



DATE: APR 21 2011

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SUBJECT: BMS 247550 (ixabepilone, Ixempra) and Bevacizumab (rhuMab VEGF) NCI IND Safety Report, AE #2 1892974

TO: Investigators Using BMS 247550 (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 agent 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 this letter to your Institutional Review Board (IRB) according to your 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 this IND and/or NSC, and the total number of patients enrolled in trials under this IND and/or NSC.

A 61-year-old female with stage IV endometrial adenocarcinoma experienced grade 3 left ventricular ~~systemic~~ *diastolic* dysfunction while on a randomized phase 2 study utilizing the investigational agents bevacizumab, ixabepilone, carboplatin and temsirolimus.

This report has been amended to reflect revised information. Changes to the attached report are indicated by bold and italics (new information) and/or strikethrough (deleted information). If this assessment is changed further, we will notify your office. Please note that this modified report will be distributed to investigators.

ADVERSE EVENTS ASSESSMENT

IND 59699	7921	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #2 Event: Gr. 3: Left ventricular diastolic dysfunction Protocol: GOG-0086P
NSC 710428	704865	
BMS 247550 (ixabepilone, Ixempra[®])	Bevacizumab (rhuMAb VEGF)	
AE: 1892974		

This report has been amended to reflect revised information. Changes to the original summary are indicated by bold and italics (new information) and/or strikethrough (deleted information). If this assessment is changed further, we will notify your office. Please note that this modified report will be distributed to investigators.

The patient is a 61-year-old female with stage IV endometrial adenocarcinoma who experienced left ventricular systolic *diastolic* dysfunction while on a phase 2 trial utilizing the investigational agents bevacizumab in combination with ixabepilone, carboplatin, and temsirolimus. She was on a study arm that did not include temsirolimus. She began the first course of the investigational therapy on September 16, 2010, receiving for no prior radiotherapy (Cycles 1-6) bevacizumab 15 mg/kg IV over 30-90 minutes on Day 1 (starting with Cycle 2 for those patient entering post surgery), ixabepilone 30 mg/m² IV over 1 hour on Day 1 and carboplatin AUC = 6 IV over 30 minutes on Day 1 every 21 days. The patient received the last dose of ixabepilone, bevacizumab and carboplatin on October 27, 2010 (Cycle 3, Day 1).

The patient was diagnosed with stage IV endometrial adenocarcinoma in August 2010, and had no prior therapies. Note: The patient never received anthracyclin. She began the investigational treatment on September 16, 2010.

On November 9, 2010 (Cycle 3, Day 14), the patient was weak and difficult to arouse. She was brought to the emergency room (ER) for evaluation, with difficulty breathing and worsening of her lower extremity (LE) edema. Her blood pressure was 134/69 mmHg, pulse 62/minute. The physical examination revealed 83-85% oxygen saturation on room air, crackles in the lung bases, and 2+ bilateral LE edema. A chest X-ray revealed an increase in bilateral pleural effusions. ECG revealed normal sinus rhythm and no abnormalities. The patient was placed on a nasal cannula which improved the O₂ saturation to 98% and a dose of Lasix[®] was given. The following day, her oxygen was weaned down to two liters, after diuresis. The patient's B-type Natriuretic Peptide (BNP) was 200 pg/mL (reference range: 8-21 pg/mL). It was felt that her symptoms might be secondary to congestive heart failure. On November 10, 2010, an echocardiogram revealed an ejection fraction of 55-65%, mild left ventricular hypertrophy, elevated right ventricular/pulmonary artery systolic pressure, and an atrial septal aneurysm. A chest CT angiogram showed no evidence of pulmonary embolism but revealed bilateral pleural effusions that appeared to have increased in size when compared to a prior exam. Lovenox[®] was stopped. The patient continued on DuoNeb treatments, as well as diuresis.

By November 12, 2010, the patient continued to improve, with occasional shortness of breath. 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 day in stable condition. It is felt that her LE edema, pleural effusion, and hypoxia were the result of the LV diastolic dysfunction

The patient's past medical/surgical history is significant for diabetes, hypertension, pleural effusion, acute renal failure and status post blood transfusion anemia. Medications taken at the time of the event (admission to the ER) included Procardia[®], hydrochlorothiazide, Phenergan[®], potassium chloride, Lortab[®], and Ativan[®].

There have been 8 other cases of left ventricular diastolic dysfunction reported to the NCI as serious

adverse events through ADeERS under the ixabepilone NSC and/or IND as summarized in the table below: LV diastolic dysfunction is an expected event for bevacizumab.


Adverse Event	Grade	Attribution
<i>Ixabepilone</i>		
Left ventricular diastolic dysfunction (n=8)	3 2	1 Unrelated, 2 Unlikely, 1 Possible 1 Unlikely, 3 Possible

To date, a total of 31,563 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC and 2,390 patients have been enrolled in NCI-sponsored clinical trials under the ixabepilone IND and/or NSC.

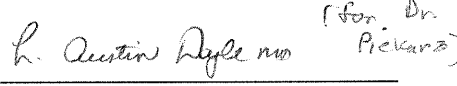
In this case, it is felt that a possible relationship exists between the event and bevacizumab and that there is an unlikely relationship between the event and ixabepilone.

	Left ventricular diastolic dysfunction
Ixabepilone	Unlikely
Bevacizumab	Possible
Carboplatin	Unlikely
Endometrial adenocarcinoma	Unlikely
History of hypertension	Possible

Date: 4/19/11

Signature: 
Helen Chen, M.D.
(IDB Monitor for bevacizumab)

Date: 4/19/11

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

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

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