



DATE: June 2, 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# 1617319 7/1/10

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 63-year-old male with acute myeloid leukemia expired 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 5: Death not associated with CTCAE term: Death NOS Protocol: CALGB-10502
AE: 1617319	

The patient was a 63-year-old male with acute myeloid leukemia who expired 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 April 24, 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. The patient was then prescribed remission consolidation therapy, and was to have received bortezomib 0.7 mg/m² IV bolus over 3-5 seconds on Days 1, 4, 8, and 11 and cytarabine 2000 mg/m² IV over 3 hours on Days 1-5, for two cycles. The patient was non-compliant and received only 3 of 5 doses prescribed for consolidation Cycle 1, and 4 of 5 doses prescribed for consolidation Cycle 2. He received his last dose of bortezomib on May 4, 2009 (Cycle 1, Day 11), his last dose of daunorubicin on April 26, 2009 (Cycle 1, Day 3), and his last dose of cytarabine on August 6, 2009 (Cycle 3, Day 4).

The patient was diagnosed with AML in April 2009 and has had no prior therapy. He began the first course of the remission induction therapy on April 24, 2009.

On September 8, 2009, the patient, who had been lost to follow-up until August 13, 2009, presented to the clinic for a routine follow-up. He had previously been admitted to an outlying hospital for orbital cellulitis which was felt to be more likely a contact dermatitis than an orbital cellulitis. The inflammation was resolving. On September 13, 2009, according to a phone conversation between the family and clinic, the patient was declining and his breathing was very shallow. The patient conveyed that he did not want to go to a hospital and wanted to die at home. Hospice services were initiated. On September 15, 2009, hospice contacted the clinic to inform them that the patient's pain was worse and his Roxanol™ was increased from 5-10 mg hourly to 15-20 mg hourly as needed. He did not show up for the 5th scheduled day of treatment and was reported to have died on September 16, 2009.

The patient's past medical/surgical history was significant for alcohol abuse, allergic rhinitis, hypertension, depression, fibromyalgia, chronic pain syndrome, lumbar disk herniation, chronic anemia, anxiety, 45 pack-year smoking history, cerebrovascular accident with brain aneurysm, and status post laser surgery and platinum clipping of lumbar disk herniation. Medications at the time of the event included Roxanol™, Xanax®, Claritin®, Prozac®, lisinopril, Lyrica®, magnesium oxide, Toprol-XL®, oxycodone, and vitamin D.

There have been 19 other cases of death NOS and 10 other cases of sudden death 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
Death NOS (n=19)	5	1 Unrelated, 17 Unlikely, 1 Possible
Sudden death (n=10)	5	9 Unlikely, 1 Possible

A total of 3,142 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.

	Death NOS
Bortezomib	Possible
Cytarabine	Possible
Daunorubicin	Possible
Acute myeloid leukemia	Probable

Date: 7/1/10

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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