

IND SAFETY REPORT: INITIAL WRITTEN REPORT

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

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1. IND NUMBER 59699 7921	2. AGENT NAME BMS 247550 (Ixabepilone) Bevacizumab (rhuMAb VEGF)	3. DATE July 1, 2011
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4. SPONSOR
Division of Cancer Treatment and Diagnosis, National Cancer Institute

5. REPORTER'S NAME, TITLE, AND INSTITUTION Richard Piekarz, MD, PhD – Senior Investigator, Investigational Drug Branch, CTEP, DCTD, NCI Helen Chen, MD-Associate Branch Chief for Investigational Therapeutics 3, Investigational Drug Branch, CTEP, DCTD, NCI	6. PHONE NUMBER 301-496-1196
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8a. PROTOCOL NUMBER (AE #) GOG-0086P (AE# 1868649)	8b. AE GRADE: AE Grade 5: Hemorrhage, pulmonary/upper respiratory: Bronchus
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9. PATIENT IDENTIFICATION 035-0086P-023	10. AGE 70 yrs	11. SEX Female
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12. DESCRIPTION OF ADVERSE EVENT
The patient was a 70-year-old female with recurrent serous endometrial carcinoma who experienced hemoptysis and then expired while on a phase 2 study using the investigational agents ixabepilone and bevacizumab, in combination with carboplatin. She began her first course of treatment on May 17, 2011, and received the last dose of ixabepilone, bevacizumab, and carboplatin on June 14, 2011 (Cycle 2, Day 1). Prior to the study, a chest CT demonstrated an increase in the size and number of bilateral pulmonary nodules as well as the mediastinal and bilateral hilar adenopathy consistent with worsening metastatic disease; the results from bronchial biopsies were consistent with metastatic serous carcinoma. On June 20, 2011 (Cycle 2, Day 7), the patient presented to the emergency room with a cough and new onset hemoptysis. She was admitted for further evaluation. She was afebrile, her blood pressure was 153/76 mmHg, her RBC count and hemoglobin were $3.74 \times 10^6/\mu\text{L}$ (reference range: $4-5.2 \times 10^6/\mu\text{L}$) and 11.1 g/dL (11.9-15.5 g/dL), respectively. A chest CT was performed and in comparison to the baseline CT, it revealed that the bilateral multiple known lung metastatic disease was less prominent, but internal cavitation was seen in the lung lesions; the known right perihilar lesion demonstrated a cavitation and was encasing and more significantly narrowing the right lower lobe bronchi, which was the most likely reason for the hemoptysis. The patient had no additional bleeding following the admission. She was feeling well and clinically stable without respiratory distress. The following morning, the patient complained of acute shortness of breath and had an unexpected loss of consciousness with apnea and no pulse. She expired after approximately 30 minutes of the attempted resuscitation. Additional information has been requested from the site. There is a reasonable possibility that the experience may have been caused by bevacizumab.

13. DOSE, ROUTE, AND SCHEDULE :
Cycle: 21 Days
No Prior Radiotherapy: Ixabepilone: 30 mg/m² IV over 1 hour on Day 1 x 6 Cycles; Bevacizumab: 15 mg/kg IV over 30-90 minutes on Day 1 x 6 Cycles. Maintenance Therapy (Cycles 7+): Bevacizumab: 15 mg/kg IV over 30-90 minutes on Day 1
Prior Radiotherapy: Ixabepilone: 25 mg/m² IV over 1 hour on Day 1 x 6 Cycles; Bevacizumab: 15 mg/kg IV over 30-90 minutes on Day 1 x 6 Cycles. Maintenance Therapy (Cycles 7+): Bevacizumab: 15 mg/kg IV over 30-90 minutes on Day 1

14. DATES OF TREATMENT
The patient started the investigational therapy on May 17, 2011, and received the last doses of of ixabepilone, bevacizumab, and carboplatin on June 14, 2011 (Cycle 2, Day 1).

15. ACCRUAL AND IND EXPERIENCE
Number of patients enrolled in NCI-sponsored clinical trials using ixabepilone = 2,631 and for bevacizumab = 33,172. There have been 4 other cases of bronchial hemorrhage reported to the NCI through AdEERS as serious adverse events for ixabepilone. Bronchial hemorrhage is an expected event for bevacizumab.

16. COMMENTS: The following were also administered:
No Prior Radiotherapy: Carboplatin: AUC = 6 IV over 30 minutes on Day 1 x 6 Cycles. Prior Radiotherapy: Carboplatin: AUC = 5 IV over 30 minutes on Day 1 x 6 Cycles.

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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