

**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<br><b>59699</b><br><b>7921</b> | 2. AGENT NAME<br><b>BMS 247550 (Ixabepilone)</b><br><b>Bevacizumab (rhuMAb VEGF)</b> | 3. DATE<br><b>September 26, 2011</b> |
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4. SPONSOR  
**Division of Cancer Treatment and Diagnosis, National Cancer Institute**

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| 5. REPORTER'S NAME, TITLE, AND INSTITUTION<br><b>Richard Piekarz, MD, PhD – Senior Investigator, Investigational Drug Branch, CTEP, DCTD, NCI</b><br><b>Helen Chen, MD - Associate Branch Chief for Investigational Therapeutics 3, Investigational Drug Branch, CTEP, DCTD, NCI</b> | 6. PHONE NUMBER<br><b>301-496-1196</b> |
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| 8a. PROTOCOL NUMBER (AE #)<br><b>GOG-0086P (AE# 1059673)</b> | 8b. AE GRADE: AE<br><b>Grade 4: Hypertension</b> |
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|---|--------------------------|--------------------------|
| 9. PATIENT IDENTIFICATION<br><b>126-0086P-002</b> | 10. AGE<br><b>77 yrs</b> | 11. SEX<br><b>Female</b> |
|---|--------------------------|--------------------------|

12. DESCRIPTION OF ADVERSE EVENT  
**The patient is a 77-year-old female with uterine cancer who experienced grade 4 hypertension 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 26, 2011, and received the last dose of bevacizumab on July 7, 2011 (Cycle 3, Day 1) and the last doses of ixabepilone and carboplatin on August 11, 2011 (Cycle 4, Day 1). On August 18, 2011, the patient was found sitting on the floor, and she was confused but responsive. She was brought to the emergency room, where she had a full-blown grand mal seizure. The patient was treated with Ativan® and Keppra®. Subsequently, she became unresponsive. The patient was then admitted to the Intensive Care Unit. She had hypertension with systolic pressure of 220 mmHg. With the treatment of Nipride®, nitropaste, and hydralazine, her BP came down to 160/70 mmHg. A brain MRI revealed focal areas of increased signal intensity involving the occipital lobes and to a lesser degree the parietal lobes, which involved the gray matter and subcortical white matter. The findings were concerning for a component of hypertensive encephalopathy (posterior reversible encephalopathy syndrome) and diffuse atrophy. 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/m<sup>2</sup> 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/m<sup>2</sup> 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 26, 2011, and received the last doses of of ixabepilone and carboplatin on August 11, 2011 (Cycle 4, Day 1), and the last dose of bevacizumab on July 7, 2011 (Cycle 3, day1).**

15. ACCRUAL AND IND EXPERIENCE  
**Number of patients enrolled in NCI-sponsored clinical trials using ixabepilone = 2,793 and for bevacizumab = 34,421. There have been 11 other cases of hypertension reported to the NCI through AdEERS as serious adverse events for ixabepilone. Hypertension 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.**