

North Central Cancer Treatment Group

N0779: Phase II Study of Vorinostat (SAHA) in Combination with Bortezomib (PS-341) in Patients with Recurrent Glioblastoma Multiforme

Addendum 4 – 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 the addition of Addendum 4 and revised NCI version date.

**Section 1.0** **Background**

Page 7:

The following background information has been added to Section 1.5 as follows:

**RPLS is a clinico-radiological entity associated with capillary leak and vasogenic edema in the brain (Scott, et al, 2005; Lamy, et al, 2004). 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- $\alpha$ , 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 7-10: Due to the additional text being added to Section 1.5 repagination has occurred.

**Section 15.0      Drug Information**

Pages 40-43: Due to the receipt of an updated CAEPR (version 2.1) for bortezomib, Section 15.26a has been replaced in its entirety.

Pages 40-61: Due to the insertion of the updated CAEPR for bortezomib, repagination has occurred.

**Section 20.0      References**

Page 61: Due to the additional background information being added, the following references have been added:

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

**Appendices IA-IB      Consent Forms**

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

**Likely** (*happening greater than 20% of the time*)

- ~~Changes in the blood counts: decrease of platelets that may increase the risk of bleeding; decrease in red cells which can result in anemia (decreased oxygen in the blood which can make you feel tired)~~
- **Decrease in a red blood cell protein that carries oxygen in the body** (*separated and reworded [above]*)
- **Decreased number of blood cells that help to clot the blood** (*separated and reworded [above]*)
- **Fever**
- ~~Gastrointestinal effects such as constipation (difficulty passing stool), diarrhea (loose stools), nausea (feeling sick to your stomach), vomiting (throwing up), and loss of appetite, which may result in dehydration (loss of body fluids) and/or weight loss (these have been separated as shown below and wording condensed)~~
- **Loss of appetite** (*separated from above*)
- **Constipation (difficulty passing stool)** (*separated from above*)
- **Diarrhea (loose stools)** (*separated from above*)
- **Nausea (feeling sick to your stomach)** (*separated from above*)
- **Vomiting (throwing up)** (*separated from above*)
- ~~Weakness, Fatigue, and general discomfort~~ (*wording condensed*)
- **Headache** (*moved to Less Likely and reworded*)

- ~~Insomnia (not able to sleep)~~ (moved to *Less Likely* and reworded)
- ~~Anxiety~~ (moved to *Less Likely*)
- ~~Cough, shortness of breath, lung infections including pneumonia~~ (all except lung infections have been moved to *Less Likely* – lung infections has been deleted)
- ~~Rash with itching and redness~~ (moved to *Less Likely* and reworded)
- ~~Painful sensations or numbness or tingling in the hands and feet (neuropathy), which may not get better after discontinuation of this drug~~ **Nerve damage causing numbness, tingling, burning (peripheral neuropathy)** (reworded)
- ~~Abdominal pain~~ (moved to *Less Likely* and reworded)
- **Infection** (newly added)
- **Swelling and fluid buildup in the arms and legs** (moved from *Less Likely*)

**Less Likely** (happening less than or equal to 20% of the time)

- ~~Decrease in white blood cell count which could increase your risk of infection including life-threatening infections~~ **Decreased total number of white blood cells** (reworded)
- **Decreased number of a type of white blood cell** (newly added)
- ~~Aches and pains in bones, muscles and joints~~ (separated as shown below)
- **Bone pain** (separated from above)
- **Joint pain** (separated from above)
- **Muscle pain** (separated from above)
- **Head pain/headache** (moved from *Likely* and reworded)
- **Back pain** (newly added)
- **Belly pain** (moved from *Likely* and reworded – formerly “abdominal pain”)
- **Nerve pain** (newly added)
- **Leg pain** (moved from below and wording condensed)
- ~~Decrease in blood pressure, dizziness, and uncommonly fainting. You should not drive any vehicle or operate any dangerous tools or machinery if you experience these symptoms~~ **Low blood pressure** (wording condensed – dizziness and fainting have been separated as shown below)
- **Dizziness** (separated from above)
- **Fainting** (separated from above)
- ~~Swelling and fluid buildup in the arms and legs~~ (moved to *Likely*)
- ~~Herpes zoster (shingles), a type of infection similar to the chickenpox, which occasionally results in persistent local pain and can sometimes spread over large areas of the body. Both may affect the brain.~~ (deleted)
- ~~Decrease in kidney function~~ (moved to *Rare but serious* and reworded)
- ~~New or worsening 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 puts you at risk of developing heart failure, you should tell your doctor.~~ (deleted)
- ~~Changes in heart rate or rhythm (possibly with the feeling of confusion, light headedness, dizziness, fainting, shortness of breath, and/or chest discomfort). An uncommon risk is a potentially life threatening abnormal heart rhythm.~~ (deleted)
- **Fluid accumulating around the heart or lung** **Excess fluid that accumulates in the pleural cavity, the fluid-filled space that surrounds the lungs** (reworded – reference to fluid around the heart has been deleted)
- ~~Infections of the bladder, sinuses, throat, stomach and intestines, blood, and skin, which can be life-threatening. The infection could be caused by bacteria, virus, or fungus.~~ (deleted)

- Symptoms of flu and other upper respiratory tract infections, such as chills, sore throat, and runny nose *(deleted)*
- Chest pain *(deleted)*
- Liver dysfunction including abnormal liver tests. Uncommon risks are hepatitis and liver failure in patients who had received multiple other medications and had other serious medical conditions *(deleted)*
- Changes in blood sugar have been reported in a few diabetic patients receiving oral anti-diabetic medication. If you 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, and calcium *(deleted)*
- Severe nerve damage resulting in profound weakness, paralysis, confusion, or seizures *(deleted)*
- Change in sense of taste *(deleted)*
- Pain, redness, swelling and/or infection at the injection site *(deleted)*
- ~~Painful Irritation or sores of the lining of the mouth and/or throat, which may make swallowing difficult~~ *(reworded)*
- Heartburn
- Nose bleeds
- ~~Yeast infections in the mouth, throat and vagina~~ *(deleted)*
- Life-threatening **blood** infections in the blood (sepsis) *(reworded)*
- Chills/shaking chills
- Ringing in the ears (tinnitus) *(deleted)*
- Hiccoughs *(deleted)*
- Flushing (blushing) *(deleted)*
- Flatulence *(deleted)*
- Changes to your eyes and vision that may include dry eye, damage to the surface of the eye, double vision, **B**lurred vision *(wording condensed)*
- Head edema (swelling of the head area) *(deleted)*
- Decrease in magnesium level in the blood *(deleted)*
- Decrease in phosphate level in the blood *(deleted)*
- Increased blood level of creatinine which can lead to kidney problems *(deleted)*
- ~~Back pain~~ *(moved above with other pain risks)*
- ~~Pain in the arms and legs~~ *(moved above with other pain risks and wording condensed – reference to pain in the arms has been deleted)*
- ~~Irritation in the mouth, stomach or intestinal tract, which can cause pain~~ *(deleted)*
- Severe bleeding, including bleeding in the stomach and intestines 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 reduce the risk of bleeding. *(deleted)*
- Lack of intestinal movement (ileus) which can lead to obstruction, surgery may be necessary to correct this. **Abnormally slow bowel contraction** *(reworded)*
- Rash *(deleted)*
- Hives *(deleted)*
- Dehydration (**loss of body fluids**) *(wording expanded)*
- ~~Bleeding in the brain~~ *(deleted)*
- **Rash/flaking or shedding of outer layer of skin** *(moved from Likely and reworded – formerly “Rash with itching and redness”)*

- **Bleeding of the digestive tract** (*newly added*)
- **Fever with dangerously low white blood cell count** (*newly added*)
- **Pneumonia** (*moved from Likely*)
- **Shortness of breath** (*moved from Likely*)
- **Cough** (*moved from Likely*)
- **Muscle weakness of the whole body** (*newly added*)
- **Anxiety** (*moved from Likely*)
- **Weakness or paralysis caused by damage to nerves** (*newly added*)
- **Difficulty sleeping or falling asleep** (*moved from Likely and reworded – formerly “Insomnia [not able to sleep”]*)
- **Nerve damage causing numbness, tingling, burning (sensory neuropathy)** (*newly added*)

**Rare but serious** (*happening less than 3% of the time*):

- ~~Potentially life threatening allergic reaction to the medication~~ (*deleted*)
- ~~Difficulty with urinating~~ (*deleted*)
- ~~Bleeding in or into the brain~~ (*deleted*)
- ~~Inflammation in the blood vessels in the arms and legs~~ (*deleted*)
- A syndrome called “reversible posterior leukoencephalopathy syndrome” (RPLS) that affects the brain and -may cause headaches, visual changes, altered mental status, or seizures (fits), but is usually reversible
- ~~A death of the cancer cells that occurs so quickly that it can cause release of toxins into the blood and injure organs, such as the kidneys~~ (*deleted*)
- ~~Loss of hearing~~ (*deleted*)
- ~~Severe, life threatening, or deadly lung diseases of unknown cause which may include inflammation of and accumulation of fluid in the lungs which can cause breathing problems. 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 (which you will not be receiving on this study).~~ (*deleted*)
- ~~Elevated pressure in the large blood vessels of 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*)
- ~~Severe, life threatening or deadly rash with shedding of the skin and mouth sores~~ (*duplicate – listed as “Rash/flaking or shedding of outer layer of skin” in Less Likely*)
- ~~Blood in the urine~~ (*deleted*)
- ~~Pain in the mouth and throat when swallowing~~ (*deleted*)
- ~~Coughing up blood~~ (*deleted*)
- ~~Severe muscle weakness and paralysis~~ (*deleted*)
- ~~Seizure~~ (*deleted*)
- ~~GI perforation (a hole in the gastrointestinal tract)~~ **A hole in the digestive tract** (*reworded*)
- **Kidney failure** (*moved from Less Likely and reworded – formerly “Decrease in kidney function”*)