



DATE: DEC 06 2010
FROM: John Wright, M.D., Ph.D., Investigational Drug Branch, CTEP, DCTD, NCI (JW)
SUBJECT: PS-341 (bortezomib; Velcade®) NCI IND Safety Report, AE# 1826902
TO: Investigators Using PS-341 (bortezomib; Velcade®) (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) (hypoxia 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 67-year-old male with acute myeloid leukemia (AML) experienced grade 4 hypoxia while on a phase 2 trial utilizing the investigational agents bortezomib in combination with cytarabine and daunorubicin.

ADVERSE EVENTS ASSESSMENT

IND 58443 NSC 681239 PS-341 (bortezomib; Velcade®) AE: 1826902	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr 4: Hypoxia Protocol: CALGB-10502
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The patient was a 67-year-old male with acute myeloid leukemia (AML) who experienced hypoxia and subsequently expired due to pneumonia while on a phase 2 trial utilizing the investigational agent bortezomib in combination with cytarabine and daunorubicin. He began his first course of treatment on January 26, 2010, 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. The patient was to receive bortezomib 1.3 mg/m² IV bolus over 3-5 seconds on Days 1 and 4, cytarabine 100 mg/m² CIV on Days 1-5, and daunorubicin 60 mg/m² IV on Days 1-2 for Cycle 2. He received his last dose of bortezomib on February 16, 2010 (Cycle 1, Day 22), cytarabine on February 17, 2010 (Cycle 1, Day 23), and daunorubicin on February 14, 2010 (Cycle 1, Day 20).

The patient was diagnosed with AML in January 2010 and has had no prior therapy. He was previously diagnosed with chronic lymphocytic leukemia (CLL) in 2003 and treated with Rituxan®. The patient began the investigational therapy on January 26, 2010.

On February 2, 2010, (Cycle 1, Day 8), the patient was admitted to the hospital due to febrile neutropenia. On February 10, 2010 (Cycle 1, Day 16), a CT scan of the chest revealed a spiculated, nodular area of the consolidation in the lateral basal segment of the right lower lobe measuring 4.9 × 4.5 cm and surrounding ground glass airspace disease. These findings were compatible with fungal/Aspergillus infection. On February 13, 2010, blood cultures were positive for *Enterococcus*. The patient was started on aztreonam, caspofungin, Flagyl®, Valtrex®, and voriconazole. On February 16, 2010, a follow-up CT scan of the chest revealed increased ground glass opacities in the lungs bilaterally with slight worsening of minute bilateral ground glass nodules, some with tree-in-bud opacities; stable right lower lobe spiculated mass-like lesion with central necrosis; increased small-to-moderate bilateral pleural effusions; and stable small pericardial effusions. A February 17, 2010 (Cycle 1, Day 23), bronchoalveolar lavage was positive for *Prevotella* and galactomannan; cultures were negative for Aspergillus. PCR was positive for *Clostridium difficile*. On February 23, 2010, a CT scan of the chest revealed progression of widespread nodular infiltrates throughout both lungs and widespread areas of new ground glass airspace disease were observed; increased size of the pleural effusions and the pericardial effusion; and a slight decrease in size of the spiculated mass-like lesion whose necrotic center suggested evolving cavitation.

On February 26, 2010 (Cycle 1, Day 32), the patient was transferred to the medical intensive care unit (MICU) for dyspnea and questionable hemoptysis; he left the MICU one day later. On March 1, 2010 (Cycle 1, Day 35), the patient was transferred back to the MICU due to adult respiratory distress syndrome (ARDS) and unstable atrial fibrillation requiring cardioversion. New-onset supraventricular tachycardia was unresponsive to adenosine, digoxin, or direct current cardioversion. The patient developed acute renal failure, most likely secondary to sepsis. The patient also became hypotensive, which was likely multifactorial and secondary to sepsis and recent cardiac issues. On March 3, 2010, the blood cultures from the PICC line were positive for gram-positive cocci. The patient required intubation on March 4, 2010, then vasopressor support. Family members decided on no further intervention, including dialysis, and withdrew care on March 5, 2010. The patient expired that day due to sepsis.

The patient's past medical/surgical history was significant for tobacco use, alcohol use, abnormal MRI of the lumbar spine, knee cartilage surgery, and inguinal hernia repair. Medications taken at the time of the event included allopurinol, ciprofloxacin, fluconazole, ondansetron, prochlorperazine, and valacyclovir.

There have been 64 other cases of hypoxia 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
Hypoxia (n=64)	5	2 Unlikely, 1 Possible
	4	1 Unrelated, 7 Unlikely, 3 Possible
	3	6 Unrelated, 32 Unlikely, 7 Possible, 2 Probable
	2	1 Unrelated, 1 Unlikely, 1 Possible

A total of 3,281 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 exists between the event and bortezomib.

	Hypoxia
Bortezomib	Possible
Daunorubicin	Unlikely
Cytarabine	Unlikely
Acute myeloid leukemia	Unlikely
Sepsis	Possible

Date: 12/2/10

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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