

## IND SAFETY REPORT: INITIAL WRITTEN REPORT

To: *Division of Biologic Oncology Products, Center for Drug Evaluation and Research, FDA*  
*Division of Drug Oncology Products, Center for Drug Evaluation and Research, FDA*

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1. IND NUMBER

100947

63383

2. AGENT NAME

IMC-A12 (HuMab IGF-1R)

OSI-774 (erlotinib, Tarceva®)

3. DATE

October 28, 2010

4. SPONSOR

Division of Cancer Treatment and Diagnosis, National Cancer Institute

5. REPORTER'S NAME, TITLE, AND INSTITUTION

Helen Chen, MD-Associate Branch Chief for Investigational Therapeutics 3, Investigational Drug Branch, CTEP, DCTD, NCI

6. PHONE NUMBER

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8a. PROTOCOL NUMBER (AE #)

S0727 (AE# 1743915)

8b. AE GRADE: AE

Grade 4: Infection: Lung (pneumonia)

9. PATIENT IDENTIFICATION

226924

10. AGE

63 years

11. SEX

Male

12. DESCRIPTION OF ADVERSE EVENT

The patient was a 63-year-old male with metastatic adenocarcinoma of the pancreas who experienced grade 4 pneumonia 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, and received the last doses of IMC-A12 and gemcitabine on October 15, 2010 (Cycle 2, Day 16), and the last dose of OSI-774 on October 20, 2010 (Cycle 2, Day 21). 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. In the ED, he 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. His oxygenation deteriorated to the point that he required 100% nonbreathing 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 groundglass 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 PCO<sub>2</sub> of 39 mmHg (reference range: 35-45 mmHg), a pH of 7.37 (reference range: 7.35-7.45), a PO<sub>2</sub> of 66 mmHg (reference range: 75-100 mmHg) on 100% nonbreathing mask with oxygen saturation of 90%. He was intubated and placed on a ventilator. On October 21, 2010 at 20:30 (Cycle 7, Day 7), the patient's condition continued to deteriorate, and he went into cardiac arrest with ventricular fibrillation and pulseless electrical activity. Resuscitative measures were stopped per the family's request and the patient expired that day. Additional information has been requested from the investigational site. There is a reasonable possibility that the experience may have been caused by the drugs.

13. DOSE, ROUTE, AND SCHEDULE

Cycle = 28 Days; IMC-A12: 6 mg/kg/dose IV over 60 minutes on Days 1, 8, 15 and 22 and OSI-774: 100 mg PO daily

14. DATES OF TREATMENT

The patient began the investigational therapy on September 2, 2010, and received the last dose of IMC-A12 on October 15, 2010 (Cycle 2, Day 16), and the last dose of OSI-774 on October 20, 2010 (Cycle 2, Day 21).

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using IMC-A12=601 and using OSI-774=3,307. There have been 4 other cases of pneumonia reported to the NCI through AdEERS as serious adverse events for IMC-A12; and 23 cases of pneumonia reported to the NCI through AdEERS as serious adverse events for OSI-774.

16. COMMENTS

Also administered on this protocol: Gemcitabine: 1000 mg/m<sup>2</sup>/dose IV over 30 minutes on Days 1, 8, and 15

AT THIS TIME, NO OTHER INFORMATION IS AVAILABLE. IF UPON FURTHER INVESTIGATION RELEVANT INFORMATION BECOMES AVAILABLE, THEN A FOLLOW-UP REPORT WILL BE SUBMITTED IN ACCORDANCE WITH 21CFR 312.32(d) (2).

**DISCLAIMER per 21 CFR 312.32(e): THIS SAFETY REPORT DOES NOT NECESSARILY REFLECT A CONCLUSION OR ADMISSION BY THE CTEP IDB SENIOR INVESTIGATOR/SPONSOR THAT THE INVESTIGATIONAL AGENT/THERAPY CAUSED OR CONTRIBUTED TO THE ADVERSE EXPERIENCE BEING REPORTED.**

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