

**IND SAFETY REPORT: INITIAL WRITTEN REPORT**

<b>TO: Division of Drug Oncology Products, Center for Drug Evaluation and Research, FDA</b>		<b>FAX: 301-796-9845</b>
1. IND NUMBER 77782 63383	2. AGENT NAME AZD6244 Hydrogen sulfate OSI-774 (erlotinib, Tarceva®)	3. DATE April 20, 2011
4. SPONSOR <b>Division of Cancer Treatment and Diagnosis, National Cancer Institute</b>		
5. REPORTER'S NAME, TITLE, AND INSTITUTION <b>L. Austin Doyle, M.D., Senior Investigator for Investigational Therapeutics 2, Investigational Drug Branch, CTEP, DCTD, NCI</b>		6. PHONE NUMBER <b>301-496-1196</b>
<b>Helen Chen, MD-Associate Branch Chief for Investigational Therapeutics 3, Investigational Drug Branch, CTEP, DCTD, NCI</b>		7. FAX NUMBER <b>301-402-0428</b>
8a. PROTOCOL NUMBER (AE #) <b>8444 (AE# 1242384)</b>	8b. AE GRADE: AE <b>Grade 3: Gastric hemorrhage</b> <b>Grade 3: Hypotension</b> <b>Grade 2: Acute kidney injury</b>	
9. PATIENT IDENTIFICATION <b>1010012</b>	10. AGE <b>83 years</b>	11. SEX <b>Male</b>
12. DESCRIPTION OF ADVERSE EVENT The patient is an 83-year-old male with metastatic non-small cell lung cancer who experienced grade 3 gastric hemorrhage, grade 3 hypotension, and grade 2 acute kidney injury while on a phase 2 trial utilizing the investigational agents AZD6244 Hydrogen sulfate and OSI-774. The patient began the investigational therapy on April 6, 2011, and received his last doses of AZD6244 Hydrogen sulfate and OSI-774 on April 11, 2011 (Cycle 1, Day 6). On April 12, 2011 (Cycle 1, Day 7), the patient presented for scheduled follow-up visit, and reported persistent diarrhea, nausea, and emesis despite Imodium® usage in the past three days. He was hypotensive with a BP of 53/39 mmHg. The patient was transferred to the hospital for IV hydration. After the initial fluid resuscitation, his creatinine was 3.36 mg/dL (reference range: 0.77-1.19 mg/dL) as compared to a baseline creatinine of 1.56 mg/dL on April 6, 2011 (Cycle 1, Day 1). He was admitted to the hospital for the management of his acute renal failure. Later that day, the patient had two episodes of marooned colored stool, his hemoglobin dropped from 13.3 g/dL to 9.7 g/dL (reference range: 13.7-17.5 g/dL), and he was transferred to the ICU. He had a PT of 69.0 sec (reference range: 11.6-15.2 sec) and an activated PTT of 53.6 sec (reference range: 25.3-37.3 sec). A nasogastric lavage yielded brown/coffee ground with occasional flecks of bright red blood. He received continuous IV Protonix® infusion, 4 units of fresh frozen plasma (FFP), red blood cell transfusion, and vitamin K based on a history of Coumadin® therapy. The investigational treatments were held. The following day, the Coumadin® therapy was held and he was made NPO. An EGD revealed three gastric ulcers and upper esophageal varices. On April 14, 2011, the patient's BP improved to 85-145/57-86 mmHg, his hemoglobin increased to 10.7 g/dL, and his creatinine decreased to 1.60 mg/dL. 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 April 6, 2011, and received his last doses of AZD6244 Hydrogen sulfate and OSI-774 on April 11, 2011 (Cycle 1, Day 6).		
15. ACCRUAL AND IND EXPERIENCE Number of patients enrolled in NCI-sponsored clinical trials using AZD6244 Hydrogen sulfate = 353, and OSI-774 = 3467. There has been one other case of gastric hemorrhage, 4 other cases of hypotension and 2 other cases of acute kidney injury reported to the NCI through AdEERS as serious adverse events for AZD6244 Hydrogen sulfate; and 36 other cases of hypotension and 12 other cases of acute kidney injury reported to the NCI through AdEERS as serious adverse events for OSI 774. Gastric hemorrhage 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). <b>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.</b>		