



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: April 15, 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_1663268

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: March 16, 2005

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

SUBJECT: PS-341 IND Safety Report, AE# 1663268

TO: Investigators Using PS-341, 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 70-year-old male with hepatocellular carcinoma developed grade 4 pulmonary embolism and later died as a result of intra-abdominal bleeding likely due to a hypervascular liver tumor while on a phase 2 trial using the investigational agent PS-341.

There have been 13 other incidences of gastrointestinal hemorrhage and 24 other incidences of thrombus/embolism reported to the NCI as serious adverse events under this IND with attributions to the study agent as follows:

Hemorrhage, GI (n=13)	2 unrelated, 7 unlikely, 4 possible
Thrombus/embolism (n=24)	2 unrelated, 17 unlikely, 5 possible

There have been 1332 patients enrolled in NCI-sponsored clinical trials under this IND.

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ADVERSE EVENTS ASSESSMENT

IND 58443 NSC 681239 PS-341 (bortezomib; Velcade)	ADVERSE EXPERIENCE REPORT NO. 39 IND Safety Report: Event: Gr: 5 Hemorrhage, GI: Liver Gr: 4 Thrombosis/thrombus/embolism Protocol: 6139
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The patient was a 70-year-old male with hepatocellular carcinoma who developed a pulmonary embolism and later died as a result of intra-abdominal bleeding likely due to a hypervascular liver tumor while on a phase 2 trial using the investigational agent PS-341. He began his first course of treatment on February 14, 2005, receiving PS-341 1.3 mg/m² by bolus intravenous injection over 3-5 seconds twice weekly for 2 weeks, every 21 days. He received two of four treatments on the first course, with the last dose on February 17, 2005.

The patient had a history of hemochromatosis, diagnosed in 2000, for which he was regularly managed with phlebotomies. On January 30, 2005, the patient presented to the hospital with left upper quadrant pain. At that time, his CT scans revealed numerous hepatic masses, and a biopsy later confirmed the diagnosis of hepatocellular carcinoma. A subsequent CT scan of the chest revealed multiple lung metastases as well. On February 22, 2005, he presented to the hospital Emergency Room (ER) with a sudden onset of severe chest pain and dyspnea. The pain was non-radiating and increased severely with deep inhalation. A CT scan of the chest revealed a right upper lobe pulmonary embolism. He was immediately placed on a heparin drip and Coumadin[®]. Additional imaging of the pelvis and lower extremities showed no evidence of DVT. During his hospitalization, he became quite agitated and was found to have an ammonia level as high as 126 µg/dL (reference range: 11-60 µg/dL), for which he was started on lactulose. A CT scan of the head did not show any metastasis or any evidence of acute intracranial bleeding or acute infarct. The patient's condition stabilized, and he was discharged 5 days after admission on Coumadin[®] daily with the appropriate follow-up for titration of Coumadin[®] levels. Due to this event, he was removed from the protocol on February 28, 2005.

He presented to the ER on March 7, 2005 with a 2-day history of extreme shortness of breath and extreme abdominal pain. His blood pressure upon arrival was 80/50 mm/Hg. His hemoglobin level was noted to have dropped dramatically from 11.7 g/dL (reference range: 13.2-17.5 g/dL) on March 1, 2005 to 6.1 g/dL upon admission. His blood gas results revealed marked acidosis, with a pH of

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7.043 (reference range: 7.35-7.45), PCO2 of 24.5 mmHg (reference range: 35.0-45.0 mmHg), and PO2 of 137.6 mmHg (reference range: 80.0-100.0 mmHg) on approximately 80% FIO2. A CT scan of the abdomen and pelvis showed catastrophic intra-abdominal bleeding likely coming from a hypervascular liver tumor. Additional blood tests revealed an INR of 5.77 and lactic acid level of 20.61 mmol/L (reference range: 0.93-1.65 mmol/L), which were felt to be almost unsurvivable. Therefore, after discussion with the patient's family and in accordance with the patient's wishes, it was decided to opt for keeping him as comfortable as possible. The patient subsequently expired in the Emergency Room on March 7, 2005.

The patient's past medical history is significant for kidney stones, symptomatic gout, hypertension, and smoking (1 pack/day). Medications at the time of the initial pulmonary event included ursodiol, mirtazapine, and Ativan®. Medications at the time of the fatal event included Coumadin®, lactulose, doxepin, Seroquel®, and ursodiol.

There have been 13 other incidences of gastrointestinal hemorrhage and 24 other incidences of thrombus/embolism reported to the NCI as serious adverse events under this IND. The attributions are summarized as follows:

Hemorrhage, GI (n=13)	2 unrelated, 7 unlikely, 4 possible
Thrombus/embolism (n=24)	2 unrelated, 17 unlikely, 5 possible

In this case, it is felt that the intra-abdominal bleeding was probably due to the patient's underlying disease, possibly due to the Coumadin®, and unlikely due to the PS-341. While the patient's underlying disease is considered to have probably caused the pulmonary embolism; the possibility that the study drug possibly contributed to this event cannot be excluded.

There have been 1332 patients enrolled in NCI-sponsored clinical trials under this IND.

	Hemorrhage, GI: Liver	Thrombosis/thrombus/embolism
PS-341	Unlikely	Possible
Hepatocellular carcinoma	Probable	Probable
Coumadin®	Possible	

Date: 3/17/05

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.

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