

## IND SAFETY REPORT: INITIAL WRITTEN REPORT

To: *Division of Drug Oncology Products, Center for Drug Evaluation and Research, FDA*

FAX: 301-796-9845

1. IND NUMBER  
58443

2. AGENT NAME  
PS-341 (bortezomib; Velcade)

3. DATE  
May 10, 2010

4. SPONSOR  
Division of Cancer Treatment and Diagnosis, National Cancer Institute

5. REPORTER'S NAME, TITLE, AND INSTITUTION  
John Wright, MD, PhD-Associate Branch Chief for Investigational Therapeutics 2,  
Investigational Drug Branch, CTEP, DCTD, NCI

6. PHONE NUMBER  
301-496-1196

7. FAX NUMBER  
301-402-0428

8a. PROTOCOL NUMBER (AE #)  
CALGB-10502 (AE# 1826902)

8b. AE GRADE: AE  
Grade 4: Hypoxia

9. PATIENT IDENTIFICATION  
119161

10. AGE  
67

11. SEX  
Male

12. DESCRIPTION OF ADVERSE EVENT

The patient was a 67-year-old male with acute myeloid leukemia (AML) who experienced grade 4 hypoxia and subsequently expired due to pneumonia while on a phase 2 study utilizing the investigational agent bortezomib in combination with daunorubicin and cytarabine. He began the investigational therapy on January 26, 2010, and received his last dose of bortezomib February 16, 2010 (Cycle 1, Day 22), the last dose of daunorubicin February 14, 2010 (Cycle 1, Day 20), and cytarabine on February 17, 2010 (Cycle 2, Day 23). 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 x 4.5 cm and surrounding ground glass halo. Those findings were compatible with fungal/aspergillus infection. On February 23, 2010, a CT scan of the chest revealed progression of widespread nodular infiltrates throughout both lungs. The widespread areas of new groundglass airspace disease were observed. On February 25, 2010, the patient was started on daily granulocyte transfusion. He was transferred to medical intensive care unit (MICU) after the transfusion. The granulocytes transfusion was stopped. On March 1, 2010, bone marrow aspirate revealed 30-70% cellular with 13% blasts and 53% promyelocytes. The presence of increased blast with significant left-shifted and toxic granulopoiesis may have been consistent with bone marrow regeneration but could not rule out involvement by AML. On March 1, 2010, the patient was transferred to the MICU with respiratory failure which required intubation. A chest X-ray revealed additionally increased infiltrates but blood cultures were negative. The patient was started on antibiotics. He developed atrial fibrillation and systolic ventricular tachycardia which were unresponsive to adenosine. He underwent cardioversion and went into sinus rhythm. The patient became hypotensive and developed renal failure, likely multifactorial secondary to sepsis and recent cardiac issues. On March 3, 2010, the blood cultures were positive. The family decided on no further intervention including dialysis and withdrew care on March 5, 2010. The patient expired on March 5, 2010, due to sepsis and infection. Additional information has been requested from the investigational site. There is a reasonable possibility that the experience may have been caused by the drug.

13. DOSE, ROUTE, AND SCHEDULE: **Remission Induction Therapy**  
Cycle 1: Bortezomib: 1.3 mg/m<sup>2</sup> IVB over 3-5 seconds on Days 1, 4, 8, and 11  
Cycle 2: Bortezomib: 1.3 mg/m<sup>2</sup> IVB over 3-5 seconds on Days 1 and 4

14. DATES OF TREATMENT

The patient began the investigational therapy on January 26, 2010, and received his last dose of bortezomib on February 16, 2010 (Cycle 1, Day 22).

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using bortezomib = 3,133. There have been 5 other cases of hypoxia reported to the NCI through AdEERS as serious adverse events for sorafenib tosylate. The pneumonia is a known event for the study drug bortezomib.

16. COMMENTS: The following was also administered on this protocol:

Cycle 1: Daunorubicin: 60 mg/m<sup>2</sup> IV on Days 1-3; Cytarabine: 100 mg/m<sup>2</sup> CIV on Days 1-7  
Cycle 2: Daunorubicin: 60 mg/m<sup>2</sup> IV on Days 1-2; Cytarabine: 100 mg/m<sup>2</sup> CIV on Days 1-5

AT THIS TIME, NO OTHER INFORMATION IS AVAILABLE. IF UPON FURTHER INVESTIGATION RELEVANT INFORMATION BECOMES AVAILABLE, THEN A FOLLOW-UP REPORT WILL BE SUBMITTED IN ACCORDANCE WITH 21CFR 312.32(d)(2). **DISCLAIMER per 21 CFR 312.32(e): THIS SAFETY REPORT DOES NOT NECESSARILY REFLECT A CONCLUSION OR ADMISSION BY THE CTEP IDB SENIOR INVESTIGATOR/SPONSOR THAT THE INVESTIGATIONAL AGENT/THERAPY CAUSED OR CONTRIBUTED TO THE ADVERSE EXPERIENCE BEING REPORTED.**

0002