



DATE: March 23, 2010

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SUBJECT: Vorinostat (suberoylanilide hydroxamic acid; SAHA) and PS-341 (bortezomib; Velcade®) NCI IND Safety Report #2, AE# 1495143

TO: Investigators Using Vorinostat (NSC 701852) and 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 agents vorinostat and bortezomib.

The following must be completed by all investigators using vorinostat, NCI IND 71976 and 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 71976 or 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 vorinostat and bortezomib, there does not appear to be a change in the risk-benefit ratio for vorinostat and 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 these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 53-year-old female with diffuse large B-cell lymphoma (DLBCL) died from multi-organ failure while on a phase 2 trial utilizing the investigational agents vorinostat and bortezomib.

The attached Adverse Events Assessment has been amended to reflect a change in assessment. Changes to the attached report are indicated by bold and italics (new information) and/or strikethrough (deleted information). If this assessment is changed further, we will notify your office. Please note that this modified report will be distributed to investigators.

ADVERSE EVENTS ASSESSMENT

| | | |
|---|------------------------------------|--|
| IND 71976 | 58443 | ADVERSE EXPERIENCE REPORT NO. |
| NSC 701852 | 681239 | IND Safety Report: #2 |
| Vorinostat (Suberoylanilide hydroxamic acid; SAHA) | PS-341 (Bortezomib; Velcade) | Event: Gr. 5: Death not associated with CTCAE term: Multi-organ failure |
| AE: 1495143 | | Protocol: 8064 |

This report has been amended to reflect a change in assessment. Changes to the original summary are indicated by bold and italics (new information) and/or strikethrough (deleted information). If this assessment is changed further, we will notify your office. Please note that this modified report will be distributed to investigators.

The patient was a 53-year-old female with diffuse large B-cell lymphoma (DLBCL) who died from multi-organ failure while on a phase 2 trial utilizing the investigational agents bortezomib and vorinostat. She began the first course of the investigational therapy on August 24, 2009, receiving vorinostat 400 mg PO on Days 1-5 and 8-12, and bortezomib 1.3 mg/m² IV bolus over 3-5 seconds on Days 1, 4, 8 and 11, every 21 days. The patient 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 was initially diagnosed with diffuse large B-cell lymphoma in July 2008, and is status post multiple-agent systemic chemotherapy and radiation therapy. She began the investigational therapy on August 24, 2009.

On September 30, 2009 (Cycle 2, Day 17), the patient was admitted for acute renal failure of unclear etiology which was complicated by urosepsis with pansensitive *E. coli*. She also had an elevated uric acid and was given rasburicase. A CT scan of the abdomen and pelvis on October 1, 2009 as compared to the report of July 7, 2009, showed an increase in right hydronephrosis secondary to mass effect from increasing lymphadenopathy. There was a significant increase in intraperitoneal, bilateral internal, external iliac and bilateral inguinal lymphadenopathy. Two new subcentimeter right lower lobe nodules were noted at the right lung base and there was persistent hepatomegaly. On October 7, 2009, after completing a 7-day course of antibiotics, the patient was discharged on an additional 7-day course of Keflex[®]. She was removed from the protocol on October 12, 2009 due to disease progression. The patient received platelet and blood transfusions on October 14, 2009, for pancytopenia.

On October 21, 2009, the patient presented to the emergency room with complaints of worsening dyspnea with minimal activity. On physical examination, the patient was alert and oriented, obese and in acute distress with labored breathing, but able to speak in full sentences. Her mucous membranes were dry, there was a large left supraclavicular lymph node measuring approximately 5 cm, massive bilateral chronic lymphedema of the lower extremities (right greater than left), and groin abrasions with oozing of serosanguinous fluid. A chest X-ray revealed a right middle lobe infiltrate. Laboratory results were notable for creatinine 4.2 mg/dL (reference range: 0.4-1.0 mg/dL), HCO₃ 13.7 mmol/L (reference range: 21-26 mmol/L), pancytopenia, and intrinsic coagulopathy. Blood culture results were pending. The patient's vital signs were: blood pressure 90/60 mmHg, heart rate 120 bpm, and oxygen saturation of 80% on room air. The ECG showed sinus tachycardia with low voltage QRS, suggestive of pulmonary disease or pericardial effusion. Her blood pressure dropped to 60/40 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 failure which was complicated by aspiration. Her hemodynamic instability was thought to be likely secondary to septic shock which might have led to the respiratory distress. The patient received a unit of PRBCs and platelets, and 3.5 liters of IV fluid which improved her blood pressure to 90/60 mmHg. She was started on a heparin drip for presumptive pulmonary embolism, cefepime for neutropenic sepsis, and was admitted to the MICU and placed on mechanical ventilation. Antibiotic therapy was instituted with early goal-directed therapy (EGDT) for sepsis. The patient was

also started on dopamine for inotropic support. 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 remained persistently hypotensive in spite of treatment with vasopressors. She remained in multi organ failure with septic shock, acute kidney injury (AKI), and acute respiratory failure. Blood cultures grew *Pseudomonas aeruginosa*. Her prognosis was very poor and plans were made to discuss end-of-life choices with the family. Later that morning, the patient was found pulseless. Despite resuscitative efforts, the patient expired at 11:13 am that day. An autopsy was not performed.

The patient's past medical/surgical history was remarkable for a painless right thigh mass for six years and C-section three times. She was a former smoker who quit 10 years ago. Medications taken at the time of the event included oxycodone, cephalexin, allopurinol, Lidoderm® 5%, Hi-Cor® 2.5%, hydroxyzine hydrochloride, lidocaine 2%, Nystex®, valacyclovir, Xenaderm® topical ointment, Imodium®, diphenhydramine, Nexium®, Colace®, and senna.

There have been 7 other cases of death from multi-organ failure reported as serious adverse events through AdEERS under the PSI-341 NSC and/or IND, and 7 other cases of death from multi-organ failure reported as serious adverse events through AdEERS under the vorinostat NSC and/or IND as shown in the table below.

| Adverse Event | Grade | Attribution |
|---|-------|---|
| Bortezomib | | |
| Death not associated with CTCAE term: Multi-organ failure (n=7) | 5 | 3 Possible 3 Unlikely 1 Unrelated |
| Vorinostat | | |
| Death not associated with CTCAE term: Multi-organ failure (n=7) | 5 | 1 Possible 1 Unlikely 5 Unrelated |

A total of 1465 patients have been enrolled in NCI-sponsored clinical trials under the vorinostat IND and/or NSC and a total of 3038 patients have been enrolled in NCI-sponsored clinical trials under the bortezomib IND and/or NSC.

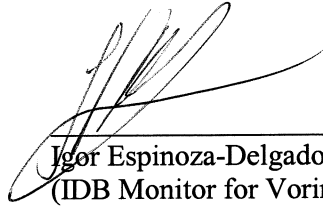
In this case, it is felt that a possible causal relationship between the patient's death and the investigational agents cannot be excluded.

| | Death not associated with CTCAE term: Multi-organ failure |
|--|---|
| Vorinostat (Suberoylanilide hydroxamic acid; SAHA) | Possible |
| PS-341 (Bortezomib, Velcade) | Possible |
| Diffuse large B-cell lymphoma | Possible |
| <i>Pseudomonas sepsis</i> | <i>Possible</i> |

Date: 03/24/10



Signature:



Igor Espinoza-Delgado, M.D.
(IDB Monitor for Vorinostat)

Date: 5/6/10

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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