

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 January 22, 2010
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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, CTEP, DCTD, NCI	6. PHONE NUMBER 301-496-1196
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8. PROTOCOL NUMBER (AE #)
S0727 (AE # 1559936)

9. PATIENT IDENTIFICATION 220732	10. AGE 70	11. SEX Female
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12. DESCRIPTION OF ADVERSE EVENT
The patient was a 70-year-old female with metastatic adenocarcinoma of the pancreas who experienced grade 5 hypotension while on a phase 1 and 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, and 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, who had previously been stable, became poorly responsive on January 1, 2010 (Cycle 2, Day 10), and was taken to the ER where she had a manual blood pressure of 80/palp, normal pulse, oxygen saturation in the 70s, mild tachypnea, dry mucous membranes, disorientation, and lethargy. The ECG revealed a right bundle branch block 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 correlated with diabetes and other factors in light of the patient's chronic troponin I leak. The possibility of a post-ictal state was not confirmed. Her hemoglobin was 10.8 g/dL (reference range: 12-16 g/dL), with no evidence of acute bleeding. It was felt that she was dehydrated based on her elevated sodium, blood urea nitrogen and creatinine. Serum glucose was 131 mg/dL (reference range: 70-110 mg/dL). She was treated with IV fluids, IV Levophed® and IV antibiotics. The patient's condition deteriorated and she 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 drug.

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
OSI-774: 100 mg PO daily

14. DATES OF TREATMENT
The patient started the investigational therapy on November 18, 2009, and received the last dose of IMC-A12 on December 31, 2009 (Cycle 2, Day 9) and the last dose of OSI-774 on December 13, 2009 (Cycle 1, Day 26).

15. ACCRUAL AND IND EXPERIENCE
Number of patients enrolled in NCI-sponsored clinical trials using IMC-A12= 271 and using OSI-774 = 2951. There have been 7 cases of hypotension reported to the NCI through AdEERS as serious adverse events for IMC-A12; and 31 cases of hypotension reported to the NCI through AdEERS as serious adverse events for OSI-774.

16. COMMENTS
Also administered on this protocol:
Gemcitabine: 1000 mg/m²/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.