



DATE: June 1, 2010

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

SUBJECT: IMC-A12 (HuMAb IGF-1R; A12; Cixutumumab[®]) and OSI-774 (erlotinib; Tarceva[®]) NCI IND Safety Report, AE # 1203166

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 agents IMC-A12 and OSI-774.

The following must be completed by all investigators using IMC-A12 under NCI IND 100947 and/or 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 INDs 100947 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 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 these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 59-year-old female with adenocarcinoma of the pancreas experienced grade 3 cardiac ischemia/infarction and a grade 3 cardiac troponin I elevation while on a phase 1/2 study utilizing the investigational agents IMC-A12 and OSI-774 in combination with gemcitabine.

ADVERSE EVENTS ASSESSMENT

IND 100947 NSC 742460 IMC-A12 (HuMab IGF-1R; A12; Cixutumumab[®]) AE: 1203166	63383 718781 OSI-774 (erlotinib; Tarceva[®])	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 3: Cardiac ischemia/infarction Gr. 3: Cardiac troponin I (cTnI) Protocol: S0727
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The patient is a 59-year-old female with adenocarcinoma of the pancreas who experienced cardiac ischemia/infarction and cardiac troponin I elevation while on a phase 1/2 study utilizing the investigational agents IMC-A12 and OSI-774 in combination with gemcitabine. She began her first course of treatment on November 16, 2009, receiving IMC-A12 6 mg/kg IV over 1 hour on Days 1, 8, 15, and 22, OSI-774 100 mg PO daily, and gemcitabine 1000 mg/m² IV over 30 minutes on Days 1, 8, and 15, every 28 days. She received her last doses of IMC-A12 and gemcitabine on December 23, 2009 (Cycle 2, Day 8), and her last dose of OSI-774 on December 28, 2009 (Cycle 2, Day 13).

The patient was diagnosed with adenocarcinoma of the pancreas in September 2009, and is status post multiple-agent systemic chemotherapy. She began the investigational therapy on November 16, 2009.

On December 28, 2009 (Cycle 2, Day 13), the patient presented to the local emergency room with nausea, vomiting, generalized body weakness, and severe retrosternal chest pain. The patient's physical examination was significant for moderate distress, and tachycardia. An ECG showed normal sinus rhythm, and her troponin was 0.07 ng/mL (reference range: 0-0.3 ng/mL). She was treated with sublingual nitroglycerin, which relieved her chest pain. The patient was also started on IV fluids, morphine, Ativan[®] and Phenergan[®].

On December 29, 2009 (Cycle 2, Day 14), the patient was transferred to another hospital for further therapy. She was chest pain free upon transfer. A repeat ECG showed normal sinus rhythm with no ischemic changes. Her initial troponin on arrival was 0.59 ng/mL, and the repeat value was 0.92 ng/mL. She was started on beta blockers, ACE inhibitors, and statins. A 2-D echocardiogram showed normal left ventricular systolic function and wall motion with an estimated ejection fraction of 60-65% and normal right ventricular function. Mild aortic insufficiency and trace tricuspid valve regurgitation were also reported. The patient was assessed by a cardiologist, who recommended continuing beta blockers, ACE inhibitors, and statins. On December 30, 2009 (Cycle 2, Day 15), a cardiac stress test with nuclear imaging was negative.

On December 31, 2009 (Cycle 2, Day 16), the patient continued to be chest pain free and her troponins had trended down. She was discharged home on the same day to be followed up at the oncology clinic. She had no cardiology follow-up.

The patient's past medical and surgical history is significant for hypertension, diabetes, hyperlipidemia, asthma, 20 pack-year smoking history, and status post mastectomy in 2002 for breast cancer and cholecystectomy. Her family history is significant for a history of myocardial infarction in her brother. Medications taken at the time of the event included Glucotrol[®], Lantus[®] insulin, Crestor[®], mirtazapine, and Lortab[®].

There has been 1 other case of cardiac ischemia/infarction (Grade 4, Unlikely) and 1 other case of cardiac troponin I (Grade 3, Possible) previously reported to the NCI as serious adverse events through AdEERS under the IMC-A12 NSC and/or IND. There have been 10 other cases of cardiac ischemia/infarction and 5 other cases of cardiac troponin I previously reported to the NCI as serious adverse events through AdEERS under the OSI-774 NSC and/or IND, as shown in the table below:


Adverse Event	Grade	Attribution
Cardiac ischemia/infarction (n=10)	4 3	1 Unrelated, 4 Unlikely, 2 Possible 1 Unrelated, 2 Unlikely
Cardiac troponin I (n=5)	4 3	1 Unlikely, 1 Possible 2 Unlikely

A total of 466 patients have been enrolled in NCI-sponsored clinical trials under the IMC-A12 IND and/or NSC. A total of 3097 patients have been enrolled in the 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 events and the investigational therapies IMC-A12 and OSI-774.

	Cardiac ischemia/infarction	Elevated cardiac troponin I
IMC-A12	Possible	Possible
OSI-774	Possible	Possible
Gemcitabine	Possible	Possible
Adenocarcinoma of the pancreas	Unrelated	Unlikely

Date: 6/2/10

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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