



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** September 17, 2004

**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\_1992202

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: June 3 2004

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

SUBJECT: PS-341 IND Safety Report, AE# 1992202 (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 63-year-old male with gall bladder cancer experienced grade 4 CNS cerebrovascular ischemia and grade 3 hypotension, and subsequently died after being treated with PS-341. The patient was initially diagnosed with gall bladder cancer in January 2003 and received adjuvant chemotherapy and radiation therapy. On Day 6 of cycle 2, the patient was admitted to the hospital with nausea, vomiting, dehydration, and uncontrollable shaking of his right arm. The treating physician felt that he either had a focal seizure of unknown etiology or a dystonic reaction to prochlorperazine. He underwent both a CT scan and a MRI scan. The CT scan performed on Day 6, cycle 2, did not demonstrate areas of infarction; however, the MRI scan on Day 7, cycle 2, revealed infarcts in the right frontal and right parietal occipital cortex, consistent with acute watershed-type infarction. Also, during this hospitalization, the patient had a paracentesis for 5.5 liters of fluid, with positive cytology. Of note, he did not have ascites prior to starting therapy with PS-341. He was discharged on Day 8, but was re-admitted on Day 10, cycle 2, with significant dysarthria, right hemiparesis, left facial droop, and extremely diminished oral intake over a few days' duration. A CT scan of the brain performed on this date revealed a new left hypodensity in the temporal lobe. His blood pressure on admission was 67/47 mmHg; therefore, attempts were made to maintain the patient's hydration status, so as not to further exacerbate the areas of infarct. His platelet count on the day of admission was 67,000/mm<sup>3</sup> (normal range 15,000-40,000/mm<sup>3</sup>), and thus, anti-platelet therapy was precluded. Ascite re-accumulation was noted on the day of admission. A discussion was held with the family, and they opted for comfort measures only. After a 9-day hospitalization, the patient was placed on a morphine infusion and died.

**CONFIDENTIAL**

There have been 11 other incidences of cerebrovascular ischemia reported as a serious adverse event to the NCI under this IND, 6 with a possible attribution to the drug. There have been 818 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. IND Safety Report: Event: Gr. 5: Death-Progressive disease Gr. 4: CNS cerebrovascular ischemia Gr. 3: Hypotension
AE: 1992202	Protocol: 6135

A 63-year-old male with gall bladder cancer developed cerebrovascular ischemia and subsequently died while on a phase 2 trial assessing the investigational agent PS-341 (bortezomib). He began his first course of treatment on February 1, 2004, receiving 1.3 mg/m<sup>2</sup> of PS-341 as an intravenous push over 3-5 seconds on days 1, 4, 8, and 11, every 21 days. He started cycle 2 of therapy on March 2, 2004, and received 2 doses, with the last dose on March 5, 2004.

The patient was initially diagnosed with gall bladder cancer in January 2003 and received adjuvant chemotherapy and radiation therapy. He did well for the first year until he was found to have progressive disease by a positive peritoneal biopsy. On March 7, 2004 (cycle 2, Day 6), the patient was admitted to the hospital with nausea, vomiting, dehydration, and uncontrollable shaking of his right arm. The treating physician felt that he either had a focal seizure of unknown etiology or a dystonic reaction to prochlorperazine. He underwent both a CT scan and a MRI scan. The CT scan performed on March 7, 2004, did not demonstrate areas of infarction; however, the MRI scan on March 8, 2004, revealed infarcts in the right frontal and right parietal occipital cortex, consistent with acute watershed-type infarction. Also, during this hospitalization, the patient had a paracentesis for 5.5 liters of fluid, with positive cytology. Of note, he did not have ascites prior to starting therapy with PS-341. He was discharged on March 9, 2004. He was re-admitted on March 11, 2004, with significant dysarthria, right hemiparesis, left facial droop, and extremely diminished oral intake over a few days' duration. A CT scan of the brain performed on this date revealed a new left hypodensity in the temporal lobe. His blood pressure on admission was 67/47 mmHg; therefore, attempts were made to maintain the patient's hydration status, so as not to further exacerbate the areas of infarct. His platelet count on the day of admission was 67,000/mm<sup>3</sup> (normal range 15,000-40,000/mm<sup>3</sup>), and thus, anti-platelet therapy was precluded. Ascite re-accumulation was noted on the day of admission. A discussion was held with the family, and they opted for comfort measures only. The patient was placed on a morphine infusion and died on March 20, 2004.

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The patient's past medical history is only significant for the gall bladder cancer and chronic obstructive pulmonary disease (COPD). Medications at the time of the event included bortezomib, ciproflaxin, prophylactic subcutaneous heparin (started on the second hospital admission), protonix, and morphine.

There have been 11 other incidences of cerebrovascular ischemia reported as a serious adverse event to the NCI under this IND, 6 with a possible attribution to the drug. In this case, it is felt that the study drug, the patient's underlying disease, and the ascites all possibly contributed to the event of cerebrovascular ischemia. Hypotension is a known side effect of PS-341; however, the presence of ascites probably contributed to the hypotension, as well as the patient's underlying disease possibly contributing to this event. It is felt that the patient's death was probably due to his underlying disease; however, a possible attribution to the study agent cannot be excluded. There have been 818 patients enrolled in NCI-sponsored clinical trials under this IND.

	Death	Cerebrovascular ischemia	Hypotension
PS-341	Possible	Possible	Probable
Gall bladder cancer	Probable	Possible	Possible
Ascites	Unlikely	Possible	Probable

Date: 6/15/04

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: Nicole Graber  
 Millennium Pharmaceuticals, Inc.

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