

## 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

57966

58443

2. AGENT NAME

17-AAG

PS-341 (bortezomib; Velcade®)

3. DATE

January 12, 2010

4. SPONSOR

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

5. REPORTER'S NAME, TITLE, AND INSTITUTION

**Alice Chen, MD-Senior Investigator for Investigational Therapeutics 2, Investigational Drug Branch, CTEP, DCTD, NCI**

**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

8. PROTOCOL NUMBER (AE #)

6121 (AE# 1658762)

9. PATIENT IDENTIFICATION

EX140771

10. AGE

57

11. SEX

Female

12. DESCRIPTION OF ADVERSE EVENT

The patient is a 57-year-old female with metastatic colon cancer who experienced a grade 3 third degree atrioventricular (AV) block while on a phase 1 trial utilizing the investigational agents 17-AAG and bortezomib. She began the first course of the investigational therapy on November 3, 2009, and received the last doses of 17-AAG and bortezomib on December 4, 2009 (Cycle 2, Day 11). On December 14, 2009 (Cycle 2, Day 21), the patient presented to the clinic for follow-up and complained of weakness, dizziness, shortness of breath, and chest tightness which developed a few days prior. Cardiovascular examination revealed profound bradycardia and 1/6 systolic murmur. The patient, who has no known history of coronary artery disease, was removed from the study and transferred to the ER for evaluation and management of her symptoms. On arrival, the patient also reported feeling exhausted with activity. An ECG showed sinus bradycardia with AV dissociation and junctional escape rhythm. There was a prolonged QTc interval with heart block. Her heart rate was 36 bpm, respiration 18 breaths per minute, blood pressure 156/91 mmHg, and oxygen saturation 98% on room air. She was given a bolus of IV fluids, started on supplemental oxygen, and admitted to the cardiology service for management of a complete third degree AV block. A dual-chamber permanent pacemaker was successfully implanted, and the patient was continued on a course of antibiotics. 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

Cycle = 21 days

17-AAG 250 mg/m<sup>2</sup> IV over 1-2 hours on Days 1, 4, 8 and 11

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

14. DATES OF TREATMENT

The patient began the investigational therapy on November 3, 2009, and received the last doses of 17-AAG and bortezomib on December 4, 2009 (Cycle 2, Day 11).

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using 17-AAG = 711 and bortezomib = 2994. There have been no other cases of third degree AV block and 1 case of second degree AV block reported to the NCI through AdEERS as serious adverse events for 17-AAG, and no other cases of third degree AV block and 2 case of second degree AV block reported to the NCI through AdEERS as serious adverse events for bortezomib.

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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