)

Date: 7/26/11

Signature:

Helen Chen  
Helen Chen, M.D.  
(IDB Monitor for OSI-774)

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

cc: Bozena A. Zietara  
Merck Sharp & Dohme Corp.

cc: Scott Giangrosso  
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