

North Central Cancer Treatment Group

N0572: A Phase I/II Trial of Sorafenib and CCI-779 in Patients with Recurrent Glioblastoma

Addendum 7 – September 5, 2008

Summary

This amendment is in response to updated information from CTEP concerning CCI-779 (drug supply and an updated CAEPR, Version 2.1).

As of September 1, 2008, Wyeth Pharmaceuticals will be supplying commercial temsirolimus (CCI-779) for this trial. The commercial product is mixed differently than the investigationally labeled product. Therefore, the drug information section of the protocol has been revised.

Risk changes in this addendum have been determined by the National Cancer Institute (NCI) to be a minor alteration in the overall risk-benefit for new 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.

Going forward, all model consent form risk sections will be based off the current CAEPR distributed by NCI per discussion with NCI in June 2008. Local sites can base their institutional consent forms off of their local IRB policies, incorporating either the current investigator brochure and/or CAEPR as local institution policies dictate. As existing protocols are amended, these changes will be incorporated into the model consents.

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 7 and revised NCI version date.

Section 15.0 **Drug Information**
Pages 64-67: Sections 15.2 – 15.27 have been replaced with the new drug information for the commercial supply of CCI-779 provided by Dr. Michelle Eby in CTEP's Pharmaceutical Management Branch. The current sections are now labeled 15.2 – 15.29c.

Pages 68-72: In Section 15.29d, CAEPR, Version 2.0 has been replaced with the newly revised CAEPR, Version 2.1, July 8, 2008.

Remainder of Section 15 renumbered accordingly.

Due to the revisions made in Section 15, repagination through the end of the document has occurred.

Appendices 1A, 1B, 1C - Consent Forms

Pages 9-11: The following changes were made under the section titled “Side effects of CCI-779” per the updated CAEPR:

Likely Risks of CCI-779 (events occurring greater than 20% of the time)

- ~~Stuffy nose~~ (moved to less likely and language expanded)
- ~~Decreased white blood cell supply (leucopenia), resulting in the potential for infection~~ (moved to less likely)
- ~~Fever~~ (moved to less likely)
- ~~Changes in taste~~ (moved to less likely)
- Stomach problems, such as diarrhea, feeling sick to your stomach, ~~or throwing up~~ (moved to less likely)
- ~~Dry skin, mouth, eyes~~ (dry skin has been moved to less likely and mouth and eyes have been deleted)
- Higher cholesterol ~~and triglyceride~~ levels in your blood (if severe, this can lead to blood vessel blockage, heart disease and other heart problems, or inflammation of the pancreas) (moved to less likely)
- High blood sugar, which can mimic the effects of diabetes (great thirst, a dry mouth, and a need to urinate often) (moved to less likely)
- ~~Cough~~ (moved to less likely)
- Rash (which may be severe), ~~including acne or severe itching~~ (moved to less likely)
- ~~Nail changes~~ (moved to less likely)
- ~~Fluid collection in arms and legs~~ (moved to less likely)
- ~~Pain, including back, joints, chest, abdomen, or muscles~~ (moved to less likely)
- ~~Shortness of breath~~ (moved to less likely)
- ~~Headache/head~~ (moved to less likely)
- ~~Nose bleeds~~ (moved to less likely)
- ~~Chills, shaking~~ (moved to less likely)
- ~~Flu-like syndrome~~ (moved to less likely)
- ~~Infection~~ (moved to less likely)
- ~~Constipation (infrequent or difficulty in passing stools)~~ (moved to less likely)
- ~~Sweating~~ (deleted)
- ~~Hair loss (alopecia)~~ (deleted)

Less Likely Risks of CCI-779 (events occurring less than or equal to 20% of the time)

- ~~Infection in the bloodstream~~ (now included below)
- ~~Lack or loss of memory, inability to remember past experiences~~ (deleted)
- ~~Confusion~~ (deleted)
- ~~Dizziness~~ (deleted)
- ~~Reactions at the site where CCI 779 was injected, which may include tenderness, warmth, redness along the vein or at the site of the injection, itching, pain at the site of the injection, blistering, or severe skin damage~~ (deleted)
- ~~Catheter infection~~ (now included below)
- ~~Fungal yeast infection~~ (now included below)

- ~~Urinary tract infection (now included below)~~
- ~~Conjunctivitis (infection around the eye, also called pink eye) (now included below)~~
- ~~Herpes simplex, which may cause sores in the mouth or on the lips, inflammation of the gums and throat, and genital herpes (now included below)~~
- ~~Herpes zoster, sometimes known as shingles, and results in a painful blistering red rash that is confined to one side of the body (now included below)~~
- **Runny/stuffy nose** (moved from likely and language expanded)
- **Distention/bloating of the belly** (newly added)
- **Weight loss** (newly added)
- Collection of fluid in the body overall, and/or in the facial area (**edema or swelling of the face, hands or feet**) (language expanded)
- ~~Inflammation of the tongue (deleted)~~
- ~~Mouth pain (deleted)~~
- ~~Increase in blood clotting (deleted)~~
- ~~Increase in an enzyme that helps produce energy. An increased level may be a sign of cell damage (deleted)~~
- ~~Changes in kidney function tests; kidney failure (moved to rare)~~
- ~~Difficulty swallowing (deleted)~~
- ~~Dehydration (deleted)~~
- **Decreased white blood cell supply (leucopenia), resulting in the potential for infection; Also other forms of infection such as infection in the bloodstream, catheter, fungal yeast, urinary tract, conjunctivitis (infection around the eye, also called pink eye), herpes simplex (which may cause sores in the mouth or on the lips, inflammation of the gums and throat, and genital herpes), herpes zoster (sometimes known as shingles, and results in a painful blistering red rash that is confined to one side of the body) (decrease white blood cell supply was moved from likely, the other infection entries have now all been combined and separate entries deleted)**
- **Fever** (moved from likely)
- **Changes in taste** (moved from likely)
- **Throwing up** (moved from likely)
- **Dry skin** (moved from likely)
- **Higher triglyceride levels in your blood (if severe, this can lead to blood vessel blockage, heart disease and other heart problems, or inflammation of the pancreas)** (moved from likely)
- **High blood sugar, which can mimic the effects of diabetes (great thirst, a dry mouth, and a need to urinate often)** (moved from likely)
- **Cough** (moved from likely)
- **Acne or severe itching** (moved from likely)
- **Nail changes** (moved from likely)
- **Pain, including back, joints, chest, abdomen, or muscles** (moved from likely)
- **Shortness of breath** (moved from likely)
- **Headache/head** (moved from likely)
- **Nose bleeds** (moved from likely)
- **Chills, shaking** (moved from likely)
- **Flu-like syndrome** (moved from likely)

- **Constipation (infrequent or difficulty in passing stools)** (*moved from likely*)
- **Decreased blood potassium level** (*newly added*)
- **Abnormal reactions in the nose and sinuses** (*newly added*)
- **Abnormal bone enzyme level** (*newly added*)
- **Inability to have an erection of the penis adequate for sexual intercourse (impotence)** ~~Impotence (inability to have sex)~~ (*reworded*)

Rare but Serious Risks of CCI-779 (*events occurring less than 2-3% of the time*)

- ~~Some people have had an allergic reaction during the CCI-779 infusion. Their symptoms have been: chest pain and tightness, having a hard time breathing, feeling hot, flushed and anxious, swelling around the eyes, dizziness, feeling sick to their stomach, a fall in blood pressure, back pain, numbness and tingling. These symptoms went away a few minutes after the CCI-779 was stopped. You will be given Benadryl® before starting treatment to try to prevent an allergic reaction to the CCI-779; however, reactions can happen even if you have been given Benadryl® first. If you react to the CCI-779 after having gotten Benadryl® first, your doctor may stop your treatment. Some patients have had an allergic reaction during CCI-779/Temsirolimus infusion. Life threatening reactions (including fatal) have occurred. Patients with allergic reactions have had chest pain and tightness, difficulty breathing, feeling hot, flushed and anxious, swelling around the eyes, dizziness, feeling sick to the stomach, a fall in blood pressure, back pain, and numbness and tingling. These symptoms went away a few minutes after the infusion was stopped, and in some cases, after treatment was given. Because an allergic reaction may happen, an antihistamine drug (e.g. diphenhydramine (Benadryl)) is given before CCI-779/Temsirolimus. If you are given an antihistamine and still have an allergic reaction, the study doctor may stop or slow down the infusion and may give you other intravenous medication.~~
- **Blood clot** (*newly added*)
- **Kidney failure** (*moved from less likely*)

Page 11:

Per NCI request the risks under “Side effects reported by patients, but not proven to be caused by CCI-779” have been deleted as follows:

Also reported side effects on CCI-779 trials but with the relationship still undetermined:

- ~~High levels of calcium in the blood stream~~
- ~~Bleeding (GI, brain)~~
- ~~If you are taking a blood thinner such as Coumadin or Warfarin, CCI-779 may change the amount of blood thinner in your blood. If this happens, you may have unexpected bleeding. Your doctor may need to do some blood tests to check the level of blood thinner in your blood.~~
- ~~Fluid around the heart~~
- ~~Inflammation of the pancreas, bladder~~
- ~~Frequent urination~~
- ~~Blood clots~~
- ~~Decrease in heart function~~
- ~~Abnormal albumin levels~~

- Abnormally high potassium level
- High level of protein in the urine
- Blurred vision, eye surface disease
- Seizure
- Separation of hemoglobin from the red blood cells with appearance in the bone marrow
- Fainting