



DATE: APR 11 2011

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 # 1743915

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 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 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 these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 63-year-old male with metastatic adenocarcinoma of the pancreas experienced grade 4 pneumonia and expired of ventricular fibrillation 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)	63383 718781 OSI-774 (erlotinib; Tarceva®)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 5: Ventricular arrhythmia: Ventricular fibrillation Gr. 4: Infection with normal ANC or Grade 1 or 2 neutrophils: Lung (Pneumonia)
AE: 1743915	Protocol: S0727	

The patient was a 63-year-old male with metastatic adenocarcinoma of the pancreas who experienced pneumonia and expired of ventricular fibrillation while on a phase 1/2 study utilizing the investigational agents IMC-A12 and OSI-774 in combination with gemcitabine. He began his first course of treatment on September 2, 2010, 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. He received his last doses of IMC-A12 and gemcitabine on October 15, 2010 (Cycle 2, Day 16), and his last dose of OSI-774 on October 20, 2010 (Cycle 2, Day 21).

The patient was diagnosed with adenocarcinoma of the pancreas in July 2010, and had no prior therapy. He began the investigational therapy on September 2, 2010.

On October 20, 2010 (Cycle 2, Day 21), the patient, who had a history of severe chronic obstructive pulmonary disease (COPD), presented to the emergency department (ED) complaining of acute onset of substernal chest discomfort, severe dyspnea, nonproductive cough and fever initiated one night prior. In the ED, the patient had sinus tachycardia with a heart rate of 133, blood pressures of 84/46 mmHg then 74/39 mmHg, temperature of 97.6 °F which increased to 101°F, and a pulse oximetry reading of 92% on five liters of oxygen via nasal cannula. Shortly after that, his oxygenation deteriorated to the point that he required 100% nonrebreathing mask in order to maintain pulse oximetry readings above 90%. A chest radiograph revealed a fairly dense left lower lobe infiltrate. A CT pulmonary angiogram with contrast revealed a small, non-occlusive filling defect in one of the right and possibly one of the left lower lobe pulmonary arteries likely representing pulmonary embolism (PE), in addition to dense consolidation in the left lower lobe with extensive ill-defined surrounding nodular ground glass opacities likely representing left lower lobe pneumonia with endobronchial spread into the left upper lobe and right upper lobe. The patient had two blood cultures drawn in the ED and received one dose of moxifloxacin 400 mg IV. He was transferred to the intensive care unit (ICU). His arterial blood gases showed a PCO₂ of 39 mmHg (reference range: 35-45 mmHg), a pH of 7.37 (reference range: 7.35-7.45) and a PO₂ of 66 mmHg (reference range: 75-100 mmHg) on 100% nonrebreathing mask with oxygen saturation of 90%. He was intubated and placed on a ventilator.

On October 21, 2010 (Cycle 2, Day 22), a transthoracic echocardiogram revealed a mildly dilated left ventricle, normal left ventricular wall thickness, and the left ventricular systolic function was severely reduced with an ejection fraction estimated at 15-20%. The right ventricle was moderate to severely dilated, and the right ventricular systolic dysfunction was mild to moderately reduced. Mild mitral regurgitation, and a mild to moderate tricuspid regurgitation was also noted. The patient was not seen by a cardiologist. At 20:30 the patient went into cardiac arrest with ventricular fibrillation and pulseless electrical activity (PEA). Resuscitative measures were initiated by the staff, including a total of 2 ampules of epinephrine and one ampule of bicarbonate. He was unresponsive and remained in PEA. Resuscitative measures were stopped per the family's request and the patient expired.

The patient's past medical/surgical history was significant for left lower extremity deep venous thrombosis (DVT), type 2 diabetes mellitus, hypertension, severe obstructive sleep apnea/hypopnea

syndrome, osteoarthritis, gastroesophageal reflux disease, cholecystectomy, vasectomy, umbilical hernia repair, right ankle fracture and surgery, 100 pound weight loss since January 2010, and 80 pack year history of cigarette smoking quitted 18 years ago. Medications taken at the time of the event included Tylenol[®], Lovenox[®], Tarceva[®], Prozac[®], Advair Diskus[®], Monopril[®], Lasix[®], Gemzar[®], Glucotrol[®], Norco[®], Glucophage[®], morphine, Protonix[®], Miralax[®], Compazine[®], Senokot[®], and Ambien[®].

There have been 16 other cases of pneumonia and no other cases of ventricular fibrillation previously reported to the NCI as serious adverse events through AdEERS under the IMC-A12 NSC and/or IND; and 32 other cases of pneumonia and no other cases of ventricular fibrillation 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
IMC-A12		
Pneumonia (n=16)	5	1 Possible
	4	2 Unlikely, 1 Unrelated
	3	5 Unlikely, 3 Unrelated, 2 Possible,
	2	1 Unlikely, 1 Possible
OSI-774		
Pneumonia (n=32)	5	2 Unlikely
	4	2 Unrelated
	3	9 Unrelated, 7 Unlikely, 5 Possible
	2	3 Unrelated, 3 Unlikely
	1	1 Unrelated

A total of 952 patients have been enrolled in NCI-sponsored clinical trials under the IMC-A12 IND and/or NSC. A total of 3,435 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 pneumonia could be community acquired but a possible relationship to the study therapy could not be excluded. The LV dysfunction and ventricular fibrillation were likely due to respiratory failure.

	Ventricular fibrillation	Pneumonia
IMC-A12	Unlikely	Possible
OSI-774	Unlikely	Possible
Gemcitabine hydrochloride	Unlikely	Possible
Adenocarcinoma of the pancreas	Unrelated	Possible
Pulmonary emboli/Pneumonia	Possible	Possible
Respiratory failure	Possible	N/A
Ventricular fibrillation	N/A	Unrelated

Date: 4/8/11

Signature: 

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

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

cc: Naseem Zojwalla, M.D.
Clinical Safety: mailindata_GSMTINDY@lilly.com
ImClone LLC

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