

## IND SAFETY REPORT: FOLLOW-UP #1

TO: *Division of Drug Oncology Products, Center for Drug Evaluation and Research, FDA*  
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1. IND NUMBER 59699 7921	2. AGENT NAME BMS 247550 (Ixabepilone, Ixempra®) Bevacizumab (rhuMAb VEGF)	3. DATE <b>November 15, 2011</b>
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
		7. EMAIL ADDRESS ctepsupportae@tech-res.com
8a. PROTOCOL NUMBER (AE #) GOG-0086P (AE#1360883)	8b. AE GRADE: AE Grade 4: Hypokalemia	
9. PATIENT IDENTIFICATION 083-0086P-034	10. AGE 72 yrs	11. SEX Female
12. PROTOCOL SPECIFIED Cycle = 21 days: No Prior Radiotherapy: Ixabepilone: 30 mg/m <sup>2</sup> IV over 1 hour on Day 1 x 6 cycles Carboplatin: AUC = 6 IV over 30 minutes on Day 1 x 6 cycles Bevacizumab: 15 mg/kg IV over 30-90 minutes on Day 1 (starting with cycle 2 for those patients entering post surgery) x 6 cycles Maintenance Therapy (Cycles 7+): Bevacizumab: 15 mg/kg IV over 30-90 minutes on Day 1 (Note: Patients continue to receive maintenance treatment until disease progression or until adverse events prohibit further therapy)  Prior Radiotherapy: Ixabepilone: 25 mg/m <sup>2</sup> IV over 1 hour on Day 1 x 6 cycles Carboplatin: AUC = 5 IV over 30 minutes on Day 1 x 6 cycles Bevacizumab: 15 mg/kg IV over 30-90 minutes on Day 1 (starting with cycle 2 for those patients entering post surgery) x 6 cycles Maintenance Therapy (Cycles 7+): Bevacizumab: 15 mg/kg IV over 30-90 minutes on Day 1 (Note: Patients continue to receive maintenance treatment until disease progression or until adverse events prohibit further therapy)		
13. TREATMENT RECEIVED AND DATES The patient started the investigational therapy on June 24, 2011, and received the last doses of ixabepilone, bevacizumab, and carboplatin on August 16, 2011 (Cycle 3, Day 1).		
14. DESCRIPTION OF ADVERSE EVENT The patient is a 72-year-old female with uterine cancer who experienced a grade 4 hypokalemia while on a phase 2 study using the investigational agents ixabepilone and bevacizumab in combination with carboplatin. On August 22, 2011, the patient was hospitalized for leakage of straw-colored ascites from her colostomy. She was removed from the protocol this same day, and on August 24, 2011, she was discharged. On August 29, 2011, the patient was re-admitted to the hospital for a prothrombin time (PT) greater than 200 seconds (reference range: 11.0-12.5 seconds). She had been taking between 5-7.5 mg of Coumadin® every other day. Laboratory results also revealed her serum potassium was decreased at 2.3 mEq/L (reference range: 3.5-5 mEq/L), in comparison to her baseline potassium of 4 mEq/L on June 22, 2011. Vitamin K and platelets were administered. On August 31, 2011, the patient's international normalized ratio (INR) was 1.7 (reference		

range for anticoagulant therapy: 2.0-3.0), and she was discharged on Coumadin® 5 mg daily. On September 6, 2011, the patient was re-admitted to the hospital for a fever of 102° F. Abdominal fluid cultures showed *Escherichia coli*, *Klebsiella pneumoniae*, *Streptococcus viridans*, and *Streptococcus B*. She was given vancomycin, IV fluids, 4 units of plasma, and 1 unit of packed red blood cells. The patient underwent an exploratory laparotomy for debridement of fascia, and received subsequent abdominal washes and wound V.A.C® care. On September 17, 2011, the patient's condition was stable and she was discharged. Additional information has been requested from the investigational site. There is a reasonable possibility that the experience may have been caused by the drug.

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using ixabepilone = 2,796, and the number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 35,152. There have been 23 other cases of hypokalemia reported to the NCI through AdEERS as serious adverse events for ixabepilone, and 207 other cases of hypokalemia reported to the NCI through AdEERS as serious adverse events for bevacizumab, as summarized in the table below.

Adverse Event	Grade	Attribution
<i>Ixabepilone</i>		
Hypokalemia (n=23)	4 3	2 Unrelated, 2 Unlikely, 1 Possible 6 Unrelated, 8 Unlikely, 4 Possible
<i>Bevacizumab</i>		
Hypokalemia (n=207)	4 3	12 Unrelated, 15 Unlikely, 3 Possible, 1 Probable 55 Unrelated, 78 Unlikely, 37 Possible, 6 Probable

16. ASSESSMENT

In this case, it is felt that a possible relationship exists between the event and the investigational agent ixabepilone, and an unlikely relationship exists between the event and the investigational agent bevacizumab.

	Hypokalemia
Ixabepilone	Possible
Bevacizumab	Unlikely
Carboplatin	Possible
Uterine cancer	Unlikely

17. COMMENTS

Medication taken at the time of the event included Coumadin®.

**BASED UPON FURTHER INVESTIGATION, THE SENIOR INVESTIGATOR HAS DECIDED THAT THIS EVENT IS EITHER EXPECTED OR NOT SERIOUS AND THUS DOES NOT REQUIRE EXPEDITED REPORTING.**