

North Central Cancer Treatment Group

N027D: A Phase I Study of CCI-779 and Temozolomide in Combination with Radiation Therapy in Glioblastoma Multiforme

Addendum 2 – September 14, 2007

Summary

- CCI-779 dose modifications have been separated out from the Non-hematologic CTCAE Category for hyperlipidemia, hypercholesterolemia, hyperkalemia, and hyperglycemia because TMZ does not need to be stopped or altered for these non-hematologic events.
- Two patients enrolled on NCCTG clinical trials with CCI-779 have developed presumed bowel perforation with accompanying retroperitoneal or abdominal infections. While this is a recognized risk of high-dose dexamethasone, we cannot exclude the possibility that CCI-779 therapy contributed to these adverse events. Therefore, the consent has been modified to include this risk.
- An updated Comprehensive Adverse Events and Potential Risks List (CAEPR) dated April 11, 2007 for CCI-779 has been received by the National Cancer Institute. Also, Edition #10 and Edition #11 of the investigator brochure for CCI-779 dated April 2005 and February 2007, respectively, have been received. Therefore, the drug information section of the protocol (Section 15.13) and the risk sections of the consent forms have been updated accordingly.
- A temozolomide investigator brochure dated December 2006 has been received. Therefore, the drug information section of the protocol (Section 15.29d) and the risk sections of the consent forms have been updated accordingly.
- Administrative/Editorial Changes

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

Title page: Now reflects Addendum 2 and revised NCI version date.

Section 8.0 **Dosage Modification Based on Adverse Event(s)**
Pages 28-29: An editorial change has been made throughout Sections 8.4, 8.5, and 8.6 to reflect (see Section 7.22) rather than 7.23.

Section 8.4: An editorial change has been made to the Gastrointestinal CTCAE Category for Grade 3 and Grade 4 to reference “Hold **CCI-779 and TMZ**” rather than to “Hold Rx.”

Sections 8.4 and 8.5: An editorial change has been made to the Non-hematology CTCAE Category for Grade 3 and Grade 4 to reference “Hold **CCI-779 and TMZ**” rather than to “Hold Rx.”

Sections 8.4, 8.5 and 8.6: Metabolic/Laboratory CTCAE Category has been newly added to separate out these events from the other non-hematologic events since TMZ does not need to be stopped or altered for them.

Sections 8.4, 8.5 and 8.6 have a clarifying statement added: Footnote 2 has the following added “**if controlled with medical measures.**”

Section 8.4, 8.5 and 8.6: Footnote 3 is newly added to clarify that if a toxicity can clearly be linked to one of the drugs, that the dose modification for that drug should be used. Footnotes in the tables have been renumbered.

Section 8.5 has been relabeled for clarity: ~~Criteria for holding treatment following adverse events are outlined in the table below for patients received adjuvant therapy with CCI-779/TMZ.~~ **Dose modifications based on interim toxicity during adjuvant CCI-779/TMZ chemotherapy**

Section 8.6 has been relabeled for clarity: ~~Dose modifications based on adverse events during adjuvant therapy with CCI-779/TMZ are outlined in the table below.~~ **Dose modifications based on toxicity at the time of retreatment with adjuvant CCI-779/TMZ chemotherapy (i.e. on day 1 of each adjuvant treatment cycle)**

Sections 8.5 and 8.6 now have the agent more clearly identified with the CTCAE Category with relationship to the dose modification. For CTCAE Categories Blood/Bone marrow and Non-hematologic, TMZ/CCI-779 is noted. For CTCAE Categories Metabolic/Laboratory and Pulmonary/upper respiratory, CCI-779 is noted.

Section 14.0

Page 41:

Translational/Pharmacologic Studies

The address in 14.31 has been updated as follows:

NCCTG Operations Office
RO_FF_03_24-CC/NW Clinic
200 First Street SW
Rochester, MN 55905
ATTN: ~~NCCTG Research Coordinator~~ **PC Office**

Section 15.0

Pages 45-48:

Drug Information

Due to the inclusion of the updated CAEPR for CCI-779, Section 15.13 has been replaced in its entirety.

Pages 45-64:

Due to the inclusion of the updated CAEPR for CCI-779, repagination has occurred.

Page 48:

Due to the receipt of Edition #10 and Edition #11 of the updated investigator brochure for CCI-779, the following side effects have been added at the end of Section 15.13:

Additional events due to Investigator Brochure: stuffy nose; hair loss; chest pain; catheter infection; infection in the bloodstream; fungal yeast infection; urinary tract infection; conjunctivitis (infection around the eye, also called pink eye); inflammation of the tongue; mouth pain; increase in an enzyme that helps produce energy. An increased level may be a sign of cell damage; lack or loss of memory, inability to remember past experiences; reactions at the site where CCI-779 is 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; decreased or delayed wound healing; a serious, often life-threatening allergic reaction that is characterized by low blood pressure, shock (poor tissue perfusion) and difficulty breathing; may cause active immunizations to be less effective. Thus, the use of live vaccines should be avoided while taking CCI-779.

Page 52: Due to the receipt of the December 2006 updated investigator brochure for temozolomide, the following changes have been made to Section 15.29d:

Less Common (1 to 10%)

- Neuromuscular and skeletal: Paresthesia, back pain, myalgia, jaw pain, **joint pain**
- Respiratory: Upper respiratory tract infection, pharyngitis, sinusitis, cough, **shortness of breath**

Rare (<1%)

- **Allergy/immunology: Allergic reaction**
- **Dermatologic: Severe skin reaction**
- **Neuromuscular and skeletal: paralysis**

Section 17.0 Pre-registration Pathology Considerations

Page 58: The address in Section 17.2 has been updated as follows:
 NCCTG Operations Office
 RO_FF_03_24-CC/NW Clinic
 200 First Street SW
 Rochester, MN 55905
 ATTN: ~~NCCTG Research Coordinator~~ **PC Office**

Section 18.0 Records and Data Collection Procedures

Page 61: A new note has been added to Footnote #3 for clarification with regard to the submission of CT/MRI scans as follows:
NOTE: When films are submitted on CD(s), they must include a viewing tool.

Appendices IA, IB Consent Forms

Appendix IA:

Page 1: A new paragraph has been added to the “What will happen if I take part in this research study” section for further clarification as follows:
In order to find the highest dose of CCI-779, the first people in this study will receive a lower dose of CCI-779. If there are no unacceptable side effects from these dosages, the dosages will be increased for the next set of people enrolled in this study.

Appendix IB:

Page 1: A new paragraph has been added to the “What will happen if I take part in this research study” section for further clarification as follows:
The current dose level is thought to be the maximum-tolerated dose (MTD), which means the highest safe dose of the CCI-779. In the part of the study that you are considering, all patients will get the same doses and have further research tests using blood samples to help find out what effect the CCI-779 has on the body. All patients will continue to be watched carefully for any serious side effects. These side effects cannot be completely known ahead of time.

Appendices IA and IB:

Page 2: In “What will happen if I take part in this research study?” section, the fourth bullet “Pregnancy test (if applicable)” under the “During the study” section has been deleted as this does not apply.

Appendices IA, IB:

Pages 4-6: The risks for CCI-779 have been updated as follows due to the receipt of Edition #10 and Edition #11 of the investigator brochure and the updated CAEPR dated April 11, 2007 and other editorial changes:

Risks and side effects related to the CCI-779 include those which are:

Likely (events occurring greater than 20% of the time)(newly added)

- Diarrhea
- Mouth sores
- Nausea and vomiting
- Constipation (**infrequent, or difficulty in passing, stools**) (*expanded wording due to IB review*)
- Skin rash ~~or fingernail/toenail changes~~ (*moved to new bullet*) **which may be severe** (*expanded wording due to IB review*)
- **Fingernail/toenail changes** (*separated from Skin rash due to IB review*)
- Acne
- **Pain: Head/Headache** (*expanded wording due to IB review*)
- ~~Dizziness~~ (*moved to Less Likely*)
- Fatigue
- Weakness, **loss of strength and energy** (*expanded wording due to IB review*)
- Loss of appetite
- Weight loss
- ~~Difficulty sleeping~~ (*moved to Less Likely*)
- ~~Low white blood cells, red blood cells and platelets. This can lead to an increased risk of infection, tiredness and bleeding.~~ (*broken into 3 separate entries as follows due to IB review*)
- **Decreased red blood cell supply (anemia), which can cause fatigue, shortness of breath, and a possible need for red blood cell transfusions**
- **Decreased white blood cell supply (leucopenia), which can put you at risk for infection**
- **Decreased number of platelets in the blood, resulting in the potential for increased bleeding and decreased ability for clotting**
- Nose bleeds
- ~~Altered levels of blood salts (phosphates)~~ (*moved to Less Likely*)
- Altered taste
- Fever and/or chills/**shaking** (*expanded wording due to updated CAEPR*)
- **Mouth dryness** (*moved from Less Likely due to IB review*)
- **Skin dryness and itchiness** (*moved from Less Likely due to IB review*)
- **Fluid buildup in arms or legs** (*moved from Less Likely due to IB review*)
- High blood sugar, **signs of which include great thirst, a dry mouth, and a need to urinate often** (*expanded wording and moved from Less Likely due to IB review*)

- ~~Elevated blood lipids and cholesterol~~ **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** (*reworded and moved from Less Likely due to IB review*)
- **Pain, including** back pain, joint pain, muscle pain, (*expanded wording and moved from Less Likely due to IB review*), **chest pain** (*newly added due to IB review*), or abdominal pain (*moved from Less Likely*)
- **Shortness of breath** (*moved from Less Likely due to IB review*)
- **Depression** (*moved from Rare but serious due to IB review*)
- **Flu-like syndrome** (*previously in CAEPR under undetermined now newly added due to IB review*)
- **Infection** (*previously in CAEPR under undetermined now newly added due to IB review*)
- **Stuffy nose** (*newly added due to IB review*)
- **Dry cough** (*moved from Less Likely due to IB review*)
- **Sweating** (*previously in CAEPR under undetermined now newly added due to IB review*)
- **High or low blood pressure** (*previously in CAEPR now newly added*)
- **Dehydration** (*previously in the CAEPR now newly added*)
- **Inflammation and sores in the GI tract** (*previously in CAEPR now newly added*)

Less Likely (events occurring less than or equal to 20% of the time) (*newly added*)

- ~~Fluid accumulation in arms or legs~~ (*moved to Likely due to IB review*)
- ~~Mouth dryness~~ (*moved to Likely due to IB review*)
- ~~Skin dryness and itchiness~~ (*moved to Likely due to IB review*)
- ~~Abnormalities in blood test for liver function~~ **Increased levels of liver enzymes, which may put you at risk for liver damage** (*reworded due to IB review*)
- Decreased testosterone in men with decrease in sex-drive
- ~~High blood sugar~~ (*moved to Likely due to IB review*)
- ~~Elevated blood lipids and cholesterol~~ (*reworded and broken into 2 entries and moved to Likely due to IB review*)
- Allergic reactions **and hypersensitivity** (*expanded wording due to IB review*)
- ~~Abdominal pain or back pain~~ (*moved to Likely due to IB review*)
- ~~Joint or muscle pain~~ (*moved to Likely due to IB review*)
- ~~Dry cough~~ (*moved to Likely due to IB review*)
- ~~Shortness of breath~~ (*moved to Likely due to IB review*)
- Increased blood clotting
- **Abnormal amount of protein in the blood that is needed for blood clotting** (*previously in the CAEPR now newly added*)
- **Low potassium level** (*previously in the CAEPR now newly added*)
- **Higher acid levels in the blood** (*previously in the CAEPR now newly added*)
- **Increased sleepiness** (*previously in CAEPR now newly added*)
- ~~If you have had a previous infection with oral or genital herpes, CCI 779 treatment may lead to a re-occurrence of this infection.~~ **Recurrence of herpes simplex infection, which may cause sores in the mouth or on the lips, inflammation of the gums and throat, and recurrence of genital herpes** (*this is now listed as two separate entries*)
- **Herpes zoster, sometimes known as shingles, and results in a painful blistering red rash that is**

confined to one side of the body

- **Reactions at the site where CCI-779 is 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** (*newly added due to IB review*)
- **Pale or reddened irregular, elevated patches of skin and severe itching, hives** (*previously in CAEPR now newly added due to IB review*)
- **Wide-spreading inflammation and/or rash that goes deep into the skin** (*previously in CAEPR now newly added due to IB review*)
- **Collection of fluid or blood in the lungs** (*previously in CAEPR under undetermined now newly added due to IB review*)
- **Inflammation of the lungs** (*previously in CAEPR now newly added due to IB review*)
- **Catheter infection** (*newly added due to IB review*)
- **Infection in the bloodstream** (*newly added due to IB review*)
- **Fungal yeast infection** (*newly added due to IB review*)
- **Urinary tract infection** (*newly added due to IB review*)
- **Conjunctivitis (infection around the eye, also called pink eye)** (*newly added due to IB review*)
- **Inflammation of the tongue** (*newly added due to IB review*)
- **Mouth pain** (*newly added due to IB review*)
- **Abnormally low calcium in the blood stream, that can result in muscle cramps, abdominal cramps, spasms** (*newly added due to IB and CAEPR review*)
- **Altered levels of blood salts (phosphates)** (*moved from Likely and expanded wording due to IB review*)
- **Increase in an enzyme that helps produce energy. An increased level may be a sign of cell damage** (*newly added due to IB review*)
- **Lack or loss of memory, inability to remember past experiences** (*previously in CAEPR now newly added due to IB review*)
- **Confusion** (*previously in CAEPR now newly added and moved from undetermined due to IB review*)
- **Dizziness** (*moved from Likely*)
- **Difficulty sleeping** (*moved from Likely*)
- **Impotence (inability to have sex)** (*previously in CAEPR now newly added*)
- **Changes in kidney function/kidney failure** (*newly added due to updated CAEPR*)
- **Collection of fluid in the body overall and/or facial area** (*previously in CAEPR now newly added and moved from undetermined due to IB review*)
- **Difficulty swallowing** (*newly added due to updated CAEPR*)
- **Decreased or delayed wound healing** (*newly added due to IB review*)

Rare but serious (events occurring less than 2-3% of the time) (*newly added*)

- **A serious, often life-threatening allergic reaction that is characterized by low blood pressure, shock (poor tissue perfusion) and difficulty breathing** (*newly added due to IB review*)
- ~~Some patients treated with CCI 779 have had bleeds into their brain tumor~~ (*moved to undetermined*)
- Lung damage or fluid accumulation around the lungs
- ~~Liver or kidney injury~~ (*deleted as this is a duplication of the entry "increased levels of liver enzymes, which may put you at risk for liver damage" in the "Likely" category*)
- ~~Seizures~~ (*moved to undetermined due to CAEPR review*)
- ~~Depression or altered mental function~~ (*moved to Likely due to IB review*)
-
- **Developing a hole in the bowel leading to life-threatening infections in the abdomen. Patients**

on high doses of steroids may be at increased risk for this complication (newly added due to Addendum 2)

- **Hair loss** (newly added due to IB review)

Also reported side effects on CCI-779 trials but with the relationship still undetermined: (previously in CAEPR now newly added to consents)

- **High levels of calcium in the blood stream** (previously in CAEPR now newly added to consents)
- **Bleeding GI, brain** (previously in CAEPR now newly added to consents)
- **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** (previously in CAEPR now newly added to consents)
- **Fluid around the heart** (previously in CAEPR now newly added to consents)
- **Inflammation of the pancreas, bladder** (previously in CAEPR now newly added to consents)
- **Frequent urination** (previously in CAEPR now newly added to consents)
- **Blood clots** (newly added due to current CAEPR review)
- **Decrease in heart function** (newly added due to current CAEPR review)
- **Abnormal albumin level** (newly added due to current CAEPR review)
- **High levels of protein in the urine** (newly added due to current CAEPR review)
- **Blurred vision, eye surface disease** (newly added due to current CAEPR review)
- **Seizure** (newly added due to current CAEPR review)
- **Separation of hemoglobin from the red blood cells with appearance in the bone marrow** (newly added due to current CAEPR review)
- **Fainting** (newly added due to current CAEPR review)

CCI-779 may cause active immunizations to be less effective. Thus, the use of live vaccines should be avoided while taking CCI-779. (newly added due to IB review)

Pages 8: The reproductive risks have been updated as follows due to the receipt of Edition #11 investigator brochure for CCI-779 dated February 2007:

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breast-feed a baby while on this study. It is important you understand that you need to use birth control while on this study **and for 3 months after treatment has stopped.** Check with your health care provider about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

Appendices IA, IB Consent Forms

Pages 6-7: The risks for temozolomide have been updated as follows due to the receipt of a new investigator brochure dated December 2006:

Likely (events occurring greater than 20% of the time)

- Nausea, and/or vomiting
- Headache
- Constipation
- Drowsiness/Fatigue
- Decreased appetite (*moved from Less Likely due to IB review*)
- ~~Decrease in blood counts that may result in infection, bleeding, or anemia~~ (*moved to Less Likely due to IB review and broken down into 3 entries*)
- ~~Diarrhea~~ (*moved to Less Likely due to IB review*)
- Fever
- ~~Arm and leg swelling~~ (*moved to Less Likely due to IB review*)
- ~~Dizziness~~ (*moved to Less Likely due to IB review*)
- Difficulty falling asleep
- Infection in mouth

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

- **Fall in the white blood cell counts that leads to a higher risk of infection** (*moved from Likely due to IB review*)
- **Fall in the platelet count leading to a higher risk of bleeding** (*moved from Likely due to IB review*)
- **Fall in the red blood cell count leading to anemia (feeling tired and low energy)** (*moved from Likely due to IB review*)
- **Diarrhea** (*moved from Likely due to IB review*)
- Decreased ability to carry out daily activities
- Pneumonia
- Loss of appetite
- ~~Weight loss and/or decrease in appetite~~ (*moved to Likely due to IB review*)
- Weakness
- Dizziness (*moved from Likely due to IB review*)
- Hair loss
- **Numbness or tingling or burning in your arms or legs** (*expanded wording due to IB review*)
- Abdominal pain/jaw pain
- Skin rash
- Weakness of hands and feet
- **Liver damage (as seen in tests that show how the liver is working)** (*expanded wording due to IB review*)
- Changes in your blood chemistries
- ~~Convulsions (violent spasms or jerking of the body)~~ (*moved to Rare but serious due to IB review*)
- ~~Weakness affecting one side of the body~~ (*moved to Rare but serious due to IB review*)
- Increased sleepiness
- ~~Poor coordination and difficulty walking~~ (*moved to Rare but serious due to IB review*)

- Confusion
- Anxiety
- Depression
- Problems with memory
- Itchy skin
- Dysphagia (difficulty swallowing)
- Weight gain
- Sores in mouth, esophagus (food tube), reproductive organs, or urinary system
- ~~Low red blood cells causing tiredness (duplication)~~
- Abnormal secretion of body hormones or steroids
- Bladder incontinence (leaking from the bladder)
- Bladder infection
- Frequent urination
- Back pain
- Muscle pain
- **Joint pain** (newly added due to IB review)
- Double vision
- Cough and infection in the lungs or throat
- Trouble seeing
- Sore throat
- Sinus infections
- **Breast pain in females** (listed in Section 15.29d of the protocol, now being added to the consents)
- **Shortness of breath** (newly added due to IB review)
- **Swelling in your arms or legs** (newly added due to IB review)

Rare but serious (events occurring less than 2-3% of the time)

- **Myelodysplastic syndrome (problem with the bone marrow that causes decreased production of red cells, white cells, or platelets that can sometimes turn into cancer of the blood (leukemia) several years from now** (expanded wording due to IB review)
- Convulsions (violent spasms or jerking of the body) (moved from Less Likely due to IB review)
- Weakness affecting one side of the body (moved from Less Likely due to IB review)
- Poor coordination and difficulty walking (moved from Less Likely due to IB review)
- **Paralysis** (newly added due to IB review)
- **Severe skin reaction** (newly added due to IB review)
- **Allergic reaction** (newly added due to IB review)

Appendices IA, IB **Consent Forms**

Page 11: Per Addendum 1, there is now only banking of tissue occurring. Therefore, under the “Biological Samples for Research” section the following three paragraphs have been revised to delete reference to the blood samples:

We would like to keep some of the tissue ~~and/or blood~~ that is left over for future research. If you agree, this tissue ~~and/or blood~~ will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research.

Your tissue ~~and/or blood~~ may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue ~~and/or blood~~ is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue ~~and/or blood~~ will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.