

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	FAX: 301-796-9845 301-796-9849
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1. IND NUMBER 59699 7921	2. AGENT NAME BMS 247550 (Ixabepilone) Bevacizumab (rhuMAb VEGF)	3. DATE December 23, 2010
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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 Therapeutics 2, 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# 1892974)	8b. AE GRADE: AE Grade 3: Left ventricular diastolic dysfunction
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9. PATIENT IDENTIFICATION 083-0086P-020	10. AGE 61 yrs	11. SEX Female
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12. DESCRIPTION OF ADVERSE EVENT
 The patient is a 61-year-old female with stage IV endometrial adenocarcinoma who developed grade 3 left ventricular (LV) diastolic dysfunction while on a phase 2 study using the investigational agents ixabepilone, bevacizumab, carboplatin, and temsirolimus. She was on a study arm that did not include temsirolimus. She began her first course of treatment on September 16, 2010, and received the last dose of ixabepilone, bevacizumab and carboplatin on October 27, 2010 (Cycle 3, Day 1). On November 9, 2010, the patient was weak and difficult to arouse. She was brought to the emergency room (ER), with difficulty breathing and worsening of her lower extremity (LE) edema. The physical examination revealed 83-85 % oxygen saturation on room air, crackles in the lung bases, and 2+ LE edema. A chest X-ray revealed bilateral pleural effusions. ECG revealed normal sinus rhythm and no abnormalities. The patient was placed on a nasal cannula which improved O₂ saturation to 98% and a dose of Lasix[®] was given. The next morning the patient denied any shortness of breath or chest pain. After diuresis, they were able to wean down her oxygen to two liters. The patient's B-type Natriuretic Peptide (BNP) was 200 pg/mL (reference range: 8-21 pg/mL) and it was felt that some of her symptoms might be secondary to congestive heart failure. An echocardiogram revealed an ejection fraction of 55-65%, mild left ventricular hypertrophy, elevated right ventricular systolic pressure, an atrial aneurysm, and a left pleural effusion. A chest CT scan showed no evidence of a pulmonary embolism and Lovenox[®] was stopped. The patient continued on DuoNeb treatments, as well as diuresis. By November 12, 2010, the patient was feeling better, only had occasional shortness of breath, and was able to ambulate in the room. However, she still required two liters of oxygen by nasal cannula in order to keep her oxygen saturation above 90%. The patient was discharged home that same day in stable condition. It is felt that her LE edema, pleural effusion, and hypoxia were the result of the LV diastolic dysfunction. Additional information has been requested from the site. There is a reasonable possibility that the experience may have been caused by the drug.

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. 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 September 16, 2010, and received the last doses of of ixabepilone, bevacizumab, and carboplatin on October 27, 2010 (Cycle 3, Day 1).

15. ACCRUAL AND IND EXPERIENCE
Number of patients enrolled in NCI-sponsored clinical trials using ixabepilone = 2,302 and for bevacizumab = 30,182. There have been 4 other cases of LV diastolic dysfunction reported to the NCI through AdEERS as serious adverse events for ixabepilone. LV diastolic dysfunction 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.