

**IND SAFETY REPORT: INITIAL WRITTEN REPORT****TO: Division of Drug Oncology Products, Center for Drug Evaluation and Research, FDA****FAX: 301-796-9845**

1. IND NUMBER <b>58443</b>	2. AGENT NAME <b>PS-341 (bortezomib; Velcade)</b>	3. DATE <b>August 12, 2009</b>
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**4. SPONSOR**  
**Division of Cancer Treatment and Diagnosis, National Cancer Institute**

<b>5. REPORTER=S NAME, TITLE, AND INSTITUTION</b> <b>John Wright, MD, Ph.D. – Associate Branch Chief for Investigational Therapeutics 2, Investigational Drug Branch, CTEP, DCTD, NCI</b>	<b>6. PHONE NUMBER</b> <b>301-496-1196</b>
	<b>7. FAX NUMBER</b> <b>301-402-0428</b>

**8. PROTOCOL NUMBER (AE #)**  
**CALGB-10502 (AE# 1887123)**

<b>9. PATIENT IDENTIFICATION</b> <b>116117</b>	<b>10. AGE</b> <b>73</b>	<b>11. SEX</b> <b>Female</b>
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**12. DESCRIPTION OF ADVERSE EVENT**  

The patient was a 73-year-old female with acute myeloid leukemia who experienced grade 5 left ventricular diastolic dysfunction while on a phase 2 study using the investigational agent bortezomib in combination with daunorubicin and cytarabine. She began the first course of the remission induction therapy on June 1, 2009, and she received the last dose of bortezomib on June 11, 2009 (Cycle 1, Day 11). On June 5, 2009 (Cycle 1, Day 5), the patient developed dyspnea with an oxygen saturation of 88% on room air. The patient was placed on a 100% non-rebreather mask and placed on Lasix<sup>®</sup>. On June 6, 2009 (Cycle 1, Day 6), the patient had a potassium level of 2.3 mmol/L (reference range: 3.5-5.1 mmol/L); she received supplemental potassium, and on June 9, 2009, the potassium level was within normal range. On June 13, 2009, the patient experienced a change in mental status. She was able to follow simple commands but was somnolent. The blood pressure was 181/100 mmHg, and Vasotec<sup>®</sup> was administered. A CT scan of the brain was performed and showed a new right sylvian subarachnoid hemorrhage. Bilateral parietal occipital lucencies suggested hypertensive encephalopathy. The patient was transferred to the MICU for monitoring and was placed on a Cardene<sup>®</sup> drip to control the hypertension. On June 19, 2009, the patient was alert, oriented and able to move all extremities. A chest X-ray revealed pulmonary edema. The physical examination revealed frothy, bloody secretions and congestion throughout bilateral lungs fields. She was placed on a bipap machine and later intubated. On June 22, 2009, the patient became hypotensive and was placed on vasopressors. The neurologic examination revealed fixed and dilated pupils. On June 24, 2009, her medications were discontinued, and the patient expired on the same day. Additional information has been requested. There is a reasonable possibility that the experience may have been caused by the drug.

**13. DOSE, ROUTE, AND SCHEDULE**  
**Remission Induction Therapy**  
**Bortezomib 1.3 mg/m<sup>2</sup> IVB over 3-5 seconds on Days 1, 4, 8, and 11****14. DATES OF TREATMENT**  
**The patient began the investigational therapy on June 1, 2009, and received the last dose of bortezomib on June 11, 2009 (Cycle 1, Day 11).****15. ACCRUAL AND IND EXPERIENCE**  
**Number of patients enrolled in NCI-sponsored clinical trials using bortezomib = 2891.**  
**There have been two other cases of left ventricular diastolic dysfunction reported to the NCI through AdeERS as serious adverse events for PS-341.****16. COMMENTS**  
**The following was also administered on this protocol:**  
**Daunorubicin: 60 mg/m<sup>2</sup> IV on Days 1-3**  
**Cytarabine: 100 mg/m<sup>2</sup> IV CIV on Days 1-7****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).****DISCLAIMER 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.**

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