



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** March 18, 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\_1400157

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:** February 7, 2005

**FROM:** John Wright, M.D., Ph.D., Investigational Drug Branch, CTEP, DCTD, NCI

**SUBJECT:** PS-341 IND Safety Report, AE# 1400157 JW

**TO:** Investigators Using PS-341, IND 58,443

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 58,443).

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 66 year-old female with multiple myeloma experienced grade 3 pericardial effusion, grade 3 right ventricular dysfunction, grade 3 pleural effusion, and grade 2 edema while on a phase 2 trial using the investigational agent PS-341 in combination with liposomal doxorubicin.

There have been 2 other incidences of pericardial effusion, 6 other incidences of ventricular dysfunction, 14 other incidences of pleural effusion, and 19 other incidences of edema reported to the NCI as serious adverse events under this IND with attributions to the study agent as follows:

Pericardial effusion (n = 2)	1 possible, 1 unlikely
Ventricular dysfunction Right (n = 0) Left (n = 6)	0 5 possible, 1 unlikely
Pleural effusion (n = 14)	1 probable, 2 possible, 7 unlikely, 4 unrelated
Edema (n = 19)	1 probable, 10 possible, 7 unlikely, 1 unrelated

There have been 1285 patients enrolled in NCI-sponsored clinical trials under this IND.

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## ADVERSE EVENTS ASSESSMENT

IND 58443 NSC 681239 PS-341 (bortezomib)	ADVERSE EXPERIENCE REPORT NO. 37 IND Safety Report: Event: Gr. 3: Pericardial effusion Gr. 3: Right ventricular dysfunction Gr. 3: Pleural effusion Gr. 2: Edema: limb
AE: 1400157	Protocol: CALGB-10301

The patient is a 66-year-old female with multiple myeloma who developed pericardial effusion, right ventricular dysfunction, pleural effusion, and edema while on a phase 2 trial using the investigational agent PS-341 in combination with pegylated liposomal doxorubicin. She began her first course of treatment on September 17, 2004 receiving PS-341 1.3 mg/m<sup>2</sup> by intravenous push over 3-5 seconds on Days 1, 4, 8, and 11, every 21 days. She also received liposomal doxorubicin 30 mg/m<sup>2</sup> intravenously over 1 hour on Day 4, every 21 days. She started Cycle 3 of therapy on October 29, 2004, receiving her last dose of PS-341 on that day.

The patient was diagnosed with multiple myeloma in August 2004 and had multiple lytic lesions noted on bone scan at the time of diagnosis. A pre-treatment chest X-ray performed on September 8, 2004 did not reveal any evidence of infiltrates or effusions. She presented to the clinic on October 29, 2004 for Cycle 3, Day 1 of therapy, which she received. At that time, she was noted to have ankle edema and was started on Lasix<sup>®</sup> (furosemide). On Day 4, she presented for treatment but was noticed to be dyspneic and she complained of fatigue. Her chemotherapy was withheld, and the patient was started on Zaroxolyn<sup>®</sup> (metolazone), in addition to the Lasix<sup>®</sup>. Home oxygen was also initiated. She presented to her local physician on November 5, 2004 markedly dyspneic and desaturating with exertion. It was elected at this time to admit her to the hospital for further evaluation. An echocardiogram performed on November 1, 2004 revealed an ejection fraction (EF) of 45%, which was decreased from 60% noted on a pre-treatment MUGA scan performed on September 8, 2004. The echocardiogram also demonstrated a small to moderate pericardial effusion. A CT scan of the chest on November 5, 2004 confirmed the pericardial effusion and demonstrated bilateral pleural effusions. Laboratory values were significant for a brain natriuretic peptide (BNP) level of 482 pg/mL (reference range: <100 pg/mL). The patient was treated with diuretics, steroids, bronchodilators, and oxygen support. A follow-up echocardiogram performed on November 8, 2004 revealed an EF of 50-55%. The patient was discharged on November 9, 2004, on a tapering dose of

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steroids, continued oxygen therapy, and Zithromax® (azithromycin). It was decided at this time to remove the patient from the study. She was seen in follow-up on January 14, 2005, at which time she was entirely off oxygen supplementation. She had been subsequently started on thalidomide/Decadron® (dexamethasone) therapy on November 12, 2004, and as of January 14, 2005, appeared to be responding to this therapy.

The patient's past medical history is significant for benign breast disease and chronic obstructive pulmonary disease. She is currently a smoker, with a 50 pack-year smoking history. Medications at the time of the event included Lasix®, Tussionex® (hydrocodone polistirex/chlorpheniramine), vitamin B-12, Ativan® (lorazepam), Lortab® (hydrocodone bitartrate/acetaminophen), and Ambien® (zolpidem tartrate).

There have been 2 other incidences of pericardial effusion, 6 other incidences of ventricular dysfunction, 14 other incidences of pleural effusion, and 19 other incidences of edema reported to the NCI as serious adverse events under this IND with attributions to the study agent as follows:

Pericardial effusion (n = 2)	1 possible, 1 unlikely
Ventricular dysfunction	0
Right (n = 0)	
Left (n = 6)	5 possible, 1 unlikely
Pleural effusion (n = 14)	1 probable, 2 possible, 7 unlikely, 4 unrelated
Edema (n = 19)	1 probable, 10 possible, 7 unlikely, 1 unrelated

In this case, it is felt that the study drug probably contributed to the pericardial effusion, right ventricular dysfunction, pleural effusion, and limb edema; however, the patient's underlying disease is considered a possible contributing factor for these events, and the liposomal doxorubicin is felt to have possibly contributed to the pericardial effusion, right ventricular dysfunction, and edema.

There have been 1,285 patients enrolled in NCI-sponsored clinical trials under this IND.

	<b>Pericardial effusion</b>	<b>Pleural effusion</b>	<b>Right ventricular dysfunction</b>	<b>Edema</b>
<b>Liposomal doxorubicin</b>	Possible	Unlikely	Possible	Possible
<b>PS-341</b>	Probable	Probable	Probable	Probable
<b>Multiple myeloma</b>	Possible	Possible	Possible	Possible

Date: 2/15/05

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, Inc.