



OCT 18 2011

**DATE:****FROM:** Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
Richard Piekarz, M.D., Ph.D., Investigational Drug Branch, CTEP, DCTD, NCI**SUBJECT:** BMS 247550 (ixabepilone, Ixempra<sup>®</sup>) and Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE # 1059673**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 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) of record 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 these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 77-year-old female with uterine cancer experienced grade 4 recurrent hypertension, grade 3 reverse posterior leukoencephalopathy syndrome (RPLS), and grade 3 cerebrovascular accident (CVA) while on a phase 2 study utilizing the investigational agents bevacizumab and ixabepilone in combination with carboplatin.

## ADVERSE EVENTS ASSESSMENT

IND <b>59699</b> NSC <b>710428</b> <b>BMS 247550</b> (ixabepilone, Ixempra®)	7921 704865 <b>Bevacizumab (rhuMAb</b> <b>VEGF)</b>	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: <b>Gr. 4: Hypertension</b> <b>Gr. 3: Reverse posterior</b> <b>leukoencephalopathy</b> <b>syndrome</b> <b>Gr. 3 Cerebrovascular accident</b>
AE: <b>1059673</b>	Protocol: <b>GOG-0086P</b>	

The patient is a 77-year-old female with uterine cancer who experienced recurrent hypertension, reverse posterior leukoencephalopathy syndrome (RPLS), and cerebrovascular accident (CVA) while on a phase 2 trial utilizing the investigational agents bevacizumab and ixabepilone in combination with carboplatin. The planned protocol therapy the patient was assigned to is as follows:

Cycle = 21 days  
 No Prior Radiotherapy  
 Ixabepilone: 30 mg/m<sup>2</sup> IV over 1 hr 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 pts 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)

The patient was diagnosed with uterine cancer in April 2011. She is status post total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and radical dissection with tumor debulking. The patient has had baseline hypertension for over thirty years, but it was well-controlled. Prior to starting the study, the patient was on prazosin, but it is documented in a later progress note that this was changed in May 2011 (new medication not provided). She began the investigational therapy on May 26, 2011, and received the last doses of ixabepilone and carboplatin on August 11, 2011 (Cycle 4, Day 1), and the last dose of bevacizumab on July 7, 2011 (Cycle 3, Day 1).

On July 18, 2011 (Cycle 3, Day 12), the patient was admitted to the hospital for a 1-week history of dizziness. She also had hypertension with BP of 220/90 mmHg. At this time, the patient was taking prazosin, Lasix®, and metoprolol; she was non-compliant with prazosin. Prazosin was held, and clonidine was added to her regimen. A brain MRI scan revealed signal changes in both occipital and parietal occipital regions bilaterally, suggestive of posterior reversible encephalopathy syndrome (PRES/RPLS). On July 23, 2011, the patient was discharged when she got better. On August 2, 2011, the patient was admitted again for dizziness, confusion, shortness of breath, and hypertension. She was found to have acute bronchitis with bronchospasm that resulted in acute respiratory failure. The patient was treated with a hand-held nebulizer, IV steroids, Levaquin®, and lisinopril. She was discharged the next day in stable condition. This was previously reported as SAE # 1266849.

The patient was taken off bevacizumab since July 7, 2011, but continued chemotherapy. On August 18, 2011 (Cycle 4, Day 8), the patient was found sitting on the floor, and she was confused but responsive. She was also noted to have her eyes rolling. The patient was taken to the emergency room, where she had a full-blown grand mal seizure. The patient was treated with Ativan® and Kepra®. Subsequently, she

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**AE #1059673**

became unresponsive. The patient was then admitted to the Intensive Care Unit. She had hypertension with systolic pressure of 220 mmHg. Upon treatment with Nipride®, nitropaste, and hydralazine, her BP came down to 160/70 mmHg. The patient was afebrile. She had mild tachycardia (HR 100 beats/min), but her heart rate and rhythm were regular. Laboratory tests revealed that her brain natriuretic peptide elevated to 2060 pg/mL (reference range: 0-100 pg/mL). Her blood gases and pH were within normal range. A brain CT scan did not show any acute infarct, hemorrhage, or tumor. An EEG revealed evidence of a severe diffuse encephalopathy consistent with a hypoxic ischemic injury. 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/PRES and diffuse atrophy. The patient also had proteinuric acute renal insufficiency with urine protein level of 300 mg/24 hr (reference range: 50-80 mg/24 hr); her blood urea nitrogen and creatinine were 34 mg/dL (reference range: 10-20 mg/dL) and 2.07 mg/dL (reference range: 0.5-1.1 mg/dL), respectively. The renal insufficiency was considered due to hypertensive urgency and the chemotherapy. During hospitalization, the patient also complained about poor vision. On August 24, 2011, a MRI of the brain revealed an acute infarct involving the posterior right parietal lobe, posterior right temporal lobe, and both occipital lobes, and cortical atrophy. A physical examination found that her eyes gazed right; she did not track images to her left, but her eyes were full in movement to the left and right; her pupils were equally reactive to light. She was considered to have cortical blindness secondary to bilateral occipital infarcts. Her condition slowly improved with blood pressure well controlled; she became alert and oriented, but she still had visual issues, especially with depth perception. On August 31, 2011, the patient was discharged to the rehabilitation unit of the hospital.

The patient's past medical/surgical history is significant for pneumonia, hypertension, gout, morbid obesity, right hip arthroplasty, thrombocytopenia secondary to chemotherapy, and chronic kidney disease. Medications taken at the time of the event included oxycodone, allopurinol, vitamin D3, Cheratussin AC® oral syrup, Advair Diskus®, hydralazine, metoprolol, Zofran®, and prochlorperazine.

Hypertension, RPLS and CVA are all expected events for bevacizumab but are being reported because the recurrence/persistence of hypertension and PRES/CVA after discontinuation of bevacizumab are rarely seen. There have been 11 other cases of hypertension, 2 cases of RPLS and 5 cases of encephalopathy reported to the NCI as serious adverse events through AdEERS under the ixabepilone NSC and/or IND as summarized in the table below:

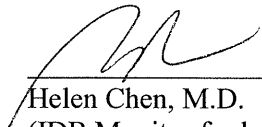
Adverse Event	Grade	Attribution
<b>Ixabepilone</b>		
Hypertension (n=11)	4	1 Unlikely
	3	4 Possible, 2 Unlikely
	2	2 Possible, 2 Unlikely
RPLS (n=2)	4	1 Probable
	3	1 Probable
Encephalopathy (n=5)	4	1 Unrelated, 2 Possible
	3	2 Possible

To date, a total of 34,421 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab INDs and/or NSC, and 2,793 patients have been enrolled in NCI-sponsored clinical trials under the ixabepilone IND and/or NSC.

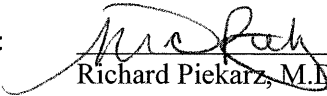
In this case, it is felt that a possible relationship exists between the events and bevacizumab and that there is an unlikely relationship between the events and ixabepilone.

	<b>Hypertension</b>	<b>RPLS</b>	<b>CVA</b>
<b>Ixabepilone</b>	Unlikely	Unlikely	Unlikely
<b>Bevacizumab</b>	Possible	Possible	Possible
<b>Carboplatin</b>	Unlikely	Unlikely	Unlikely
<b>Uterine cancer</b>	Unrelated	Unrelated	Unrelated

Date: 10/14/11

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

Date: 11 Oct 11

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

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

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