



DATE: 6/27/11

FROM: *L. Austin Doyle*
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SUBJECT: AZD6244 Hydrogen sulfate and OSI-774 (erlotinib) NCI IND Safety Report, AE #
1276865

TO: Investigators Using AZD6244 Hydrogen sulfate (NSC 748727) 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 AZD6244 Hydrogen sulfate and OSI-774.

The following must be completed by all investigators using AZD6244 Hydrogen sulfate under NCI IND 77782 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 INDs 77782 and/or 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 AZD6244 Hydrogen sulfate and OSI-774, there does not appear to be a change in the risk-benefit ratio for AZD6244 Hydrogen sulfate and OSI-774 studies; 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 this IND and/or NSC, and the total number of patients enrolled in trials under this IND and/or NSC.

A 72-year-old male with metastatic non-small cell lung cancer experienced grade 3 hypoxia and grade 3 pneumonitis while on a phase 2 trial utilizing the investigational agents AZD6244 Hydrogen sulfate and OSI-774.

ADVERSE EVENTS ASSESSMENT

IND 77782 63383 NSC 748727 718781 AZD6244 (Hydrogen sulfate) AE: 1276865	63383 718781 OSI-774 (erlotinib, Tarceva®)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Gr. 3: Hypoxia Gr. 3: Pneumonitis Protocol: 8444
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The patient is a 72-year-old male with metastatic non-small cell lung cancer who experienced hypoxia and pneumonitis while on a phase 2 trial utilizing the investigational agents AZD6244 Hydrogen sulfate and OSI-774. The planned protocol therapy the patient was assigned to is as follows:

Cycle = 28 days:
 AZD6244 Hydrogen sulfate: 150 mg PO QAM
 Erlotinib: 100 mg PO QPM

The patient was diagnosed with non-small cell lung cancer in December 2010, and is status post radiation therapy and multiple-agent systemic chemotherapy from January to March 2011. He began the first course of the investigational therapy on May 25, 2011 and received the last dose of AZD6244 Hydrogen sulfate on June 7, 2011 (Cycle 1, Day 14), and the last dose of OSI-774 on June 6, 2011 (Cycle 1, Day 13).

On June 7, 2011 (Cycle 1, Day 14), the patient presented to the clinic for an unscheduled visit, and reported diarrhea of 2-3 bowel movements per day with an episode of fecal incontinence, increasing fatigue, chills without fever, dysgeusia, head and facial rash, and weight loss of 3 kg in 2 weeks. He had a pulse rate of 113 bpm, blood pressure of 119/74 mmHg, respiratory rate (RR) of 18 breaths per minute, and an oxygen saturation of 93% on room air. The patient also had dry mucous membranes and decreased breath sounds bilaterally. The patient was admitted to the hospital for IV fluids, and the study drugs were held. A chest X-ray showed diffuse interstitial lung infiltrates with ground glass opacities and scattered ill-defined densities in the right lung. The next day, the patient developed a fever of 38.5 °C and had a grossly heme-positive stool. His RR was 20 breaths per minute, oxygen saturation was 96% on 2 liters of oxygen, and his hemoglobin was 9.7 g/dL (reference range: 13.7-17.5 g/dL).

On June 9, 2011, the patient underwent sigmoidoscopy with biopsy which revealed no obvious source of GI bleed. He received 2 units of packed red blood cells. On June 10, 2011, the patient's oxygen saturation decreased to 90-91% on 4 liters of oxygen and his maximum temperature was 39.2 °C. However, his hemoglobin improved to 11.3 g/dL, and his blood cultures from June 8, 2011 had no growth. A CT scan of the chest was consistent with worsening right lung infiltrates and volume loss which were concerning for infection, drug induced pneumonitis, radiation, or lymphangitic spread of malignancy. Infectious disease service considered the possibilities of *Pseudomonas* pneumonia, *Legionella*, and other causes of community acquired pneumonia. The patient was started on Zosyn® and Zithromax®. Later that day, he underwent a bronchoscopy with bronchoalveolar lavage (BAL) of the right middle lung lobe which was well tolerated.

On June 13, 2011, the patient had another hypoxic episode with a RR of 14 breaths per minute and an oxygen saturation of 84% on 5 liters of oxygen. He had a pH of 7.54 (reference range: 7.35-7.45), PO₂ of 40 mmHg (reference range: 80-100 mmHg), and PCO₂ of 35 mmHg (reference range: 25-45 mmHg). A chest X-ray showed stable right lung infiltrate. The patient was given ipratropium and nebulized albuterol which improved his oxygen saturation to 95%. He was also given Lasix® and started on IV steroid. The patient's hemoglobin decreased to 9.6 g/dL, and he was transfused with additional two units of PRBCs. His BAL was positive for *Pneumocystis jiroveci*, and he was started on Bactrim®. Zosyn® was switched to IV meropenem. By June 16, 2011, the patient's oxygen saturation improved to 96% on 2 liters of

oxygen, and he was discharged home the following day with plans for follow up. Follow up information on the patient is pending at this time.

The patient's past medical/surgical history is significant for hypertension, hyperlipidemia, type 2 diabetes, chronic obstructive airway disease (COPD), benign prostatic hypertrophy, hemoptysis, abdominal aortic aneurysm, pilonidal cystectomy, and tonsillectomy. Medications taken at the time of the event included lisinopril, Crestor®, Spiriva®, glimepiride, aspirin, nifedipine, ipratropium, ursodiol, Uroxatral®, pantoprazole, nystatin topical powder, oxycodone, metoprolol, benzonatate, guaifenesin, and isosorbide.

There have been no other cases of pneumonitis and one other case of hypoxia (grade 3, possibly related) reported to the NCI through AdEERS as serious adverse events for AZD6244 Hydrogen sulfate; 7 other cases of pneumonitis and 2 other cases of hypoxia reported as serious adverse events for AZD6244; and 46 other cases of hypoxia reported to the NCI through AdEERS as serious adverse events for OSI-774 as summarized in the table below:

Adverse Event	Grade	Attribution
AZD6244		
Pneumonitis (n=7)	5	2 Unlikely, 1 Possible
	3	1 Unlikely, 2 Possible
	2	1 Unlikely
Hypoxia (n=2)	4	1 Unrelated
	3	1 Possible
OSI-774		
Hypoxia (n=46)	5	1 Unrelated, 1 Probable
	4	1 Unrelated, 3 Unlikely, 1 Possible
	3	18 Unrelated, 16 Unlikely, 2 Possible
	2	1 Unlikely, 2 Probable

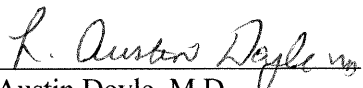
Pneumonitis is an expected event for OSI-774.

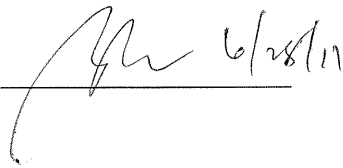
To date, a total of 435 patients have been enrolled in NCI-sponsored clinical trials under the AZD6244 Hydrogen sulfate IND and/or NSC, 183 patients have been enrolled in NCI-sponsored clinical trials under the AZD6244 IND and/or NSC, and 3537 patients have been enrolled in NCI-sponsored clinical trials under the OSI-774 IND and/or NSC.

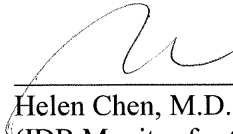
In this case, it is felt that possible causal relationships exist between the events and the investigational therapies AZD6244 Hydrogen sulfate and OSI-774.

	Hypoxia	Pneumonitis
AZD6244 Hydrogen sulfate	Possible	Possible
OSI-774	Possible	Possible
Non-small cell lung cancer	Possible	Possible

Date: 6/27/11

Signature: 
L. Austin Doyle, M.D.
(IDB Monitor for AZD6244 Hydrogen sulfate)

Date:  6/28/11

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

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

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