

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 3 – January 9, 2009

**Summary**

- Treatment off protocol with this drug combination is not allowed. Safety with this combination in glioma patients has not yet been established and the efficacy is unclear. Therefore, clarification has been made in Section 13 (Treatment/Follow-up Decision at Evaluation of Patient).
- Upon review of the CAEPR listings for Vorinostat and Bortezomib, the consent forms have been revised accordingly

**Replacement pages are included. Please incorporate into the protocol and keep this addendum with your protocol.**

**Title page**

Updated to reflect the addition of Addendum 3 and revised NCI version date.

**Section 13.0**

Page 32:

**Treatment/Follow-up Decision at Evaluation of Patient**

The second sentence in Section 13.5 has been deleted as follows as the safety and efficacy of this combination has not yet been determined:

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. ~~The patient may continue treatment off protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered.~~ The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

Page 33:

The second to the last sentence in Section 13.6 has been deleted as follows as the safety and efficacy of this combination has not yet been determined:

A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will be observed 28-42 days following discontinuation of treatment and no additional follow-up will be required after that. ~~The patient may continue treatment off protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered.~~ Event monitoring will be required per Section 18.0 of the protocol.

### **Appendices IA and IB Consent Forms**

After review of the CAEPR listings, the risks for vorinostat and bortezomib have been revised as follows:

Risks and side effects related to the vorinostat include those which are:

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

- Nausea (feeling sick to your stomach), which is temporary and may require additional medication.
- Diarrhea (loose stools), which is temporary and may require additional medication and/or a delay in your treatment.
- Low white blood counts which increase risk of infection
- Anemia: (low red blood cell count), which may make you feel tired and short of breath. If this happens, you may be started on a drug to increase your red blood cell count. Severe anemia may require a transfusion of red blood cells.
- Decreased platelet count, which increases the risk of easy bleeding and/or bruising. This could result in the need for a platelet transfusion.
- Fatigue, which is temporary and should get better when treatment is stopped.
- Loss of appetite, which is temporary and should get better when treatment is stopped.
- Vomiting (throwing up), which is temporary and may require additional medication.
- High blood sugar, which is temporary and may require additional medication.
- ~~Low blood calcium, which is temporary and may require additional medication.~~ (*moved to Less Likely*)
- Changes in kidney function, which is temporary, seen on blood tests and is without symptoms. It should return to normal when treatment is stopped.
- Weight loss
- ~~Shortness of breath~~ (*moved to Less Likely*)
- Thinning of the blood, which may lead to increased risk of bleeding time
- ~~Constipation (difficulty passing stool)~~ (*moved to Less Likely*)

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

- Dehydration, which is temporary and may require additional fluids, either by mouth or by IV (intravenous, through a small tube inserted into your vein) infusion
- Changes in taste, which is temporary and should get better when treatment is stopped.
- Stomach pain.
- Changes in blood tests that measure liver function and minerals
- Low potassium, which is temporary, seen on blood tests and may require potassium supplements.
- Slowing of the conduction of electrical signals in the heart (QTc prolongation) that can lead to an abnormal heart beat that can be serious or life threatening
- Fevers
- Chills/Rigors
- Change in blood salts such as magnesium or sodium
- Dizziness
- Changes in the nervous system leading to numbness and tingling of fingers and toes
- ~~Problems with urination (i.e., increased frequency, not able to release urine, not able to hold urine)~~ (*deleted as this is not reflected in the CAEPR*)

- Cough
- Pain/difficulty swallowing
- ~~Back pain (deleted as this is not reflected in the CAEPR)~~
- Hair loss
- Dry mouth
- Heartburn
- Swelling of the limbs, head or neck
- Muscle weakness
- Head/headache pain
- Infection with or without fever
- Blood clots
- Low levels of protein in the blood
- Muscle spasms
- Decreased phosphate levels in the blood
- Abnormal blood clotting tests
- **Low blood calcium, which is temporary and may require additional medication.** (*moved from Likely*)
- **Shortness of breath** (*moved from Likely*)
- **Constipation (difficulty passing stool)** (*moved from Likely*)

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

- Death of the skin tissue

Under the direction of the National Cancer Institute (NCI), the undetermined section for vorinostat has been deleted as follows:

**~~Also reported on vorinostat trials but with the relationship to vorinostat still undetermined~~**

- ~~Inflammation of blood vessels~~
- ~~Low levels of oxygen in the blood~~
- ~~Abnormal heart beats~~
- ~~Low or high blood pressure~~
- ~~Decreased blood supply to the heart which may cause a heart attack~~
- ~~Difficulties walking~~
- ~~Confusion~~
- ~~Sinus congestion~~
- ~~Not able to sleep~~
- ~~Itching~~
- ~~Red spots on the skin~~
- ~~Pain including chest, joint, side, dental/teeth/gum, muscles, arms and legs~~
- ~~Bruising~~
- ~~Rash~~
- ~~Inflammation of the esophagus~~
- ~~Passing gas~~
- ~~Inflammation of the lining of the stomach~~
- ~~Nose bleeds~~
- ~~Bleeding of the bladder~~

- ~~Coughing up blood~~
- ~~Higher levels of calcium in the blood~~
- ~~Higher levels of potassium in the blood~~
- ~~Low blood sugar levels~~
- ~~Higher levels of protein in the urine~~
- ~~Sweating~~
- ~~Nail changes~~
- ~~Mouth sores~~
- ~~Death~~

Risks and side effects related to the bortezomib include those which are:

**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)
- 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
- Weakness, fatigue, and general discomfort
- Headache
- Insomnia (not able to sleep)
- Anxiety
- Cough, shortness of breath, lung infections including pneumonia
- Rash with itching and redness
- Painful sensations or numbness or tingling in the hands and feet (neuropathy), which may not get better after discontinuation of this drug
- ~~Irritation in the mouth, stomach or intestinal tract, which can cause pain (moved to Less Likely)~~
- Abdominal pain

**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
- Aches and pains in bones, muscles and joints
- 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.
- Swelling and fluid buildup in the arms and legs
- 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.
- Decrease in kidney function
- 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.
- 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.

- Fluid accumulating around the heart or lung
- 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.
- Symptoms of flu and other upper respiratory tract infections, such as chills, sore throat, and runny nose
- Chest pain
- 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
- 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.
- Increase or decrease in critical salts from the blood including sodium, potassium, and calcium
- Severe nerve damage resulting in profound weakness, paralysis, confusion, or seizures
- Change in sense of taste
- Pain, redness, swelling and/or infection at the injection site
- Painful sores of the mouth and/or throat, which may make swallowing difficult
- Heartburn
- Nose bleeds
- Yeast infections in the mouth, throat and vagina
- Life-threatening infections in the blood (sepsis)
- Chills/shaking chills
- Ringing in the ears (tinnitus)
- Hiccoughs
- Flushing (blushing)
- Flatulence
- Changes to your eyes and vision that may include dry eye, damage to the surface of the eye, double vision, blurred vision
- Head edema (swelling of the head area)
- Decrease in magnesium level in the blood
- Decrease in phosphate level in the blood
- Increased blood level of creatinine which can lead to kidney problems
- Back pain
- Pain in the arms and legs
- **Irritation in the mouth, stomach or intestinal tract, which can cause pain**
- **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.** *(moved from Rare but serious)*
- **Lack of intestinal movement (ileus) which can lead to obstruction, surgery may be necessary to correct this.** *(moved from Rare but serious)*
- **Rash** *(newly added)*
- **Hives** *(newly added)*
- **Dehydration** *(newly added)*
- **Bleeding in the brain** *(newly added)*

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

- ~~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. (moved to Less Likely)~~
- Lack of intestinal movement (ileus) which can lead to obstruction, surgery may be necessary to correct this. (moved to Less Likely)
- Potentially life threatening allergic reaction to the medication
- Difficulty with urinating
- Bleeding in or into the brain
- Inflammation in the blood vessels in the arms and legs
- 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
- Loss of hearing
- 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).
- 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.
- Severe, life-threatening or deadly rash with shedding of the skin and mouth sores
- Blood in the urine
- Pain in the mouth and throat when swallowing
- Coughing up blood
- Severe muscle weakness and paralysis
- Seizure
- GI perforation (a hole in the gastrointestinal tract)

Under the direction of the National Cancer Institute (NCI), the undetermined section for bortezomib has been deleted as follows:

**~~The following side effects have also been reported by patients on other bortezomib trials, but the relationship to bortezomib is not known:~~** cardiac arrest; a starch-like substance formation in the heart; high blood pressure; heart attack; sweating; weight gain; sudden death; hair loss; bruising; inflammation of the skin vessels; dry skin; abdominal distension; fluid in the abdominal cavity; dry mouth; difficulty swallowing; belching; inflammation of the stomach; lack of blood flow to the bowel; failure to thrive; bleeding in the membrane around the eyelids; collection of blood in an organ, etc. round purple red spot due to bleeding under the skin; catheter-related infection; sinus infection; urinary tract infection; lymph node disease; changes in the following laboratory values that affect kidney and liver function (ALT; amylase; AST; CPK; hyperbilirubinemia; hyperkalemia; hyperuricemia; hypocalcemia; hypokalemia; hyponatremia; hypoproteinemia; proteinuria); fracture; joint swelling; weakness; agitation; lack of muscle coordination; coma; confusion; cranial palsy; depression; emotional instability; memory impairment; mental status; psychotic disorder; seizure; speech impairment; spinal cord compression; increase tearing; bladder pain; buttock pain; oral cavity pain; ARDS; collapse of the lung; imperfect speech; low oxygen content in the blood; obstructive airways disease; pneumonitis/pulmonary infiltrates; fluid in the lungs;

~~wheezing; obstruction of the kidney; bladder spasms; renal calculus; renal dysfunction; renal failure due to liver disease; acute swelling; blood clot in the portal vein~~