

North Central Cancer Treatment Group

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)

Addendum 11 – February 20, 2009

Summary

This addendum is in response to a special request from Dr. John Wright of the National Cancer Institute (NCI) dated January 14, 2009 concerning bortezomib (PS-341). The background section, the drug information section, and the risks section of the consent forms have been updated to reflect current drug safety information.

Risk changes in this addendum have been determined by NCI to not significantly alter the risk-benefit profile for patients.

New patients cannot be enrolled until this addendum has been approved by the local IRB. Patients who are newly enrolled or presently on study treatment are to be re-consented and a notation of this interaction is to be made in the patient chart or research record. Patients are to sign a revised IRB-approved informed consent form or other IRB-approved document including this information.

Determination of the level of IRB review for minor risk changes (expedited versus full board review) is at the discretion of the local IRB.

A replacement protocol is provided. Please replace the current copy with the one attached. Please keep this addendum with your protocol

Title Page

Updated to reflect Addendum 11 and revised NCI version date.

Section 1.0

Page 9:

Background

The following background information has been added to Section 1.6 as follows:
RPLS is a clinico-radiological entity associated with capillary leak and vasogenic edema in the brain (27,28). Clinical presentations are nonspecific and may include headache, altered mental status, seizure, and cortical visual disturbance. An MRI is required for diagnosis, typically demonstrating vasogenic edema predominantly involving the white matter of posterior parietal and occipital lobes, although gray matter and abnormalities in the anterior distributions may also be seen. [Vasogenic edema typically presents as hyperintensity in the T2-weighted images and fluid-attenuated inversion recovery (FLAIR) sequences, and hypointensity or isointensity on T1-weighted images; new MRI technologies such as diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps may help in differentiating RPLS from ischemic events.] RPLS is often reversible after correction of the underlying conditions, but in more severe cases, permanent neurological deficit may ensue. RPLS has been described in a number of clinical settings such as hypertensive encephalopathy, pregnancy/eclampsia,

and renal failure, and has been reported in association with cancer drugs such as interferon- α , G-CSF, cyclosporine, cisplatin, capecitabine, sunitinib, bevacizumab, and others. The mechanism of bortezomib-related RPLS is unknown, but it is possible that bortezomib may induce vasogenic edema/capillary leak in the brain through direct effect on endothelial cells, and/or through indirect mechanisms related to vasospasm and hypertension.

Pages 9-11: Due to the additional text being added to Section 1.6 repagination has occurred.

Section 15.0 Drug Information

Pages 39-42: Due to the receipt of an updated CAEPR (version 2.1) for bortezomib, Section 15.16 has been replaced in its entirety.

Pages 39-57: Due to the insertion of the updated CAEPR for bortezomib, repagination has occurred.

Appendices IA and 1B Consent Forms

Page 5: In order to reflect current drug safety information for bortezomib, the risks section of the consent form has been revised as follows:

Likely related side effects of PS-341 (events occurring greater than 20% of the time):

- Fatigue (~~feeling tired or weak~~); lethargy, malaise, general discomfort (*wording condensed*)
- Loss of appetite
- ~~Weight loss (deleted)~~
- Nausea (feeling sick to your stomach)
- Vomiting (throwing up)
- ~~Pain—abdominal, headache/head, bone, joints, muscles—(moved to Less Likely and separated)~~
- ~~Pain or Swelling and fluid buildup~~ in the arms or legs (*reworded – leg pain has been moved to Less Likely*)
- ~~Weakness caused by damage of the nerves (moved to Less Likely and wording expanded)~~
- Diarrhea (**loose stools**) (*wording expanded*)
- Constipation (difficulty passing stool)
- Fever
- ~~Lowering of the red blood cell count causing anemia (deleted)~~
- ~~Lowering of blood clotting cells with an increased risk of bleeding and may lead to life threatening bleeding~~ **Decreased number of blood cells that help to clot the blood** (*reworded*)
- ~~Lowering of the white blood cell counts with an increased risk of infection and even life threatening infections (moved to Less Likely and reworded)~~
- ~~Problems with the central nervous system (the brain and spinal cord) which controls mental activities, movements and nerves (deleted)~~
- ~~Dehydration—Loss of fluid in the body, may need to stay in the hospital (moved to Less Likely and wording condensed)~~
- ~~Painful sensations, numbness, tingling or weakness in the arms and legs (neuropathy), which may not get better after discontinuation of this drug~~ **Nerve damage causing numbness, tingling, burning (peripheral neuropathy)** (*reworded*)
- ~~Feeling dizzy or lightheaded and, uncommonly, fainting. You should not drive any vehicle or operate any dangerous tools or machinery if you experience these symptoms. (moved to Less Likely and wording condensed)~~

- ~~Anxiety (moved to Less Likely)~~
- ~~Cough (moved to Less Likely)~~
- ~~Shortness of breath (moved to Less Likely)~~
- ~~Rash with itching and redness. An uncommon risk is a severe, life-threatening or deadly rash with shedding of the skin and mouth sores. (moved to Less Likely and reworded)~~
- ~~Low blood pressure (moved to Less Likely)~~
- ~~Decrease in kidney function, kidney damage or failure (moved to Rare but serious and wording condensed)~~
- ~~Pneumonia (moved to Less Likely)~~
- ~~Irritation in the stomach or intestinal tract, or mouth, which can cause pain (deleted)~~
- ~~Trouble sleeping (moved to Less Likely and reworded)~~
- ~~Herpes zoster (shingles), which occasionally results in persistent local pain, can sometimes spread over large areas of the body and, uncommonly, can affect the brain (deleted)~~
- **Decrease in a red blood cell protein that carries oxygen in the body (newly added)**
- **Infection (newly added)**

Less likely related side effects of PS-341 (events occurring greater than 3% but less than 20% of the time):

- ~~Runny, stuffy, or itchy nose (deleted)~~
- ~~Ringing or buzzing in the ears (deleted)~~
- ~~Drop in heart's ability to pump blood (deleted)~~
- ~~Fluid around the heart (deleted)~~
- ~~Uncontrollable shaking and Chills, shivering (reworded)~~
- ~~Redness in the face (deleted)~~
- ~~Bruising, bleeding, soreness or redness of the skin where the injection is given (deleted)~~
- ~~Itching (deleted)~~
- ~~Skin peeling (deleted)~~
- ~~Hives or welts on the skin (deleted)~~
- ~~Passing gas (deleted)~~
- ~~Heartburn~~
- ~~Slowing of the small intestine causing stomach pain, bloating and cramping (ileus) which can lead to obstructions and in very rare instances surgery **Abnormally slow bowel contraction (reworded)**~~
- ~~Irritation or sores in the lining of the throat (wording expanded)~~
- ~~Changes in taste (deleted)~~
- ~~Bleeding anywhere in the body (i.e., intestine, brain) which may or may not be associated with low platelet counts and blood clotting changes. This bleeding may result in bloody diarrhea and/or bloody vomit. Your doctor may recommend preventative platelet transfusions to rescue the risk of bleeding. (deleted)~~
- ~~Fever with **dangerously** low white blood cell count (wording expanded)~~
- ~~Infection (sinus, bladder, throat, stomach, intestines, skin) which can be life-threatening and result in multi-organ failure or death. The infection could be caused by bacteria, virus, or fungus.~~
- ~~Swelling in the head and neck (deleted)~~
- ~~Abnormal tests of liver function. Uncommon risks are hepatitis and liver failure in patients who had received multiple other medications and had other serious medical conditions. (deleted)~~
- ~~High/low blood sugar. If you are a diabetic and are taking oral anti-diabetic agents, you may require close monitoring of your blood sugar levels. (deleted)~~

- ~~Increase or decrease in critical salts from the blood including sodium, potassium, magnesium, phosphate, calcium~~ *(deleted)*
- ~~Change in walking stride or function (walking with a limp)~~ *(deleted)*
- ~~Mood changes (feeling agitated)~~ *(deleted)*
- ~~Dry eye syndrome~~ *(deleted)*
- ~~Damage to the surface of the eye~~ *(deleted)*
- Double or blurred vision
- ~~Pain in the back **pain**, chest, throat, voice box, or nerves~~ *(with the exception of back pain, all others have been deleted)*
- ~~Hiccups~~ *(deleted)*
- ~~Fluid around the lungs~~ **Excess fluid that accumulates in the pleural cavity, the fluid-filled space that surrounds the lungs** *(wording expanded)*
- ~~Potentially life-threatening allergic reaction to the medication~~ *(deleted)*
- ~~Changes in heart rate or rhythm (possibly with the feeling of confusion, lightheadedness, dizziness, fainting, shortness of breath, and/or chest discomfort). An uncommon risk is a potentially life-threatening abnormal heart rhythm.~~ *(deleted)*
- ~~New onset or worsening of heart failure (which may appear as shortness of breath, swelling in the legs, and/or chest pain) or decreased heart function. If you have heart failure or other disease that put you at risk of developing heart failure, you should tell your doctor.~~ *(deleted)*
- ~~Sepsis (severe infection which could lead to multi-organ dysfunction or death)~~ *(deleted)*
- ~~Inflammation of the pancreas~~ *(deleted)*
- ~~Inflammation in the intestinal tract~~ *(deleted)*
- ~~Severe nerve damage resulting in profound weakness, paralysis, confusion, or seizures~~ *(deleted)*
- ~~Symptoms of flu and other upper respiratory tract infections, such as chills, sore throat, and runny nose~~ *(deleted)*
- ~~Weight gain~~ *(deleted)*
- **Weakness or paralysis caused by damage to nerves** *(moved from Likely)*
- **Infection which occurs due to a decreased number of a type of white blood cell** *(moved from Likely and reworded)*
- **Dehydration (loss of body fluids)** *(moved from Likely and wording expanded)*
- **Nerve damage causing numbness, tingling, burning (sensory neuropathy)** *(newly added)*
- **Dizziness** *(moved from Likely and wording condensed- formerly “Feeling dizzy...”)*
- **Anxiety** *(moved from Likely)*
- **Cough** *(moved from Likely)*
- **Shortness of breath** *(moved from Likely)*
- **Rash/flaking or shedding of out layer of skin** *(moved from Likely and reworded- formerly “Rash with itching...”)*
- **Low blood pressure** *(moved from Likely)*
- **Pneumonia** *(moved from Likely)*
- **Difficulty sleeping or falling asleep** *(moved from Likely and reworded – formerly “Trouble sleeping”)*
- **Decreased total number of white blood cells** *(newly added)*
- **Decreased number of a type of white blood cell** *(newly added)*
- **Bleeding of the digestive tract** *(newly added)*
- **Nosebleed** *(newly added)*
- **Blood infection** *(newly added)*

- **Muscle weakness of the whole body** (*newly added*)
- **Fainting** (*newly added*)
- **Belly pain** (*moved from Likely and reworded – formerly “Abdominal pain”*)
- **Bone pain** (*moved from Likely*)
- **Leg pain** (*moved from Likely*)
- **Head pain** (*moved from Likely*)
- **Joint pain** (*moved from Likely*)
- **Muscle pain** (*moved from Likely*)
- **Nerve pain** (*newly added*)

Rare but serious side effects of PS-341 (events occurring less than 3% of the time):

- ~~Abnormal hole in the GI tract~~ **A hole in the digestive tract** (*reworded*)
- ~~Difficulty with urinating~~ (*deleted*)
- ~~Inflammation in the peripheral blood vessels with bleeding into the brain~~ (*deleted*)
- ~~Loss of hearing~~ (*deleted*)
- ~~A syndrome called “reversible posterior leukoencephalopathy syndrome” (RPLS) that affects the brain and can cause headaches, visual changes, altered mental status, or seizures, but it reversible.~~
Syndrome associated with high blood pressure characterized by headache, confusion, seizures, and vision loss associated with imaging findings (*reworded*)
- ~~A death of the cancer cells that occurs so quickly that it can cause release of toxins and injure organs, such as the kidneys.~~ (*deleted*)
- ~~Severe, life-threatening, or deadly lung disease of unknown cause which may include inflammation of and accumulation of fluid in the lungs. This problem has been seen most commonly in Japan. Other risk factors for this complication include co-administration of a drug called cytarabine and a drug called daunorubicin.~~ (*deleted*)
- ~~Elevated pressure in the lungs, called pulmonary hypertension, has also been reported. This can cause difficulty breathing and can be life threatening. If you have new or worsening breathing problems, you should tell your doctor.~~ (*deleted*)
- **Kidney failure** (*moved from Likely and wording condensed*)

Section 20.0

Page 57:

References

Due to the additional background information being added, the following references have been added:

27. **Stott VL, Hurrell MA, Anderson TJ. Reversible posterior leukoencephalopathy syndrome: a misnomer reviewed. Intern Med J 2005;35:83-90.**
28. **Lamy C, Oppenheim C, Meder JF, Mas JL. Neuroimaging in posterior reversible encephalopathy**