



DATE: 5/13/11 *L. Austin Doyle MD*

FROM: L. Austin Doyle, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
Helen Chen, M.D., Senior Investigator, Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: AZD6244 (Hydrogen sulfate) and OSI-774 (erlotinib, Tarceva™) NCI IND Safety Report, AE # **1242384**

TO: Investigators Using AZD6244 (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 and OSI-774.

The following must be completed by all investigators using AZD6244 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 and OSI-774, there does not appear to be a change in the risk-benefit ratio for AZD6244 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.

An 83-year-old male with metastatic non-small cell lung cancer experienced grade 3 gastric hemorrhage, grade 3 hypotension, grade 2 acute kidney injury, and grade 4 respiratory failure while on a phase 2 trial utilizing the investigational agents AZD6244 and OSI-774.

ADVERSE EVENTS ASSESSMENT

IND 77782	63383	ADVERSE EXPERIENCE REPORT NO.
NSC 748727	718781	IND Safety Report: #1
AZD6244	OSI-774	Gr. 3: Gastric hemorrhage
(Hydrogen sulfate)	(erlotinib, Tarceva®)	Gr. 3: Hypotension
		Gr. 2: Acute kidney injury
		Gr. 4: Respiratory failure
AE: 1242384		Protocol: 8444

The patient is an 83-year-old male with metastatic non-small cell lung cancer who experienced gastric hemorrhage, hypotension, acute kidney injury, and respiratory failure while on a phase 2 trial utilizing the investigational agents AZD6244 and OSI-774. He began the first course of treatment on April 6, 2011, receiving AZD6244 150 mg PO daily, and OSI-774 100 mg PO daily, every 28 days. The patient received the last doses of AZD6244 and OSI-774 on April 11, 2011 (Cycle 1, Day 6).

The patient was diagnosed with non-small cell lung cancer in November 2009, and is status post radiation therapy in the same month of diagnosis. He began the investigational therapy on April 6, 2011.

On April 12, 2011 (Cycle 1, Day 7), the patient presented for a 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), packed red blood cell (PRBC) 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 became increasingly hypoxic and needed increasing amounts of supplemental oxygen to maintain an oxygen saturation > 88%. His BP improved to 85-145/57-86 mmHg. A transthoracic echocardiogram was significant for moderate pulmonary hypertension. On April 15, 2011, a CT scan of the chest was consistent with bilateral pleural effusions, and lung consolidation with atelectasis. The patient's hemoglobin increased to 10.7 g/dL, and his creatinine decreased to 1.60 mg/dL. He was intubated, placed on mechanical ventilation, and started on pantoprazole, clarithromycin, and amoxicillin for possible *H. pylori* infection. The patient was also started on vancomycin and meropenem. On April 16, 2011, the patient remained intubated and under sedation, but was hemodynamically stable. On April 19, 2011, he tolerated extubation, and was continued on 1 liter oxygen by nasal cannula. The patient's swallow study was normal, and he was advanced to a soft diet the following day. On April 22, 2011, his oxygen saturation improved to 93% on oxygen, his BP was 112/61 mmHg, his creatinine was 0.95 mg/dL, and his hemoglobin was 10.1 g/dL. The patient was discharged to a nursing facility after being removed from the protocol that day.

The patient's past medical/surgical history is significant for hypertension, gout, deep vein thrombosis in 2009, chronic obstructive pulmonary disease (COPD), prostate cancer status post prostatectomy in 1997, and tonsillectomy during childhood. Medications taken at the time of the event included loperamide, gabapentin, metoprolol, enoxaparin, allopurinol, Advair®, Spiriva®, Lasix®, calcium plus vitamin D, and potassium chloride.

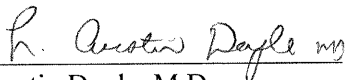
There has been one other case of gastric hemorrhage (grade 2, unlikely related), and 4 other cases of hypotension, reported to the NCI through AdEERS as serious adverse events for AZD6244. Gastric hemorrhage is an expected event for OSI-774.

To date, a total of 357 patients have been enrolled in NCI-sponsored clinical trials under the AZD6244 IND and/or NSC, and 3490 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 gastric hemorrhage and the investigational therapies AZD6244 and OSI-774.

	Gastric hemorrhage	Hypotension	Acute kidney injury	Respiratory failure
AZD6244	Possible	Unlikely	Unlikely	Unlikely
OSI-774	Possible	Unlikely	Unlikely	Unlikely
Non-small cell lung cancer	Unrelated	Unrelated	Unrelated	Probable
Coumadin®	Possible	Unrelated	Unrelated	Unrelated
Metoprolol	Unrelated	Possible	Unlikely	Unrelated
GI haemorrhage and complications	NA	Definite	Probable	Possible

Date: 5/13/11

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

Date: 5/14/11

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

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

cc: Graeme Smith, M.D.
 Michaelene P. Llewellyn, R.N., B.S.N., M.A.S.
 Michael G. Wayne
 AZD6244nci.wilmington@astrazeneca.com
 ISSSAE.wilmington@astrazeneca.com
 AstraZeneca Pharmaceuticals

cc: Christine Boisclair
 Scott Giangrasso
 Safety-us@us.astellas.com
 OSI Pharmaceuticals, Inc.