



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: August 26, 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_1456035

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: July 8, 2005
FROM: John Wright, M.D., Ph.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: PS-341 IND Safety Report, AE# 1456035
TO: Investigators Using PS-341, IND 58443

(JW) 7/29/05

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 event, previous experience under this IND, and the total number of patients enrolled under this IND is attached:

The patient is a 41-year-old male with gastric cancer and peritoneal carcinomatosis who experienced grade 4 cardiac ischemia/infarction while on a phase 2 trial using the investigational agent PS-341 in combination with irinotecan.

ADVERSE EVENTS ASSESSMENT

IND 58443	ADVERSE EXPERIENCE REPORT NO. #42 IND Safety Report: Event: Gr 4: Cardiac ischemia/infarction Protocol: 5941
NSC 681239	
PS-341 (bortezomib; Velcade™)	
AE: 1456035	

The patient is a 41-year-old male with gastric cancer and peritoneal carcinomatosis who experienced cardiac ischemia/infarction while on a phase 2 trial using the investigational agent PS-341 in combination with irinotecan. The patient began his cycle 1 of treatment on May 9, 2005, receiving PS-341 1.3 mg/m² by intravenous push (IVP) on days 1, 4, 8, and 11, every 21 days. The patient also received irinotecan 125 mg/m² by IV over 90 minutes on days 1 and 8, every 21 days. The patient completed his cycle 1 of therapy, with the last dose of PS-341 administered on May 19, 2005, and the last dose of irinotecan administered on May 16, 2005.

The patient was originally diagnosed with gastric cancer and peritoneal carcinomatosis in April 2005. He started on the PS-341 trial on May 9, 2005. He tolerated his cycle 1 therapy well. On May 31, 2005, he presented to the clinic for his cycle 2 therapy with a 2-day history of intermittent chest pain radiating to his left arm. In the clinic, he stated that he had chest tightening and pain radiating across his chest wall and to his left arm. His pain started that morning and increased in severity throughout the morning. He denied any shortness of breath or diaphoresis. Of note, prior to this episode, he had no known cardiac risks factors except for smoking one pack of cigarettes per day for 19 years. He was referred to the Emergency Room (ER) where an EKG was performed, which showed trigeminy and ST elevation. He was found to have an acute myocardial infarction and was immediately sent to the cardiac catheter lab where he underwent a successful thrombectomy of a proximal distal left anterior descending coronary artery (LAD) lesion by balloon angioplasty with partial restoration of flow distally (LVEF of 40%). He was then admitted to the CCU for further monitoring and evaluation. His chest pain remained unchanged. He was started on a nitroglycerin drip, morphine IVP, ReoPro®, and a heparin drip. An EKG later that day showed partial resolution of repolarization abnormalities. By June 1, 2005, the patient had no further chest pain, and the nitroglycerin drip and ReoPro® were subsequently discontinued. His cardiac status continued to improve. Echocardiograms performed on June 4, 2005, revealed an LVEF of 45%, no effusion, normal mitral valve leaflets, and possible segmental wall motion abnormalities suggestive of coronary artery disease. An EKG performed at that time showed sinus bradycardia with a heart rate of 44 bpm. He completed heparin therapy that day and was discharged home with instructions to follow-up with his oncologist and cardiologist in 1 week.

The patient's past medical/surgical history is significant for a gastric bypass, colostomy, cholecystectomy, and donor pancreatectomy. Medications taken at the time of event included Aldactone®.

There have been five (5) other incidences of cardiac ischemia/infarction reported to the NCI as serious adverse events under this IND, and they were considered unlikely related to the study drug.

In this case, given the patient's relatively young age, the cardiac ischemia/infarction was considered possibly related to the investigational agent PS-341. There have been 1444 patients enrolled in NCI-sponsored clinical trials under this IND.

	Cardiac ischemia/infarction
PS-341	Possible
Irinotecan	Possible
Gastric cancer	Unlikely
Aldactone®	Unlikely
ASCVD	Probable

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Smoking hx
Obesity

Possible
Possible

Date: 7/29/05

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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