



DATE: DEC 07 2010

FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI *OK for HC*

SUBJECT: IMC-A12 (HuMAb IGF-1R; A12) and OSI-774 (erlotinib) NCI IND Safety Report, AE # 1398066

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 65-year-old female with metastatic adenocarcinoma of the pancreas experienced grade 5 hypoxia and grade 3 pneumonitis while on phase 1/2 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 (HuMAb IGF-1R; A12; Cixutumumab®)	OSI-774 (erlotinib; Tarceva®)	Event: Gr. 5: Hypoxia Gr. 3: Pneumonitis/pulmonary infiltrates
AE: 1398066		Protocol: S0727

The patient was a 65-year-old female with metastatic adenocarcinoma of the pancreas who experienced pneumonitis and died of hypoxia 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 February 11, 2010, 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/m²/dose IV over 30 minutes on Days 1, 8, and 15, every 28 days. She received the last doses of IMC-A12 and gemcitabine on May 20, 2010 (Cycle 4, Day 15), and the last dose of OSI-774 on May 22, 2010 (Cycle 4, Day 17).

The patient was diagnosed with pancreatic cancer metastatic to the lungs in February 2010, when a work-up revealed a large left-sided malignant pleural effusion and hydropneumothorax in addition to the primary pancreatic lesion. She began the investigational therapy on February 11, 2010.

On May 22, 2010 (Cycle 4, Day 17), the patient, who had been experiencing recurrent pleural effusions, contacted the clinic with complaints of increasing dyspnea of 2-3 weeks duration. She was instructed to discontinue her OSI-774 medication and report to the emergency room, which she declined.

On May 25, 2010 (Cycle 4, Day 20), the patient presented to the clinic with complaints of dyspnea, back pain, poor appetite, weight loss, some confusion, and occasional non-bloody diarrhea. A chest X-ray revealed a previously known small pneumothorax, a small to moderate left pleural effusion which was similar to previous exams, and increased alveolar and interstitial disease in the right lung. Her oxygen saturation was 84% on room air, while her arterial blood gases revealed a PO₂ of 50.0 mmHg (reference range: 67.5-84.4 mmHg), a PCO₂ of 45.3 mmHg (reference range: 38.0-42.0 mmHg), and a pH of 7.383 (reference range: 7.380-7.420). The patient was admitted to the hospital and started on Solu-Medrol®.

On May 26, 2020 (Cycle 4, Day 21), the patient's chest CT scan revealed increased diffuse ground-glass appearing infiltrate in the right lung along with multiple pulmonary nodules; interval development of a small right-sided pleural effusion; and an unchanged large loculated left pleural effusion when compared to an April 2010 scan. Her oxygen saturation was 97% with an oxygen mask, while her arterial blood gases showed a PO₂ of 164.0 mmHg, a PCO₂ of 46.3 mmHg, and a pH of 7.409. It was felt that her interstitial lung disease could have been a reaction to the OSI-774 medication versus the progression of pancreatic cancer. The patient's condition continued to deteriorate, and she died on May 28, 2010 (Cycle 4, Day 23).

The patient's past medical/surgical history is significant for cellulitis of the left leg, chronic anemia, degenerative spine disease, chronic back pain, and multiple cervical and lumbar spinal fusions. Medications taken at the time of the event included methadone, Norco®, ibuprofen, Ritalin®, Zolof®®, Lovenox®, Zofran®, Compazine®, Imodium®, and clobetasol lotion.

Pneumonitis is an expected event for OSI-774. There have been 8 other cases of hypoxia and 3 other cases of pneumonitis previously reported to the NCI as serious adverse events through AdEERS under the IMC-A12 NSC and/or IND; and there have been 45 other cases of hypoxia 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:

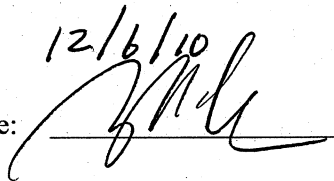
Adverse Event	Grade	Attribution
IMC-A12		
Hypoxia (n=6)	4	2 Unlikely
	3	1 Possible, 2 Unlikely, 3 Unrelated
Pneumonitis (n=3)	5	1 Possible
	3	1 Unlikely, 1 Unrelated
OSI-774		
Hypoxia (n=45)	5	1 Unrelated
	4	1 Possible, 3 Unlikely, 1 Unrelated
	3	1 Possible, 17 Unlikely, 18 Unrelated
	2	2 Probable, 1 Unlikely

A total of 651 patients have been enrolled in NCI-sponsored clinical trials under the IMC-A12 IND and/or NSC. A total of 3,356 patients have been enrolled in the NCI-sponsored clinical trials under the OSI-774 IND and/or NSC.

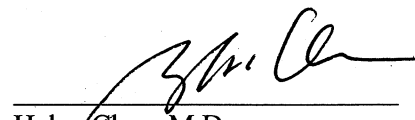
In this case, it is felt that a probable causal relationship exists between the events and the investigational therapy OSI-774, but not with the investigational therapy IMC-A12.

	Hypoxia	Pneumonitis
IMC-A12	Unlikely	Unlikely
OSI-774	Probable	Probable
Gemcitabine hydrochloride	Unlikely	Unlikely
Adenocarcinoma of the pancreas	Probable	Probable

Date:

12/6/10


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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