DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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National Cancer Institute
Bethesda, Maryland 20892

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FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: IMC-A12 (HuMAb IGF-1R) and OSI-774 (erlotinib) NCI IND Safety Report, AE # **1559936**

TO: Investigators Using IMC-A12 (NSC 742460) 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 agent IMC-A12 and OSI-774.

The following must be completed by all investigators using IMC-A12 under NCI IND 100947 and OSI-774 under NCI IND 63383:

- Send a copy of the IND Safety Report to your Institutional Review Board (IRB) according to your local IRB's policies and procedures.
- File a copy of the IND Safety Report in your protocol file.

If your study is not covered under IND 100947 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 IMC-A12 and OSI-774, there does not appear to be a change in the risk-benefit ratio for IMC-A12 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 70-year-old female with metastatic adenocarcinoma of the pancreas experienced grade 5 hypotension while on a phase 1 and randomized phase 2 study utilizing the investigational agents IMC-A12 and OSI-774 in combination with gemcitabine.

ADVERSE EVENTS ASSESSMENT

IND	**100947**	**63383**	ADVERSE EXPERIENCE REPORT NO.
NSC	**742460**	**718781**	IND Safety Report: **#1**
IMC-A12		**OSI-774**	Event: **Gr. 5: Hypotension**
(HuMAb IGF-1R)		**(erlotinib)**	**Gr. 4: Cardiac troponin I (cTnI)**
AE:	**1559936**		Protocol: **S0727**

The patient was a 70-year-old female with metastatic adenocarcinoma of the pancreas who experienced hypotension while on a phase 1 and randomized phase 2 study utilizing the investigational agents IMC-A12 and OSI-774 in combination with gemcitabine. She began her first course of treatment on November 18, 2009, receiving IMC-A12 6 mg/kg/dose IV over 60 minutes on Days 1, 8, 15 and 22; OSI-774 100 mg PO daily; and gemcitabine 1000 mg/m^2/dose IV over 30 minutes on Days 1, 8 and 15. She received her last doses of IMC-A12 and gemcitabine on December 31, 2009 (Cycle 2, Day 9) and the last dose of OSI-774 on December 13, 2009 (Cycle 1, Day 26).

The patient was diagnosed with adenocarcinoma of the pancreas with metastases to the lungs, liver, spleen, and perisplenic lymph nodes in October 2009. She began the investigational therapy on November 18, 2009.

On December 14, 2009 (Cycle 1, Day 27), the patient presented to the ER and was then admitted to the hospital after having sustained a fall; she had had several prior such episodes preceded by dizziness, yet this episode was not accompanied by dizziness. She had her usual nausea, vomiting and diarrhea after taking her medications. She appeared alert and oriented and had a blood pressure of 126/81 mmHg and a pulse rate of 91 bpm. Laboratory results showed guaiac-positive stool and a hemoglobin of 10.9 mg/dL (reference range: 12-16 mg/dL). The ECG result revealed a new right bundle branch block (RBBB). The abdominal CT scan showed a pancreatic tail mass which appeared slightly more extensive than previous scans, stable multiple liver and spleen metastases, and no evidence of perforation. Incidentally, she was also found to have diffuse atherosclerotic disease in the aorta, which did not change from baseline. On December 15, 2009, an echocardiogram showed moderate concentric left ventricular hypertrophy with a left ventricular ejection fraction of 60%. A routine renal ultrasound showed left kidney atrophy and bubbles in the porta hepatis, but the possibility of an asymptomatic intestinal perforation was ruled out by a repeat abdominal CT scan. At this time, OSI-774 was held and the patient was treated with IV fluids, aspirin, morphine and Zofran®. During the hospitalization, the patient had 2 episodes of coffee ground emesis between December 24, 2009 (Cycle 2, Day 2), and December 25, 2009 (Cycle 2, Day 3). She was treated with IV Protonix®, and her aspirin therapy was discontinued.

The patient's condition improved, and she was discharged to the nursing home on December, 28, 2009. At her follow-up visit on December 31, 2009 (Cycle 2, Day 9), the patient appeared slightly improved. She received the IMC-A12, erlotinib and gemcitabine (gemcitabine was given at a lower dose due to platelet count of 81, 000/mm3).

On January 1, 2010 (Cycle 2, Day 10), the patient became poorly responsive and was taken to the ER where she had a manual blood pressure of 80/palpable, normal pulse, oxygen saturation in the 70s, mild tachypnea, dry mucous membranes, disorientation, and lethargy. The ECG revealed a persistent RBBB with T wave inversions in V2 and V3. A high CPK-MB of 9.4 ng/mL (reference range: <5.0 ng/mL) and troponin I of 0.290 ng/mL (reference range: 0-0.049 ng/mL), were thought to be correlated with diabetes and other risk factors. B-type natriuretic peptide (BNP) was elevated at 2593 pg/mL. Her hemoglobin was 10.8 g/dL with no evidence of acute bleeding, and the platelet count was 61,000/mm3. Sodium was 151 mmol/L (reference range: 135-145 mmol/L), blood urea nitrogen 47 mg/dL (reference range: 6-22 mg/dL) and creatinine was 1.68 mg/gL (reference range: 0.5-1.1 mg/dL). Serum glucose was 131 mg/dL (reference range: 70-110 mg/dL). A chest X-ray did not show evidence of congestive heart failure. The possibility of a post-ictal state was not confirmed. The troponin and BNP elevation were thought to be nonspecific. She was treated with IV fluids, IV Levophed® and IV antibiotics, but she continued to have persistent hypotension and general deterioration. Because she was DNR, CPR and intubation were not

performed. The patient expired on the same day.

The patient's past medical and surgical history was significant for type II diabetes, hypertension, hyperlipidemia, hysterectomy (1967), atherosclerotic disease status post bilateral iliac stent placement, bipolar disorder, chronic renal insufficiency, and gout. Medications taken at the time of the event included prochlorperazine, oxycodone, Paxil®, hydrochlorothiazide, docusate sodium, MiraLax®, senna, allopurinol, senna, metoprolol, lactulose, pantoprazole, lorazepam, acyclovir, Nystatin®, cream, multivitamins, morphine, doxycycline and insulin.

The precise etiology of hypotension and death is not certain. However, the clinical picture suggested the possibility of a cardiac event. Other factors such as infection or progressive disease cannot be ruled out. The event was most likely due to the patient's underlying atherosclerotic disease, but attribution to the study drug cannot be completely ruled out. There have been 9 other cases of hypotension and 1 other case of elevated troponin I previously reported to the NCI as serious adverse events through AdEERS under the IMC-A12 NSC and/or IND and 33 other cases of hypotension and 4 other cases of troponin I previously reported to the NCI as serious adverse events through AdEERS under the OSI-774 NSC and/or IND as summarized in the table below:

Adverse Event	Grade	Attribution
IMC-A12		
Hypotension (n=9)	4 3 2	1 Unrelated 1 Possible, 3 Unlikely, 1 Unrelated 3 Unrelated
Troponin I (n=1)	3	1 Possible
OSI-774		
Hypotension (n=33)	4 3 2	1 Unlikely, 3 Unrelated 1 Possible, 13 Unlikely, 5 Unrelated 1 Probable, 1 Possible, 5 Unlikely, 3 Unrelated
Troponin I (n=4)	4 3	2 Unlikely 2 Unlikely

A total of 466 patients have been enrolled in NCI-sponsored clinical trials under the IMC-A12 IND and/or NSC, and a total of 3097 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 IMC-A12.

	Hypotension	**Troponin I elevation**
IMC-A12	Possible	Unlikely
OSI-774	Unlikely	Unlikely
Gemcitabine	Possible	Unlikely
Adenocarcinoma of the pancreas	possible	Unlikely
Possible cardiac event	Possible	Unlikely
History of atherosclerosis	Possible	Probable

Date: 6/12/10

Signature:

Helen Chen, M.D.
(IDB Monitor for IMC-A12 and OSI-774)

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

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