

## 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**

**71976**

2. AGENT NAME

**PS-341 (bortezomib; Velcade)**

**Vorinostat (suberoylanilide hydroxamic acid; SAHA)**

3. DATE

**November 4, 2009**

4. SPONSOR

**Division of Cancer Treatment and Diagnosis, National Cancer Institute**

5. REPORTER'S NAME, TITLE, AND INSTITUTION

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2, Investigational Drug Branch, CTEP, DCTD, NCI**

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6. PHONE NUMBER

**301-496-1196**

7. FAX NUMBER

**301-402-0428**

8. PROTOCOL NUMBER (AE #)

**8064 (AE# 1495143)**

9. PATIENT IDENTIFICATION

**026**

10. AGE

**53**

11. SEX

**Female**

12. DESCRIPTION OF ADVERSE EVENT

The patient was a 53-year-old female with diffuse large B-cell lymphoma who died suddenly during hospitalization for respiratory distress while on a phase 2 trial using the investigational agents bortezomib and vorinostat. She began the first course of the investigational therapy on August 24, 2009, and received the last dose of bortezomib on September 24, 2009 (Cycle 2, Day 11), and the last dose of vorinostat on September 25, 2009 (Cycle 2, Day 12). The patient had previously been admitted on September 30, 2009, for acute renal failure of unclear etiology which was complicated by urosepsis with pansensitive *E. coli*, and discharged on October 7, 2009. She was removed from the protocol on October 12, 2009 due to disease progression. On October 21, 2009, the patient presented to the emergency room with complaints of worsening dyspnea with minimal activity. Her vital signs were: blood pressure 90/60 mmHg, heart rate 120 bpm, and oxygen saturation of 80% on room air. The patient's blood pressure dropped to 60/40s mmHg and her heart rate increased to 130 bpm. She was placed on 100% non-rebreather mask and her oxygen saturation improved to 100%. The patient was intubated for respiratory distress which was complicated by aspiration. The patient was started on IV fluids, heparin drip for presumptive pulmonary embolism, cefepime for neutropenic sepsis, and was admitted to the MICU. A transthoracic echocardiogram (TTE) revealed an ejection fraction of 45-50%, right atrial dilation, and regional wall motion of the apex and anterior wall suggestive of coronary artery disease (CAD). On October 22, 2009, the patient was found pulseless. Despite resuscitative efforts, the patient expired at 11:13 am that day. An autopsy was not performed. Additional information has been requested. There is a reasonable possibility that the experience may have been caused by the drug.

13. DOSE, ROUTE, AND SCHEDULE

**Cycle = 21 days ; Vorinostat 400 mg PO daily on Days 1-5 and 8-12**

**Bortezomib 1.3 mg/m<sup>2</sup> IV bolus over 3-5 seconds on Days 1, 4, 8, and 11**

14. DATES OF TREATMENT

**The patient began the investigational therapy on August 24, 2009, and received the last dose of bortezomib on September 24, 2009 (Cycle 2, Day 11), and the last dose of vorinostat on September 25, 2009 (Cycle 2, Day 12).**

15. ACCRUAL AND IND EXPERIENCE

**Number of patients enrolled in NCI-sponsored clinical trials using bortezomib = 2961 and vorinostat = 1441. There have been 8 other cases of sudden death and 12 other cases of death NOS reported to the NCI through AdEERS as serious adverse events for PS-341, and 5 other cases of sudden death and 8 other cases of death NOS reported to the NCI through AdEERS as serious adverse events for Vorinostat.**

16. COMMENTS

**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.**

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