



DATE: MAR 22 2011

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

SUBJECT: PS-341 (bortezomib; Velcade®) NCI IND Safety Report, AE# 1762261 (JW)

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 70-year-old male with acute myeloid leukemia (AML) experienced grade 4 adult respiratory distress syndrome (ARDS) 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) Protocol: CALGB-10502
AE: 1762261	

The patient is a 70-year-old male with acute myeloid leukemia (AML) who experienced adult respiratory distress syndrome (ARDS) while on a phase 2 trial utilizing the investigational agent bortezomib in combination with cytarabine and daunorubicin. He began the first course of the investigational therapy (induction therapy) on July 14, 2009, receiving bortezomib 1.3 mg/m² IV on Days 1, 4, 8, and 11, cytarabine 100 mg/m² IV on Days 1-7, and daunorubicin 60 mg/m² IV on Days 1-3. On Cycles 2 and 3 (consolidation therapy), he received bortezomib 0.7 mg/m² IV on Days 1, 4, 8, and 11, and cytarabine 2 g/m² on Days 1-5. The patient received his last dose of bortezomib on November 13, 2009 (Cycle 3, Day 11), his last dose of cytarabine on November 7, 2009 (Cycle 3, Day 5), and his last dose of daunorubicin on July 16, 2009 (Cycle 1, Day 3).

The patient was diagnosed with AML in July 2009, and has had no prior therapies. He began the investigational therapy on July 14, 2009.

On November 19, 2009 (Cycle 3, Day 17), the patient was admitted to the hospital for neutropenic fever. Shortly after the admission, he developed respiratory failure and was intubated in the ICU. The patient has a history of fungal pneumonia, which was diagnosed in September 2009, and he had been treated with antifungal for three months. A chest X-ray on November 20, 2009, revealed interval worsening aeration of the chest with a development of patchy bibasilar airspace opacities, which was concerning for pneumonia or aspiration pneumonitis. An arterial blood gas analysis on November 23, 2009, showed: pO₂ 113.8 mmHg (reference range: 80-100 mmHg), pCO₂ 52.6 mmHg (reference range: 35-45 mmHg), and pH 7.29 (reference range: 7.35-7.45). A CT scan on November 26, 2009, revealed new right lower lobe consolidation concerning for pneumonia as well as new moderate right and small left pleural effusions. On the same day, it was revealed that the respiratory culture was positive for *Enterococcus faecium*. The hospital course of the patient was very complicated: besides the respiratory failure, he also developed cardiovascular compromise requiring pressors, acute renal failure requiring hemodialysis, and typhlitis requiring broad-spectrum antibiotic therapy. He underwent aggressive medical management of these problems, and his condition slowly improved. The patient was discharged on January 6, 2010, when a repeat chest CT revealed interval decrease in the small amount of residual opacity in the right middle lobe, favoring scarring from prior infection, and no new opacities were noted. At a clinic visit on January 22, 2010, the patient appeared well. He did not have any shortness of breath or cough, and there were no wheezes, crackles or rhonchi heard from the lung bilateral auscultation.

The patient's past medical/surgical history is significant for hypertension, allergic rhinitis, asthma, cholecystectomy, hyperlipidemia, situational depression, peripheral neuropathy, fungal pneumonia (aspergillosis), hemorrhoids, and melena. Medications at the time of the event included Prevacid®, Reglan®, vitamin D, simethicone, Remeron®, oxycodone, Travatan®, magnesium oxide, potassium chloride, lidocaine-prilocaine, voriconazole, Ambien®, Avelox®, acyclovir, and Colace®.

There have been 9 other cases of ARDS 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=9)	5	1 Unlikely, 2 Possible
	4	2 Unlikely, 2 Possible
	3	2 Possible

A total of 3,539 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 therapy.

	ARDS
Bortezomib	Possible
Cytarabine	Possible
Daunorubicin	Unrelated
Acute myeloid leukemia	Unrelated
Infection	Possible

Date: 3/19/11

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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