



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: November 14, 2008

To: NCCTG Primary Clinical Research Associates

From: Alicia Elsing
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_1203812

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 Alicia Elsing at Elsing.alicia@mayo.edu or 507-538-3893.

AE/kjm
enclosure

INITIAL IND SAFETY REPORT: FOLLOW-UP #1

#57

TO: *Division of Drug Oncology Products, Center for Drug Evaluation and Research, FDA*

FAX: 301-796-9845

1. IND NUMBER 57966 58443	2. AGENT NAME 17-AAG (17-Allylaminogeldanamycin) PS-341 (bortezomib)	3. DATE October 20, 2008
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4. SPONSOR
Division of Cancer Treatment and Diagnosis, National Cancer Institute

5. REPORTER=S NAME, TITLE, AND INSTITUTION S. Percy Ivy, MD - Associate Branch Chief for Investigational Therapeutics 1, Investigational Drug Branch, CTEP, DCTD, NCI John Wright, MD, PhD - Associate Branch Chief for Investigational Therapeutics 2, Investigational Drug Branch, CTEP, DCTD, NCI	6. PHONE NUMBER 301-496-1196	7. FAX NUMBER 301-402-0428
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8. PROTOCOL NUMBER (AE #)
6121 (AE # 1203812)

9. PATIENT IDENTIFICATION 69366862	10. AGE 76	11. SEX Male
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12. DESCRIPTION OF ADVERSE EVENT
The patient was a 76-year-old male with metastatic rectal cancer who experienced grade 5 colitis while on a phase 1 study using the investigational agent 17-AAG in combination with PS-341. He began his first course of treatment on September 30, 2008, and received the last doses of 17-allyminogeldanamycin/bortezomib, on October 3, 2008, (Cycle 1, Day 4). On October 4, 2008, the patient presented to the emergency room complaining about abdominal pain and rectal bleeding, started that morning (Cycle 1, Day 5). The patient had episodes of hypertension in the ER, and metoprolol IV was administered to lower his blood pressure. Pulse remained stable, and vital signs were normal. Hyponatremia was revealed, and despite normal saline fluid resuscitation, the patient continued to lose significant amounts of fluid but no blood was visualized. He was admitted to the hospital on October 4, 2008, and he was found to have diffuse colitis as well as lactic acidosis. On October 5, 2008, the patient developed respiratory compromise accompanied by an acute rise of lactate levels and BNP. His cardiac enzymes were elevated, and the echocardiogram showed an ejection fraction of 30-35%. He rapidly deteriorated and developed multisystem organ failure with acute renal failure, acute liver failure, hypoxic hypercapnic respiratory failure with metabolic acidosis, and myocardial dysfunction with an ejection fraction of 30% and elevated cardiac enzymes. Overnight, he had worsening respiratory failure and was started on BiPAP but became somnolent and nonresponsive to verbal and painful stimuli. The patient passed away on October 6, 2008. Additional information has been requested. There is a reasonable possibility that the experience may have been caused by the drug.

13. DOSE, ROUTE, AND SCHEDULE
Cycle = 21 days; 17-AAG 200mg/m² IV infusion on Days 1, 4, 8 and 11 and PS-341 1mg/m² IV push on Days 1, 4, 8 and 11

14. DATES OF TREATMENT
The patient started the investigational therapy on September 30, 2008, and received the last doses of 17 AAG/PS-341 on October 3, 2008.

15. ACCRUAL AND IND EXPERIENCE
Number of patients enrolled in NCI-sponsored clinical trials using 17-AAG=659 and PS=2534
There have been 2 other cases of colitis, and 1 other case of acidosis for PS-341 and no cases of colitis and 1 other case of acidosis for 17-AAG reported to the NCI through AdeERS as serious adverse events.

16. COMMENTS
~~The following was also administered every cycle (21 days): paclitaxel: 175 mg/m² IV over 3 hours on Day 1 x 6 eyes, and carboplatin: AUC 6 IV over 30 minutes on Day 1 x 6 eyes, and her last doses of paclitaxel and carboplatin were administered on March 28, 2008.~~

AT THIS TIME, NO OTHER INFORMATION IS AVAILABLE. IF UPON FURTHER INVESTIGATION RELEVANT INFORMATION BECOMES AVAILABLE, THEN A FOLLOW-UP REPORT WILL BE SUBMITTED IN ACCORDANCE WITH 21CFR 312.32(d)(2).

DISCLAIMER per 21 CFR 312.32(e): THIS SAFETY REPORT DOES NOT NECESSARILY REFLECT A CONCLUSION OR ADMISSION BY THE CTEP IDB SENIOR INVESTIGATOR/ SPONSOR THAT THE INVESTIGATIONAL AGENT/THERAPY CAUSED OR CONTRIBUTED TO THE ADVERSE EXPERIENCE BEING REPORTED.

FOLLOW-UP: TO DELETE THE INFORMATION PROVIDED IN SECTION 16 (COMMENTS) WHICH DOES NOT APPLY TO THIS REPORT