

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	
1. IND NUMBER 59699 7921	2. AGENT NAME BMS 247550 (Ixabepilone) Bevacizumab (rhuMab VEGF)	3. DATE July 16, 2010	
4. SPONSOR Division of Cancer Treatment and Diagnosis, National Cancer Institute			
5. REPORTER'S NAME, TITLE, AND INSTITUTION Richard Piekarz, MD – Senior Investigator, Investigational Drug Branch, CTEP, DCTD, NCI Kevin Conlon, MD-Senior Investigator, Investigational Therapeutics 3, Investigational Drug Branch, CTEP, DCTD, NCI		6. PHONE NUMBER 301-496-1196 7. FAX NUMBER 301-402-0428	
8a. PROTOCOL NUMBER (AE #) CALGB-40502 (AE# 1035078)	8b. AE GRADE: AE Grade 3: Cholecystitis		
9. PATIENT IDENTIFICATION 118490	10. AGE 57 yrs	11. SEX Female	
12. DESCRIPTION OF ADVERSE EVENT <p>The patient is a 57-year-old female with invasive breast carcinoma who experienced grade 3 cholecystitis while on a phase 3 study using the investigational agents ixabepilone and bevacizumab. She began her first course of treatment on December 4, 2009, and received the last dose of ixabepilone and bevacizumab on June 4, 2010 (Cycle 7, Day 15). On June 17, 2010 (Cycle 7, Day 28) the patient presented to the emergency room with an episode of chest pain, lasting 45-60 minutes associated with radiation down her ribs and abdomen. She also had ongoing right abdominal upper quadrant pain and right flank pain for the last 2 days. The patient became clammy, diaphoretic and had one episode of emesis. Laboratory results revealed an alkaline phosphatase of 192 units/L (reference range: 30-125 units/L), an AST of 175 units/L (reference range: 5-50 units/L), and an ALT of 70 units/L (reference range: 5-50 units/L). A CT of the chest showed positive cholecystitis with a gallbladder stent in place. The patient was diagnosed with acute cholecystitis and was admitted to the hospital. On June 18, 2010, the laboratory findings revealed an alkaline phosphatase of 273 units/L, an AST of 786 units/L and an ALT of 450 units/L. She was treated with bowel rest, IV fluids, IV antibiotics and analgesics. ERCP was attempted multiple times but the common bile duct could not be cannulated. On June 24, 2010, the patient's condition continued to improve and she was discharged in stable condition. Additional information has been requested from the site. There is a reasonable possibility that the experience may have been caused by the drug.</p>			
13. DOSE, ROUTE, AND SCHEDULE : Cycle: 28 Days Ixabepilone: 16 mg/m² IV over 1 hour on Days 1, 8 and 15 Bevacizumab: 10 mg/kg IV over 30-90 minutes on Days 1 and 15			
14. DATES OF TREATMENT The patient started the investigational therapy on December 4, 2009, and received the last doses of ixabepilone and bevacizumab on June 4, 2010 (Cycle 7, Day 15).			
15. ACCRUAL AND IND EXPERIENCE Number of patients enrolled in NCI-sponsored clinical trials using ixabepilone = 2101 and for bevacizumab = 27,798. There have been no other cases of cholecystitis reported to the NCI through AdEERS as serious adverse events for ixabepilone and have been 44 other cases of cholecystitis reported to the NCI through AdEERS as serious adverse events for bevacizumab.			
16. COMMENTS: 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). <u>DISCLAIMER</u> 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.			