



**DATE:** SEP 10 2010

**FROM:** Kevin Conlon, M.D, Investigational Drug Branch, CTEP, DCTD, NCI  
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**SUBJECT:** BMS 247550 (ixabepilone, Ixempra) and Bevacizumab (rhuMab VEGF) NCI IND Safety Report, AE # 1035078

**TO:** Investigators Using Ixabepilone (NSC 710428) and Bevacizumab (NSC 704865)

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. Please find attached a copy of an IND Safety Report recently submitted to the FDA for the CTEP-sponsored investigational agents ixabepilone and bevacizumab.

The following must be completed by all investigators using ixabepilone under NCI IND 59699 and/or bevacizumab under NCI INDs 7921 and 11460:

- Send a copy of the IND Safety Report to your Institutional Review Board (IRB) according to your local IRB's policies and procedures.
- File a copy of the IND Safety Report in your protocol file.

If your study is not covered under IND 59699 and/or INDs 7921 and 11460, it is strongly recommended that you follow the instructions above.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

Based on CTEP's assessment of the current information in light of previous experience with ixabepilone and bevacizumab, there does not appear to be a change in the risk-benefit ratio for ixabepilone and bevacizumab studies; therefore, CTEP is not requiring a protocol amendment at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The attached Adverse Events Assessment describes the adverse event (synopsis provided below), relevant previous experience under these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 57-year-old female with invasive breast carcinoma experienced grade 3 cholecystitis while on a randomized phase 3 study utilizing the investigational agents bevacizumab and ixabepilone.

## ADVERSE EVENTS ASSESSMENT

IND <b>59699</b> NSC <b>710428</b> <b>BMS 247550</b> (ixabepilone, <b>Ixempra</b> ) AE: <b>1035078</b>	<b>7921</b> <b>704865</b> <b>Bevacizumab (rhuMab</b> <b>VEGF)</b>	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: <b>#1</b> Event: <b>Gr. 3: Cholecystitis</b>  Protocol: <b>CALGB-40502</b>
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The patient is a 57-year-old female with invasive breast carcinoma who experienced cholecystitis while on a phase 3 trial utilizing the investigational agents bevacizumab and ixabepilone. She began the first course of the investigational therapy on December 4, 2009, receiving bevacizumab 10 mg/kg IV over 30-90 minutes on Days 1 and 15, and ixabepilone 16 mg/m<sup>2</sup> IV over 60 minutes on Days 1, 8 and 15, every 28 days. The patient received her last doses of bevacizumab and ixabepilone on June 4, 2010 (Cycle 7, Day 15).

The patient was diagnosed with invasive breast carcinoma in September 2003 and is status post right mastectomy, radiation, and multiple-agent systemic chemotherapy. She began the investigational treatment on December 4, 2009.

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. The patient became clammy; and diaphoretic, and had one episode of emesis. She also had been experiencing ongoing right upper quadrant abdominal pain and right flank pain for the previous 2 days that worsened with exposure to cold; or bending over, but improved with warm applications and was associated with indigestion. She was admitted to the hospital, and the study agent was held. Her abdomen was soft; there was right upper quadrant tenderness and guarding with palpation, and a positive Murphy's sign. It was noted that the patient had a history of urinary stents changed 7 days earlier with hematuria. 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. 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 conservatively with bowel rest, IV fluids, IV antibiotics, and analgesics. An attempt to place a percutaneous cholecystostomy tube was unsuccessful. The patient's LFTs gradually improved. MRCP showed a filling defect in the common bile duct with possible extrinsic compression secondary to acute inflammation in the retroperitoneal space. ERCP was attempted, but the common bile duct could not be cannulated. Because the LFTs had normalized, a sphincterotomy was not performed. The patient's condition continued to improve with her remaining pain free and afebrile, and her diet was slowly advanced. On June 27, 2010, she was discharged in stable condition on Augmentin<sup>®</sup> and Lortab<sup>®</sup>.

The patient's past medical/surgical history is significant for bilateral ureteral obstruction, ureteral stent placement, nephrostomy tube placement, and abdominal hysterectomy. Medications taken at the time of the event included multivitamins, MiraLax<sup>®</sup>, and Advil<sup>®</sup>.

There have been 43 cases of cholecystitis reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND and no cases of cholecystitis reported to the NCI as serious adverse events through AdEERS under the ixabepilone NSC and/or IND as summarized in the table below:

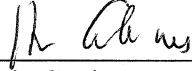
Adverse Event	Grade	Attribution
<b>Bevacizumab</b>		
Cholecystitis (n=43)	4	2 Possible
	3	1 Probable, 12 Possible, 7 Unlikely, 15 Unrelated
	2	1 Possible, 3 Unlikely, 2 Unrelated

To date, a total of 28,686 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC and 2,209 patients have been enrolled in NCI-sponsored clinical trials under the ixabepilone IND and/or NSC.

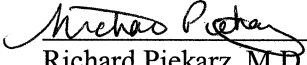
In this case, it is felt that a possible relationship exists between the event and ixabepilone, and that there is an unlikely relationship between the event and bevacizumab.

	<b>Cholecystitis</b>
<b>Ixabepilone</b>	Possible
<b>Bevacizumab</b>	Unlikely
<b>Invasive breast carcinoma</b>	Unrelated

Date: 8 Sept 2010

Signature:   
 Kevin Conlon, M.D.  
 (IDB Monitor for bevacizumab)

Date: 8 September 2010

Signature:   
 Richard Piekarz, M.D.  
 (IDB Monitor for ixabepilone)

If this assessment is changed, we will notify your office.

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