



DATE: August 12, 2010

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

SUBJECT: PS-341 (bortezomib; Velcade®) NCI IND Safety Report, AE# 1705612

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) (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 62-year-old male with acute myeloid leukemia (AML) experienced grade 4 respiratory failure 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®) AE: 1705612	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 4: Pulmonary/Upper Respiratory- Other: Respiratory failure Protocol: CALGB-10502
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The patient is a 62-year-old male with acute myeloid leukemia (AML) who experienced respiratory failure while on a phase 2 trial utilizing the investigational agents bortezomib in combination with cytarabine and daunorubicin. He began the first course of the investigational therapy on July 15, 2009, receiving bortezomib 1.3 mg/m² IV bolus over 3-5 seconds on Days 1, 4, 8, and 11, daunorubicin 60 mg/m² IV on Days 1-3, and cytarabine 100 mg/m² CIV on Days 1-7 for Cycle 1. On Cycle 2 (in patients with residual disease), he was to receive bortezomib 1.3 mg/m² IV bolus over 3-5 seconds on Days 1 and 4, daunorubicin 60 mg/m² IV on Days 1-2, and cytarabine 100 mg/m² CIV on Days 1-5. He received his last dose of bortezomib on July 25, 2009 (Cycle 1, Day 11), his last dose of daunorubicin on July 17, 2009 (Cycle 1, Day 3), and the last dose of cytarabine on July 21, 2009 (Cycle 1, Day 7).

The patient was initially diagnosed with sideroblastic anemia/refractory anemia with ringed sideroblasts (RARS) in 1997, and is status post erythropoietin therapy. He was then diagnosed on July 6, 2009, with AML in the setting of myelodysplastic syndromes (MDS) which was confirmed by a bone marrow biopsy. He began the investigational therapy on July 15, 2009.

On July 14, 2009, the patient was admitted to the hospital for planned induction chemotherapy. The patient developed neutropenia, then a temperature of 103.4° F on July 22, 2009 (Cycle 1, Day 8), and he was started on ceftazidime. His blood cultures grew coagulase-negative *Staphylococcus*. Vancomycin was given. He received a 3-day course of empirical Flagyl® which was discontinued on July 28, 2009, when stool cultures were negative for *Clostridium difficile*.

On July 28, 2009 (Cycle 1, Day 14), a CT scan of the thorax with contrast revealed small bilateral pleural effusions with patchy ground glass opacities likely pulmonary edema and tiny pericardial effusion as well as small volume ascites. The patient was afebrile until on July 30, 2009, when he developed a temperature of 101.5° F with sharp pleuritic left chest pain and dyspnea. A CT scan of the chest that day revealed small bilateral pleural effusions, mild bilateral lower lobe pulmonary edema, scattered areas of ground glass opacity in the bilateral lobes, and new left apical 3 cm consolidative nodule with surrounding ground glass opacity as compared to the CT scan of July 28, 2009. This was concerning for a fungal infection. The patient was started on Micafungin® which was later changed to AmBisome® for a broader anti-fungal therapy.

On August 2, 2009 (Cycle 1, Day 19), a portable chest X-ray showed that the left upper lobe consolidation had worsened. Despite ongoing treatment, the patient developed worsening hypoxia on August 3, 2009. He was intubated for respiratory failure and admitted to the MICU. A CT scan of the chest confirmed increased size of the consolidation with multifocal new parenchymal opacities concerning for worsening pneumonia. The patient developed renal failure due to acute tubular necrosis from amphotericin and required the initiation of hemodialysis on August 5, 2009. The patient was extubated on August 14, 2009. On August 17, 2009, a percutaneous CT-guided fine needle aspiration showed pulmonary macrophages and reactive bronchial cells which were non-diagnostic, but all cultures were negative. The pathology report indicated some inflammatory alveolar macrophages but no growth. A repeat CT scan of the chest on August 20, 2009, demonstrated interval improvement in the large consolidative opacity in the left lung apex and bilateral multi-nodular opacities. The AmBisome® was switched to voriconazole the next day, he remained on Levaquin®, and all other antibiotics were stopped. The patient received four blood transfusions during his hospital course. His renal function recovered, and he was discharged off hemodialysis and oxygen on August 27, 2009.

On September 4, 2009 (Cycle 1, Day 52), during a follow-up visit, the patient was found to be remarkably well since his discharge, he was continued on voriconazole, and followed by infectious disease for his pulmonary infection. On September 13, 2009, the patient presented to the emergency room with fever and rigors. His temperature was 102.6 ° F, blood pressure 166/72 mmHg, heart rate 89 bpm, and oxygen saturation of 96%. He was treated with cefepime and vancomycin. The next day an infectious disease specialist recommended that the patient continue the antibiotics and voriconazole. On September 25, 2009, infectious disease confirmed that the patient has a biopsy-proven invasive mold infection of his left upper lobe and recommended continuation of voriconazole and repeat imaging in a couple of weeks.

The patient's past medical/surgical history is significant for iron overload syndrome/hemochromatosis, depression, obsessive compulsive disorder, anxiety, hypogonadism, benign colon adenomas, degenerative disc disease, benign hypertrophy prostate, alcoholism (last drink 1993), chronic sinusitis/otitis media, hemorrhoidectomy, traumatic rib and leg fractures, asthma, cirrhosis on 1993 liver biopsy possible Gilbert's disease, and two mole removals. The patient smoked 3 packs per day from age 20 to 50, and quit smoking in 1997. Medications taken at the time of the event included Androgel®, clorazepate, Effexor® XR, flunisolide, ibuprofen, magnesium oxide, mirtazapine, nystatin cream, albuterol inhaler, and triamcinolone 0.1%.

There have been two other cases of respiratory failure (grade 3, possible and grade 4, unlikely) reported to the NCI as a serious adverse event through AdEERS under the bortezomib NSC and/or IND.

A total of 3,222 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 relationship exists between the event and bortezomib.

	Respiratory failure
Bortezomib	Possible
Cytarabine	Possible
Daunorubicin	Possible
AML	Possible

Date: 8/15/10

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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 Millenium Pharmaceuticals Inc.