



DATE: March 18, 2010
FROM: John Wright, M.D., Ph.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: PS-341 (bortezomib; Velcade®) NCI IND Safety Report, AE# 1649799
TO: Investigators Using PS-341 (bortezomib; Velcade®) (NSC 681239)

JW
5/6/10

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 69-year-old female with acute myeloid leukemia experienced grade 4 adult respiratory distress syndrome (ARDS), grade 4 hypoxia, and a grade 4 catheter-related infection while on a phase 2 trial utilizing the investigational agent bortezomib in combination with cytarabine and daunorubicin.

ADVERSE EVENTS ASSESSMENT

IND 58443 NSC 681239 PS-341 (bortezomib; Velcade®)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 4: Adult Respiratory Distress Syndrome (ARDS) Gr. 4: Hypoxia Gr. 4: Infection: Catheter-related
AE: 1649799	Protocol: CALGB-10502

The patient was a 69-year-old female with acute myeloid leukemia (AML) who developed adult respiratory distress syndrome (ARDS), hypoxia, and catheter-related infection while on a phase 2 trial utilizing the investigational agent bortezomib in combination with cytarabine and daunorubicin. She began her first course of treatment on November 20, 2009, receiving bortezomib 1.3 mg/m² IV bolus over 3-5 seconds on Days 1, 4, 8, and 11, cytarabine 100 mg/m² CIV on Days 1-7, and daunorubicin 60 mg/m² IV on Days 1-3 for Cycle 1. In patients with residual disease, this was to be followed in Cycle 2 by bortezomib 1.3 mg/m² IV bolus over 3-5 seconds on Days 1 and 4, cytarabine 100 g/m² CIV on Days 1-5, and daunorubicin 60 mg/m² IV on Days 1-2. She received her last dose of bortezomib on November 30, 2009 (Cycle 1, Day 11), her last dose of cytarabine on November 27, 2009 (Cycle 1, Day 8), and her last dose of daunorubicin on November 22, 2009 (Cycle 1, Day 3).

The patient was diagnosed with AML in November 2009, and has had no prior therapy. She began the investigational therapy on November 20, 2009, with normal spirometry results.

On November 16, 2009, the patient was admitted for evaluation and management of AML. Her baseline chest X-ray was unremarkable. A MUGA scan on November 17, 2009, was within normal limits with a left ventricular ejection fraction of 66%. On November 19, 2009, she developed somnolence from oxycodone which was administered to tolerate the pain associated with the Groshong® catheter placement the previous day. The catheter site was unremarkable in appearance; and the pain resolved the next day in time to begin the investigational therapy. On November 23, 2009 (Cycle 1, Day 4), the patient had no complaints and an unremarkable physical examination with diminished, but clear, lung sounds. On November 24, 2009 (Cycle 1, Day 5), however, she developed chest heaviness, dyspnea, nausea, and hypoxia with an oxygen saturation of 80% on room air. Her lungs exhibited coarse, bibasilar crackles on examination. She had experienced periods of hypotension since admission for which her labetalol had been held. The results of an ECG and cardiac enzymes were normal. However, the chest X-ray showed low left lung volume with elevated left hemidiaphragm, and she was placed on 2 L of supplemental oxygen. She was already on Valtrex®. By the next day, the dyspnea and chest heaviness had resolved, and her oxygen saturation was 93% on room air. Her lung sounds were again diminished but clear. She was started on posaconazole prophylactically and Zofran® and promethazine for intermittent nausea and vomiting.

On November 27, 2009 (Cycle 1, Day 8), the patient complained of continual bouts of diarrhea and fatigue with a BP of 98/52 mmHg. *Clostridium difficile* cultures were sent, and Questran® was added. Later that night she developed a temperature of 100.2° F. *Clostridium difficile* cultures were negative, and her diarrhea improved the next day. Labetolol was restarted on November 30, 2009, for hypertension, and posaconazole was held for transaminitis.

On December 1, 2009 (Cycle 1, Day 12), the patient complained of left upper extremity weakness, tingling, and numbness which she claimed had been present for a few days, and ongoing nausea, vomiting, and diarrhea. The CT scan of the head showed no intracranial hemorrhage, an MRI of the brain revealed no acute infarct and evidence of chronic small vessel ischemic disease, and an MRI of the cervical spine revealed a possible atypical hemangioma at the level of C3 vertebral body, metastatic disease could not be excluded. She was placed on telemetry.

At 2AM on December 2, 2009 (Cycle 1, Day 13), the patient became unresponsive, collapsed, and developed agonal respirations. She was transferred to the ICU, intubated, and placed on mechanical ventilation. Physical examination revealed restlessness, diffuse mottling, and a fever of 103°F. The patient was sedated on high-dose propofol and given IV Levophed® for vasopressor support. The final blood and central line cultures were positive for gram-negative bacilli and gram-positive bacilli: *Serratia marcescens*, *Klebsiella pneumoniae*, and *Clostridium septicum*. The central line was removed, and she was started on amikacin, caspofungin, Zosyn®, and vancomycin. An echocardiogram revealed global left ventricular hypokinesis with an estimated ejection fraction of 25-30%. The patient's condition deteriorated, she was made DNR/comfort care, and she expired on the same day. An autopsy was not performed.

The patient's past medical/surgical history is significant for hypertension, hypercholesterolemia, anxiety/depression, cervical cancer status post hysterectomy, cholecystectomy, appendectomy, and tonsillectomy. Her family history is significant for leukemia in her mother, thrombocytopenia in two brothers, and colon cancer in her son. Medications taken at the time of the event included valacyclovir, Celexa®, Xanax®, simvastatin, and labetalol.

There have been 5 other cases of ARDS, 58 other cases of hypoxia, and 10 other cases of catheter-related infection 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
ARDS (n=5)	5	2 Possible, 1 Unlikely
	3	2 Possible
Hypoxia (n=58)	5	1 Possible, 2 Unlikely
	4	2 Possible, 5 Unlikely, 1 Unrelated
	3	1 Probable, 6 Possible, 31 Unlikely, 6 Unrelated
Infection: Catheter-related (n=10)	3	1 Possible, 1 Unlikely, 1 Unrelated
	3	3 Possible, 5 Unlikely, 2 Unrelated

A total of 3,073 patients have been enrolled in NCI-sponsored clinical trials under the bortezomib IND and/or NSC.

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

	ARDS	Hypoxia	Infection: Catheter-related
Bortezomib	Possible	Possible	Possible
Cytarabine	Possible	Possible	Possible
Daunorubicin	Possible	Possible	Possible
AML	Possible	Possible	Possible

Date: 3/19/10

Signature: John Wright M.D.
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(IDB Monitor for bortezomib)

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

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