



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** May 13, 2005

**To:** NCCTG Primary Clinical Research Associates

**From:** Janis Gjervik  
Protocol Development Coordinator

**Re:** N0321, Phase I/II Study of PS-341 in Combination with Paclitaxel, Carboplatin, and Concurrent Thoracic Radiation Therapy for Non-small Cell Lung Cancer (NSCLC)

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with PS-341 for a study where the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) is distributing this agent. You may have also received this communication directly from DCTD.

AE\_1110133

Please note that all risks currently cited in the NCCTG consent form cannot be omitted; it is at the discretion of your local IRB as to whether they wish to add risks based on the enclosed information. If a determination has been made by the NCCTG Research Base that a protocol amendment is necessary, you will receive the NCI-approved protocol addendum at a later date; for purposes of cross-reference, this communication will cite the adverse event noted above.

**Please submit this adverse event to your Institutional Review Board.**

If you have any questions concerning this communication, please contact Janis Gjervik at 507/284-4852.

JG  
enclosure



**DATE:** May 3, 2005  
**FROM:** John Wright, M.D., Ph.D., Investigational Drug Branch, CTEP, DCTD, NCI JW  
**SUBJECT:** PS-341 IND Safety Report, AE# 1110133  
**TO:** Investigators Using PS-341 (bortezomib; Velcade), IND 58443

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 PS-341 (IND 58443).

Please complete the following:

- 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.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

CTEP's evaluation of this IND Safety Report in light of previous experience with PS-341 does not require a change in the clinical protocols for this agent at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The Adverse Events Assessment that describes the following adverse events is attached:

A 62-year-old female with multiple myeloma experienced grade 3 left ventricular systolic dysfunction while on a phase 2 trial using the investigational agent PS-341.

There have been 6 other incidences of grade 3 left ventricular systolic dysfunction reported to the NCI as a serious adverse event under this IND, 5 incidences were considered possibly related to the study drug and 1 incidence was considered unlikely related to the study drug.

There have been 1339 patients enrolled in NCI-sponsored clinical trials under this IND.

## ADVERSE EVENTS ASSESSMENT

|                                                         |                                                                                                                                                     |
|---------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| IND 58443<br>NSC 681239<br>PS-341 (bortezomib; Velcade) | ADVERSE EXPERIENCE REPORT NO. 40<br>IND Safety Report:<br>Event: Gr: 3 Cardiac General: Left Ventricular<br>Systolic Dysfunction<br>Protocol: E2A02 |
| AE: 1110133                                             |                                                                                                                                                     |

The patient is a 62-year-old female with multiple myeloma who experienced left ventricular systolic dysfunction while on a phase 2 trial using the investigational agent PS-341. She began her first course of treatment on January 31, 2005, receiving PS-341 1.3 mg/m<sup>2</sup> by intravenous (IV) push on days 1, 4, 8, and 11, every 21 days. For Cycle 1, she received treatment for days 1 and 8 only because the treatment for days 4 and 11 was held due to low ANC values. She started Cycle 2 of therapy on February 21, 2005, receiving a reduced dose of 1.0 mg/m<sup>2</sup> on days 1, 4, and 8, with the last dose administered on February 28, 2005.

The patient presented with back pain in September 2004 and an X-ray confirmed a compression fracture at T12. During the work-up for the back pain, a right kidney mass was found. The patient underwent a radical nephrectomy on November 19, 2004, with the pathology revealing a clear cell carcinoma; the margins were negative. During this evaluation, a protein electrophoresis showed a 2.5 gm monoclonal spike. A bone marrow aspirate and biopsy confirmed multiple myeloma, and she was started on the clinical trial with PS-341 in January, 2005. After her first cycle of treatment she had a decrease in her monoclonal spike. She received her Cycle 2, Day 8 therapy on February 28, 2005, and that evening she developed severe shortness of breath with a fever of 103°F. She presented to the Emergency Room on March 1, 2005, with symptoms of congestive heart failure. She was placed on oxygen and treated with Lasix<sup>®</sup> and nebulizers with a rapid improvement in her breathing within the hour. Upon admission, her blood cultures were negative, BNP was 724 pg/mL (reference range: <100 pg/mL), and troponin levels were within normal limits. A chest X-ray showed bilateral pulmonary infiltrates, and her echocardiogram revealed left ventricular hypertrophy with an ejection fraction in the 40s, and some septal wall hypokinesis. Of note, an echocardiogram performed in November 2004 showed left ventricular hypertrophy with a normal ejection fraction. Her EKG revealed left ventricular hypertrophy with marked left axis deviation. An X-ray performed on March 2, 2005 indicated cardiac enlargement. The patients also underwent a dobutamine echocardiogram stress test without any signs of inducible ischemia. She was discharged from the hospital on March 4, 2005, and was seen in clinic on March 14, 2005 to resume therapy. At that

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time, she had no shortness of breath and she denied any peripheral edema. She was reevaluated on March 18, 2005 and was found to have no further symptoms of congestive heart failure. Per site, the patient will have repeat echocardiogram on April 7, 2005.

The patient's past medical history is significant for hypertension, hypothyroidism, elevated liver functions tests, and gout. However, the patient had no prior history of congestive heart failure. Medications at the time of the initial pulmonary event included atenolol, Synthroid<sup>®</sup>, hydrocodone, triamterene, Tylenol<sup>®</sup>, Fosamax<sup>®</sup>, and lisinopril.

There have been 6 other incidences of grade 3 left ventricular systolic dysfunction reported to the NCI as serious adverse events under this IND, 5 incidences were considered possibly related to the study drug and 1 incidence was considered unlikely related to the study drug.

In this case, it is thought that the left ventricular systolic dysfunction was possibly related to the study drug, the patient's underlying disease, and the left ventricular hypertrophy. There have been 1339 patients enrolled in NCI-sponsored clinical trials under this IND.

|                                     | <b>Left Ventricular Systolic<br/>Dysfunction</b> |
|-------------------------------------|--------------------------------------------------|
| <u>PS-341</u>                       | <u>Possible</u>                                  |
| <u>Myeloma</u>                      | <u>Possible</u>                                  |
| <u>Left Ventricular Hypertrophy</u> | <u>Possible</u>                                  |
| <u>Hypothyroidism</u>               | <u>Possible</u>                                  |

Date: 5-3-05

Signature:

John Wright M.D.  
John Wright, M.D., Ph.D.  
(IDB Monitor for PS-341)

If this assessment is changed, we will notify your office.

cc: Jean-Claude Tetreault

Millennium Pharmaceuticals, Incorporated

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