



DATE: September 3, 2009 *JW 11/12/09*
FROM: John Wright, M.D., Ph.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: PS-341 (bortezomib; Velcade®) NCI IND Safety Report, AE# 1073953
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 74-year-old male with acute myeloid leukemia experienced grade 5 adult respiratory distress syndrome 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: 1073953	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 5: Adult Respiratory Distress Syndrome (ARDS) Protocol: CALGB-10502
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The patient was a 74-year-old male with acute myeloid leukemia (AML) who developed adult respiratory distress syndrome (ARDS) and subsequently died 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 29, 2009, and was to receive bortezomib 1.3 mg/m² IV bolus over 3-5 sec on Days 1, 4, and 8 and 11, cytarabine 100 mg/m² CIV on Days 1-7, and daunorubicin 60 mg/m² IV on Days 1-3 for Cycles 1 and 2 (Cycle 2 being for patients with residual disease). This was to be followed by bortezomib 0.7 mg/m² IV bolus over 3-5 sec on Days 1, 4, 8, and 11 and cytarabine 2 gm/m² IV over 3 hours on Days 1-5 for a maximum of 2 cycles. He received his last dose of bortezomib on February 1, 2009 (Cycle 1, Day 4), and his last dose of daunorubicin on January 31, 2009 (Cycle 1, Day 3).

The patient was initially diagnosed with adenocarcinoma of the transverse colon in 2001 and was status post transverse colectomies × 2 and adjuvant chemotherapy ending in 2003. He was diagnosed with AML in January 2009 by a bone marrow biopsy which revealed AML, M2 type. He began the investigational therapy on January 29, 2009.

On January 26, 2009, the patient was admitted to the hospital to receive induction therapy. He neither described nor exhibited abnormal pulmonary or cardiac signs or symptoms during admission. On January 27, 2009, the patient exhibited cough and upper respiratory symptoms. He had an oxygen saturation of 98% on room air with otherwise normal vital signs and his examination was unremarkable except for oral ulcers. He was pancytopenic with a white blood cell count of $2.6 \times 10^9/L$ (reference range: $5-10 \times 10^9/L$), hemoglobin of 8.8 g/dL (reference range: 14-18 g/dL), hematocrit of 25.4% (reference range: 42-52%), platelet count of $36 \times 10^9/L$ (reference range: $150-400 \times 10^9/L$), and 45% neutrophils (reference range: 55-70%). He was started on levofloxacin.

On January 28, 2009, the patient developed sinus drainage and neutropenic fever on Primaxin®; cultures were negative. His neutropenic fever persisted the next day. He received Diflucan® and acyclovir for prophylaxis, and the investigational therapy was started. On January 30, 2009, the patient's oxygen saturation decreased to 90% on room air. He had rales on lung examination, worsening bilateral infiltrates, and was put on BiPAP. The possibilities of sinus infection, atypical pneumonia, and/or fungal pneumonitis were entertained as were fluid overload and/or drug reaction. On February 1, 2009 (Cycle 1, Day 4), the patient was still febrile and continued to have respiratory difficulties. He had gained 15 pounds since admission and was still retaining fluids. His fluid intake was minimized, and he was started on vancomycin and Lasix®. The investigational therapy was held after this day. His oxygen saturation decreased to the 80s despite being on BiPAP, and he was transferred to the ICU. He was later intubated and attempts to wean him off the ventilator were unsuccessful.

By February 16, 2009, the patient had elevated liver function tests, prolonged PT/PTT, and was still pancytopenic. He was bacteremic and had gallbladder sludge with mild ascites on ultrasound (biliary stasis was suspected). Further complications included unsustained ventricular tachycardia, for which he was placed on an amiodarone drip, and hypotension requiring vasopressor support. He remained on the ventilator for more than 2 weeks. After an extensive discussion with the patient's family, it was decided to discontinue all treatment efforts and keep the patient comfortable. A morphine drip was initiated. The patient was extubated and expired on February 19, 2009, with his family at his bedside.

The patient's past medical/surgical history is significant for extensive transverse colectomy and surgery for recurrent colon cancer. Medications taken at the time of the event included Lipitor®.

There have been three other cases 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
ARDS (n=3)	5 3	2 Unlikely 1 Possible
Respiratory distress (n=1)	5	1 Unlikely

A total of 2,891 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
<u>Bortezomib</u>	Possible
<u>Cytarabine</u>	Possible
<u>Daunorubicin</u>	Unlikely
<u>AML</u>	Probable
<u>Influenza A pneumonia</u>	Probable
<u>Pancytopenia</u>	Probable

Date: 10/26/09

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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