



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: May 13, 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_1292914

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: April 11, 2005 JW 4/29/05

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

SUBJECT: PS-341 IND Safety Report, AE# 1292914

TO: Investigators Using PS-341 (bortezomib; Velcade®), 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 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 71-year-old male with multiple myeloma who died of a gastrointestinal perforation while on a phase 2 trial using the investigational agent PS-341 in combination with liposomal doxorubicin.

There has been one other incidence of gastrointestinal perforation (grade 4), ten incidences of obstruction, one incidence of colonic wall thickening, one incidence of ischemic bowel, four incidences of ileus, and two incidences of ulcer reported to the NCI as serious adverse events under this IND.

Obstruction (n=10)	1 probable, 4 possible, 2 unlikely, 3 unrelated
Colonic wall thickening (n=1)	1 possible
Ischemic bowel (n=1)	1 possible
Perforation (n=1)	1 possible
Ileus (or neuroconstipation) (n=4)	1 probable, 3 unlikely
Ulcer (n=2)	2 unlikely

There have been 1314 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. 41 IND Safety Report: Event: Gr: 5 Perforation, GI: Colon
AE: 1292914	Protocol: CALGB-10301

The patient is a 71-year-old male with multiple myeloma who died while on a phase 2 trial using the investigational agent PS-341 in combination with liposomal doxorubicin. He began his first course of treatment on November 2, 2004, receiving PS-341 1.3 mg/m² by intravenous (IV) push over 3-5 seconds on days 1, 4, 8, and 11 and liposomal doxorubicin 30 mg/m² IV over 1 hour on day 4, every 21 days. He completed 6 courses of treatment receiving his last dose of liposomal doxorubicin on March 4, 2005 and his last dose of PS-341 on March 11, 2005.

The patient was presented to the emergency room in July 2004 with complaints of severe lower back pain. An MRI scan conducted July 21, 2004 revealed T9 compression fracture with bony retropulsion and moderate canal stenosis. On September 15, 2004 he underwent a kyphoplastic of T9, with the pathology revealed a plasma cell myeloma. At the time of study entry in November, the patient had multiple lytic lesions. He was seen in clinic for the start of cycle 6 on March 1, 2005. At that time it was noted that his bone pain was decreased and he had grade 2 anorexia with a 14 lb weight loss from the start of therapy. On March 11, 2005, he was complaining of grade 3 fatigue, grade 2 bone, back, and leg pain, grade 2 abdominal pain, grade 2 constipation, grade 2 nausea, and continued grade 2 anorexia. On March 15, 2005 (course 6, day 15) the patient presented to the emergency room with severe nausea, vomiting, and severe abdominal and back pain. A CT scan of the abdomen revealed free air and complex fluid within the upper abdomen surrounding the liver and greater curvature of the stomach on the left side and tracking into the paracolic gutters indicative of bowel perforation. The source of the perforation was not identified. Of note, a pre-study abdominal CT or abdominal X-ray was not conducted. The patient was managed for pain and hydrated. The patient's condition deteriorated quickly, and the patient's family requested the patient status changed to DNR. He expired on March 16, 2005.

The patient's past medical history is significant for smoking (50 years), stomach ulcers, colon surgery in 2003, and vertebral compression. Medications at the time of the event included Aranesp®, Zometa®, MS Contin®, Percocet®, Prilosec®, Carafate®, vitamin B6, and laxatives.

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In this case, it is thought that the gastrointestinal perforation was possibly related to PS-341, liposomal doxorubicin, the patient's underlying disease, and duodenitis. There have been 1314 patients enrolled in NCI-sponsored clinical trials under this IND.

	Perforation, GI: Colon
PS-341	Possible
Liposomal doxorubicin	Possible
Myeloma	Possible
Duodenitis	Possible

Date: 4/29/05

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