




**DATE:** January 13, 2009

**FROM:** John Wright, M.D., Ph.D., Investigational Drug Branch, CTEP, DCTD, NCI 

**SUBJECT:** PS-341 (bortezomib; Velcade®) NCI IND Safety Report, AE# 1567424

**TO:** Investigators Using Bortezomib (NSC 681239)

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 bortezomib.

The following must be completed by all investigators using bortezomib under NCI IND 58443:

- 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 58443, 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 bortezomib, there does not appear to be a change in the risk-benefit ratio for bortezomib 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(s) (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 19-year-old male with treatment-related acute myeloid leukemia experienced grade 4 hyperbilirubinemia, grade 4 hypokalemia, grade 3 ARDS, and subsequently died from renal failure while on a phase 2 trial utilizing the investigational agent bortezomib in combination with cytarabine and etoposide.

## ADVERSE EVENTS ASSESSMENT

IND <b>58443</b> NSC <b>681239</b> <b>PS-341 (bortezomib; Velcade®)</b>	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: <b>#1</b> Event: <b>Gr. 5: Renal failure</b> <b>Gr. 4: Bilirubin</b> <b>Gr. 4: Potassium, serum-low</b> <b>Gr. 3: Adult Respiratory Distress Syndrome (ARDS)</b>
AE: <b>1567424</b>	Protocol: <b>AAML07P1</b>

The patient was a 19-year-old male with treatment-related acute myeloid leukemia (AML) who developed hyperbilirubinemia, hypokalemia, ARDS, and subsequently died from renal failure while on a phase 2 pilot study utilizing the investigational agent bortezomib in combination with cytarabine and etoposide. He began his first course of treatment on October 1, 2008 (Day 0), receiving bortezomib 1 mg/m<sup>2</sup> IV bolus on Days 1, 4, and 8, cytarabine 30-70 mg/m<sup>2</sup> (age-based dosing) IT on Day 0, cytarabine 1000 mg/m<sup>2</sup> IV over 1 hour, every 12 hours, on Days 1-5, and etoposide 150 mg/m<sup>2</sup> over 1 hour on Days 1-5, every 28 days. He received the last dose of bortezomib on October 5, 2008 (Cycle 1, Day 4), and the last doses of cytarabine and etoposide on October 6 (Cycle 1, Day 5).

The patient was initially diagnosed with metastatic osteosarcoma of the right humerus in 2005. On August 19, 2005, he underwent a limb salvage procedure which showed 98% tumor necrosis and in September 2005, he underwent bilateral thoracotomies to remove pulmonary nodules. He then received multiple-agent systemic chemotherapy. In December 2007, his follow-up scans were negative for disease; however, he was found to be pancytopenic. On January 2, 2008, a bone marrow biopsy revealed myelodysplastic syndrome, hypocellular refractory anemia with excess blasts (12%). On April 25, 2008, he received an 8/8 HLA-matched unrelated allogeneic bone marrow transplant, but despite that he still developed AML. On September 30, 2008, the patient was admitted to the hospital and began the investigational therapy on October 1, 2008.

On October 3, 2008 (Cycle 1, Day 2), the patient became febrile and was started on clindamycin, amikacin, piperacillin, Ambisome®, and acyclovir. Over the next few days while undergoing treatment, he developed hypotension, tachycardia, severe bone pain, worsening hypoxia, electrolyte abnormalities, and renal insufficiency, requiring oxygen, fluid, and blood product support. On October 7, 2008, he developed respiratory distress and was transferred to the intensive care unit and placed on oxygen via a non-rebreather mask. The following day, his chest X-ray showed increasing perihilar airspace disease and persistent diffuse reticular opacities, and he was started on Solu-Medrol®, Bactrim®, and Zithromax®. On October 10, 2008, his chest X-ray showed worsening airspace disease, suggestive of pulmonary edema, his creatinine was 3.3 mg/dL (reference range: 0.3-1.2 mg/dL), and his urine output was decreased. He was intubated, sedated, placed on vasopressor support, and started on continuous venovenous hemofiltration (CVVH). Bronchoalveolar lavage cultures were obtained, and *Mycobacterium* was isolated by polymerase chain reaction assay; all other cultures were negative. Additional laboratory values are listed in the table below. On October 15, 2008 (Cycle 1, Day 14), the patient underwent a bone marrow biopsy which was consistent with persistent acute myeloid leukemia. An AFB stain was performed on biopsy section and was negative for microorganisms. He had an increased bilirubin of 14.3 mg/dL (reference range: 0.1-1.3 mg/dL). On October 17, 2008, his chest X-ray showed resolution of his pulmonary congestion with some persisting mild interstitial prominence, and he was extubated and placed on oxygen via facemask. He continued to be oliguric requiring dialysis. On October 18, 2008, his chest X-ray showed fine subcentimeter nodular densities throughout the lungs bilaterally. On October 20, 2008 (Cycle 1, day 19), after discussion with the patient's family regarding the patient's poor prognosis and worsening condition, the patient's care was changed to comfort measures only. He was taken off of CVVH, and he died the following day. No autopsy was performed.

Pertinent laboratory values:

	9/29/08 Baseline	10/4/08 C1, D3	10/5/08 C1, D4	10/7/08 C1, D6	10/8/08 C1, D7	10/14/08 C1, D13	10/15/08 C1, D14	10/20/08 C1, D19
<b>Hematology</b>								
<b>WBC</b> (reference range: 4.5-11.0 K/ $\mu$ L)	8.1	5.8	2.8	0.6	0.2	0.1	0.1	0.5
<b>Hemoglobin</b> (reference range: 13.5-17.5 g/dL)	10.4	9.0	9.0	10.0	9.5	10.7	10.8	10.5
<b>Platelets</b> (reference range: 150-450 K/ $\mu$ L)	66	28	64	34	18	30	58	59
<b>Chemistries</b>								
<b>Creatinine</b> (reference range: 0.3-1.2 mg/dL)	0.8	0.8	0.7	1.4	1.5	2.5	1.9	2.3
<b>Bilirubin-total</b> (reference range: 0.1-1.3 mg/dL)	0.1	0.5	*	*	*	*	14.3	17.1
<b>Potassium</b> (reference range: 3.5-5.0 mmol/L)	4.3	3.9	3.2	2.3	2.6	3.8	3.8	3.4
<b>Calcium</b> (reference range: 8.4-10.5 mg/dL)	8.9	7.9	6.7	7.9	*	*	*	*
<b>Magnesium</b> (reference range: 1.7-2.4 mEq/L)	1.8	1.7	1.1	1.7	1.6	2.7	2.4	2.2
<b>GGT</b> (reference range: 3-35 U/L)	*	*	*	136	*	*	177	91

\* = Not Done

The patient's past medical/surgical history is significant for osteosarcoma of the right humerus as described above, tonsillectomy, and pressure equalization tube placement. Medications taken at the time of the event included gabapentin, Prevacid<sup>®</sup>, Pen VK<sup>®</sup>, voriconazole, valganciclovir, Celexa<sup>®</sup>, and Claritin<sup>®</sup>.

There have been 17 other cases of renal failure, 23 other cases of increased bilirubin, 26 other cases of hypokalemia, 1 other case of ARDS and one other case of respiratory distress reported to the NCI as serious adverse events through AdEERS under the bortezomib NSC and/or IND, as shown in the table below:

Adverse Event	Grade	Attribution
Renal failure (n = 17)	4	2 Possible, 1 Unrelated
	3	1 Possible, 12 Unlikely, 1 Unrelated
Bilirubin (n = 23)	4	2 Possible, 5 Unlikely, 1 Unrelated
	3	6 Unlikely, 4 Unrelated
	2	3 Possible, 2 Unlikely,
Hypokalemia (n = 26)	4	1 Possible, 5 Unlikely
	3	7 Possible, 9 Unlikely, 3 Unrelated
	1	1 Unrelated
ARDS (n = 1)(respiratory distress n=1)	5	ARDS-1 Possible Respiratory distress- 1 Unlikely

A total of 2,646 patients have been enrolled in NCI-sponsored clinical trials under the bortezomib NSC.

In this case, it is believed that a possible causal relationship between the events and bortezomib exists.

	<b>Renal failure</b>	<b>Bilirubin</b>	<b>Potassium</b>	<b>ARDS</b>
<b>Bortezomib</b>	Possible	Possible	Possible	Possible
<b>Cytarabine</b>	Possible	Possible	Possible	Possible
<b>Etoposide</b>	Possible	Possible	Possible	Unlikely
<b>Treatment-related AML</b>	Unlikely	Unlikely	Unlikely	Unlikely

Date: 1/15/09

Signature: John Wright M.D.  
John Wright, M.D. Ph.D.  
(IDB Monitor for Bortezomib)

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

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