IND SAFETY REPORT: INITIAL WRITTEN REPORT

TO: *Division of Drug Oncology Products, Center for Drug Evaluation and Research, FDA*	FAX: *301-796-9845*

1. IND NUMBER	2. AGENT NAME	3. DATE
77782 63383	AZD6244 Hydrogen sulfate OSI-774 (erlotinib, Tarceva®)	June 15, 2011

4. SPONSOR
Division of Cancer Treatment and Diagnosis, National Cancer Institute

5. REPORTER'S NAME, TITLE, AND INSTITUTION	6. PHONE NUMBER
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8a. PROTOCOL NUMBER (AE #)	8b. AE GRADE: AE
8444 (AE# 1276865)	Grade 3: Hypoxia Grade 3: Pneumonitis

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
1010017	72 years	Male

12. DESCRIPTION OF ADVERSE EVENT

The patient is a 72-year-old male with metastatic non-small cell lung cancer who experienced grade 3 hypoxia and grade 3 pneumonitis while on a phase 2 trial utilizing the investigational agents AZD6244 Hydrogen sulfate and OSI-774. The patient began the investigational therapy on May 25, 2011, and received his 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. 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 toxicity 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 of the right middle lung lobe which was well tolerated. Additional information has been requested from the investigational site. There is a reasonable possibility that the experience may have been caused by the drugs.

13. DOSE, ROUTE, AND SCHEDULE **Cycle = 28 days**
AZD6244 Hydrogen sulfate: 150 mg PO daily
OSI-774: 100 mg PO daily

14. DATES OF TREATMENT
The patient began the investigational therapy on May 25, 2011, and received his 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).

15. ACCRUAL AND IND EXPERIENCE
Number of patients enrolled in NCI-sponsored clinical trials using AZD6244 Hydrogen sulfate = 435, and OSI-774 = 3537. There has been 1 other case of hypoxia and no other cases of pneumonitis reported to the NCI through AdEERS as serious adverse events for AZD6244 Hydrogen sulfate, and 46 other cases of hypoxia reported to the NCI through AdEERS as serious adverse events for OSI 774. Pneumonitis is an expected event for OSI-774.

16. COMMENTS
AT THIS TIME, NO OTHER INFORMATION IS AVAILABLE. IF UPON FURTHER INVESTIGATION RELEVANT INFORMATION BECOMES AVAILABLE, THEN A FOLLOW-UP REPORT WILL BE SUBMITTED IN ACCORDANCE WITH 21CFR 312.32(d) (2).

DISCLAIMER per 21 CFR 312.32(e): THIS SAFETY REPORT DOES NOT NECESSARILY REFLECT A CONCLUSION OR ADMISSION BY THE CTEP IDB SENIOR INVESTIGATOR/SPONSOR THAT THE INVESTIGATIONAL AGENT/THERAPY CAUSED OR CONTRIBUTED TO THE ADVERSE EXPERIENCE BEING REPORTED.