



# 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\_1618501

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 25, 2005  
**FROM:** John Wright, M.D., Ph.D., Investigational Drug Branch, CTEP, DCTD, NCI  
**SUBJECT:** PS-341 IND Safety Report, AE# 1618501  
**TO:** Investigators Using PS-341, IND 58443

(JW)

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 56-year-old female with multiple myeloma experienced grade 5 conduction abnormality/atrioventricular heart block - asystole while on a phase 2 trial using the investigational agent PS-341.

There have been a total of seven incidences of grade 5 cardiovascular events reported to the NCI as serious adverse events under this IND, including the present case. These events are summarized in the following table:

AdEERS #	Sex/Age	Disease	Event	Relative to Treatment	Attributions			
					IND Agent	Other Agents	Disease	Other Causes
1073805	F/42	Lip & oral cavity squamous cell carcinoma	Cardiopulmonary arrest	24 days after last dose (C1)	Unlikely		Definite	Definite New metastatic pulmonary effusions  Possible Multiple infections
1340809	M/76	Non-Hodgkin's lymphoma	Cardiopulmonary arrest	>30 days after last dose (C2)	Unlikely		Probable	Possible Meningeal involvement
1511254	F/53	Chronic lymphocytic leukemia	Cardiac arrest	>30 days after last dose (C1)	Unlikely		Probable	Possible Diabetic ketoacidosis  Probable Leukocytosis
1517445	M/87	Gastric cancer	Sudden death	4 days after last dose (C2)	Unlikely	Probable Irinotecan	Probable	
1927146	M/76	Mantle Cell Lymphoma	Exacerbation of congestive heart failure	30 days after last dose (C3)	Unlikely		Possible	Possible Renal failure  Probable Congestive heart failure
1986820	M/49	Lip & oral cavity squamous cell carcinoma	Respiratory arrest	>30 days after last dose (C1)	Unlikely		Probable	Probable Mucus plug
1618501	F/56	Multiple myeloma	Asystole	<24 hours	Probable		Possible	Probable Possible MI

There have been 1317 patients enrolled in NCI sponsored clinical trials under this IND.

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## ADVERSE EVENTS ASSESSMENT

IND 58443 NSC 681239 PS-341	ADVERSE EXPERIENCE REPORT NO. 38 IND Safety Report: Event: Gr. 5: Conduction abnormality/ Atrioventricular heart block - Asystole
AE: 1618501	Protocol: E2A02

The patient was a 56-year-old female with multiple myeloma who died while on a phase 2 trial using the investigational agent PS-341. She began her first course of treatment on December 27, 2004 with the intent of receiving PS-341 1.3 mg/m<sup>2</sup> by intravenous push on days 1, 4, 8, and 11, every 21 days. She only received two of the four planned doses, with the last dose administered on December 30, 2004.

The patient was diagnosed with multiple myeloma in October 2004. At the time of study entry, the patient was on Flagyl<sup>®</sup> for a *C. difficile* infection, resulting from antibiotic usage; she was also on chronic prednisone for adrenal insufficiency. She had a history of chronic renal insufficiency attributed to long-standing use of NSAIDs. She began PS-341 treatment on December 27, 2004 and tolerated the first two doses, except for complaints of fatigue and grade 2 diarrhea. According to her family, she felt fine after the second treatment and went to a party that evening with relatives. When she returned home later that night, she had several episodes of syncope, and her family took her to the emergency room (ER) early in the morning. Upon admission, she was noted to have a decreased level of consciousness, with a small contusion on her forehead. She was also severely bradycardic, for which she received atropine. An emergency head CT scan was performed, which did not show any evidence of hemorrhage or fracture. A chest X-ray revealed an infiltrate at the right base. Significant laboratory values included an ionized calcium level of 0.73 mmol/L (reference range: 1.13-1.29 mmol/L), a troponin I level of 0.27 ng/mL (reference range: 0.04-0.10 ng/mL), a CKMB isoenzyme level of 4.3 ng/mL (reference range: 0.5-3.7 ng/mL), a positive CKMB interpretation, and a myoglobin level of 911 ng/mL (reference range 1-85 ng/mL). No toxicology screen was done. The patient was given calcium gluconate for the hypocalcemia. It was felt that the myoglobin level was elevated due to muscle damage from the fall. It was noted that the cardiac markers were consistent with ischemic changes. The patient was transported from the ER to the telemetry unit. Shortly after

arrival in the telemetry unit, the patient went into asystole. Cardiopulmonary resuscitation efforts were unsuccessful, and the patient died on December 31, 2004. The family refused an autopsy.

The patient's past medical history is significant for rheumatoid arthritis, gastroesophageal reflux, osteoporosis, depression, adrenal insufficiency, chronic renal insufficiency, and narcotic addiction with seizures at the time of narcotic withdrawal.

Medications at the time of the event included Actonel<sup>®</sup>, Lexapro<sup>®</sup>, Estrace<sup>®</sup>, Reglan<sup>®</sup>, Aciphex<sup>®</sup>, amitriptyline, Provera<sup>®</sup>, prednisone, Dilantin<sup>®</sup>, Arava<sup>®</sup>, Neurontin<sup>®</sup>, calcium, and vitamins.

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In this case, it is felt that the study drug probably contributed to the hypotension and the subsequent cardiac events and the patient's underlying disease possibly contributed to the event; however, it is also probable that a myocardial infarction (MI) contributed to the event. There have been 1317 patients enrolled in NCI sponsored clinical trials under this IND.

	<b>Conduction Abnormality --</b>
<b>PS-341</b>	<b>Asystole</b>
<b>Multiple myeloma</b>	<b>Possible</b>
<b>Possible MI</b>	<b>Possible</b>
	<b>Probable</b>

Date: 2/25/05

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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