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SUBJECT: BMS 247550 (ixabepilone, Ixempra) and Bevacizumab (fhumaMab VEGF) NCI IND Safety Report, AE # **1839475**

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 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 this IND and/or NSC, and the total number of patients enrolled in trials under this IND and/or NSC.

A 69-year-old female with invasive breast carcinoma experienced a grade 3 seizure while on a randomized phase 3 study utilizing the investigational agents bevacizumab and ixabepilone.

ADVERSE EVENTS ASSESSMENT

IND 59699	7921	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 3: Seizure Protocol: CALGB-40502
NSC 710428	704865	
BMS 247550 (ixabepilone, Ixempra)	Bevacizumab (rhUMAb VEGF)	
AE: 1839475		

The patient is a 69-year-old female with invasive breast carcinoma metastatic to the lung and no prior history of seizures who experienced a seizure while on a phase 3 trial utilizing the investigational agents bevacizumab and ixabepilone. She began the first course of the investigational therapy on April 27, 2009, receiving bevacizumab 10 mg/kg IV over 30-90 minutes on Days 1 and 15, and ixabepilone 16 mg/m² IV over 1 hour on Days 1, 8 and 15. The patient received her first and only dose of bevacizumab on April 27, 2009 (Cycle 1, Day 1) and the last dose of ixabepilone on May 4, 2009 (Cycle 1, Day 8).

The patient was initially diagnosed with invasive breast carcinoma in July 2004 and has undergone prior surgery (August 2004) in addition to chemotherapy with multiple agents (September 2004 to October 2004) followed by radiation therapy (November 2004 to December 2004). She began the investigational treatment on April 27, 2009.

On May 7, 2009 (Cycle 1, Day 11), the patient presented to the Emergency Department (ED) after suffering a single generalized tonic-clonic seizure that lasted for one minute. The incident was witnessed by her daughter who reported that the patient lost consciousness while standing outside a store and fell down, abrading her left knee and shin. Upon arrival at the ED, she was conscious and back to her baseline with no signs of confusion, dysphasia, headache, paresis, paralysis or visual changes. She was mildly hyponatremic and hypokalemic with a sodium of 134 mmol/L (reference range: 135-145 mmol/L) and potassium of 3.3 mmol/L (reference range: 3.5-5.0 mmol/L). Her cardiac enzymes and CBC were unremarkable.. She was treated with fosphenytoin in the ED. A CT scan of the head and brain without contrast showed no acute intracranial findings. A portable chest x-ray revealed a 5 cm mass within the left middle lung unchanged from February 2009 and a prominent left hilum. On May 8, 2009 (Cycle 1, Day 12), an MRI of the brain with and without contrast revealed no abnormal mass, acute intracranial process or enhancement except for a few tiny scattered white matter hyperintensities likely within normal limits for her age. After a neurology consult, the patient was started on Keppra[®] 500 mg PO bid. The patient also received Ativan[®] during her hospital stay. The consulting neurologist suspected that the seizure was caused by bevacizumab. An EEG performed subsequently revealed no abnormalities. She did not have any further seizures and was reportedly stable. She was discharged home on May 9, 2009 (Cycle 1, Day 13).

The patient's past medical/surgical history is significant for hypertension and hypercholesterolemia. Medications taken at the time of the event included Claritin[®], Lipitor[®] and lisinopril.

There have been 47 cases of seizure reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND and 5 cases of seizure reported to the NCI as serious adverse events through AdEERS under the ixabepilone NSC and/or IND as summarized in the table below:

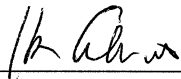
Adverse Event	Grade	Attribution
Bevacizumab (NSC 704865)		
Seizure (n=47)	4	2 Possible, 3 Unlikely, 1 Unrelated
	3	1 Probable, 15 Possible, 10 Unlikely, 6 Unrelated
	2	2 Possible, 3 Unlikely, 4 Unrelated
Ixabepilone (NSC 710428)		
Seizure (n=5)	3	1 Unlikely, 3 Unrelated
	2	1 Unlikely

To date, a total of 21,442 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab NSC and 1,785 patients have been enrolled in NCI-sponsored clinical trials under the ixabepilone NSC.

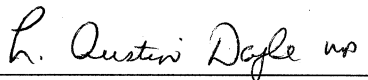
In this case, it is felt that a possible causal relationship between the event and both ixabepilone and bevacizumab therapy cannot be excluded.

	Seizure
Ixabepilone	Possible
Bevacizumab	Possible
Invasive breast carcinoma	Unrelated

Date: 8 July 2009

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

Date: 7/8/09

Signature: 
L. Austin Doyle, M.D.
(IDB Monitor for ixabepilone)

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

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