

North Central Cancer Treatment Group

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

Addendum 3 – July 6, 2007

Summary

Scientific:

- Version #6 of the investigator brochure and subsequent Amendments 1, 2, and 3 for sorafenib (BAY43-9006) have been received. Therefore, the risk section of the consent forms have been revised accordingly.
- The risk section of the consent form for CCI-779 has been updated in accordance with the investigator brochure Edition 10 dated April 1, 2005 and the current CAEPR Version 2.0 dated April 11, 2007.
- 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.

Editorial:

- Administrative changes.

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

Title page Reflects the addition of Addendum 3 and revised NCI version date.

Protocol Resource Page

Page 2: Kathleen Welch has been named the NCCTG *Research Base* Data Management Specialist.

Section 4.0

Test Schedule

Page 21: Column heading “Prior to each new cycle” is now labeled “Prior to each cycle after cycle 1” to clarify that the tests under this column are to be done after cycle 1.

The row labeled “Blood sample (see Section 14.0)” has the X⁸ moved from the column labeled “Prior to each cycle after cycle 1” to “Weekly” to clarify that the blood draw is actually done on Day 1 of Cycle 1.

The row labeled “frozen tissue sample” has the X⁶ moved from the column labeled “Prior to each cycle after cycle 1” to “Weekly” to clarify that the tissue is needed during Cycle 1.

The following have been removed from the column labeled “Prior to each cycle after cycle 1” since they are already noted in the column labeled “Weekly (1st 4 weeks) then every 2 weeks” due to redundancy of the information: Adverse Event Assessment, Hematology, Chemistry, Chemistry: Lipid Panel, PT/INR, Blood Pressure Check, Recording of steroid dose, Blood pressure diary

Footnote 2 has been removed from the column labeled “Tests and Procedures” for the row labeled “MRI with contrast or CT with contrast” and has instead been added to the X’s in the row for editorial purposes.

Footnote 3 has been removed from the column labeled “Tests and Procedures” for the row labeled “Serum pregnancy test” and added to the X under the column “21 Days prior to reg” for editorial purposes.

Footnote 7 has been removed from the column labeled “Tests and Procedures” for the row labeled “Blood pressure diary” for editorial purposes.

Footnote 5 has been removed from the column labeled “Tests and Procedures” for the row labeled “Blood Pressure Diary” for editorial purposes.

Section 14.0

Page 44:

Translational/Pharmacologic Studies

Section 14.11 has the following deleted because the samples are mandatory: ~~for patients who have consented to sample submission~~

Section 15.0

Page 62:

Drug Information

An additional section at the end of Section 15.16 has been added as follows to identify new risks per the Version 6 investigator brochure for Sorafenib:

Other adverse events as per BAY 43-9006 Investigator Brochure, Version #6, dated August 12, 2005:

Depression, ringing in the ears, hoarseness, upset stomach, peeling rash, acne, weakness, decrease in amount of testosterone or other hormones the body makes which could lead to a decrease in sex drive, skin problems, irregular menstrual cycles, teeth and bone changes, decrease in thyroid function, with symptoms of tiredness, sensitivity to cold, slow metabolic rate, rare brain dysfunction (reversible posterior leukoencephalopathy syndrome), severe increases in the blood pressure, persistent runny nose, decreases in liver function, enlargement of breast tissue in males, pain in mouth, and tumor pain. If patient is taking a blood thinner such as coumadin or warfarin, BAY 43-9006 may change the amount of blood thinner in the blood which could cause unexpected bleeding.

Page 66-69:

Section 15.28 has been replaced with the new CCI-779 CAEPR information.

Page 69: An additional section at the end of Section 15.28 has been added as follows to identify new risks per the Edition 10 investigator brochure for CCI-779:

Other adverse events as per CCI-779 Investigator Brochure, Edition 10 dated April 1, 2005:

Constipation, inflammation of the throat, stuffy nose, hair loss, sweating, dizziness, hypersensitivity, reactions at the site of injection, collection of fluid or blood in the lungs, catheter infection, fungal yeast infection, urinary tract infection, conjunctivitis, herpes simplex, herpes zoster, inflammation of the tongue, mouth pain, increase in blood clotting, low calcium, increase in an enzyme that helps produce energy, impotence.

Section 17.0 Pre-registration Pathology Considerations

Page 79: The opening paragraph of Section 17.2 has been revised to include a second phone number for the NCCTG pathology coordinator as follows:

A call needs to be made to the NCCTG pathology coordinator (507/266-0724 or **507/266-8919**) after pre-registration...

Page 80: The address for pathology material submission listed in Section 17.2 has been updated as follows:

NCCTG Operations Office
ATTN: NCCTG Research Coordinator
~~NW Clinic 3-24 RO_FF_03_24-CC/NW Clinic~~
 200 4th First Street SW
 Rochester, MN 55905
~~Attention: Helen Tollefson~~

Appendices IA and IC – Consent forms

Page 2: Table that outlines what will happen to the patient now has the research blood draw accurately listed under “Cycle 1/Day 1” rather than with “Weekly (first cycle) and every other week (subsequent cycles)” to clarify the timing of the draw.

Appendix IB – Consent form

Page 3: Table that outlines what will happen to the patient now has the research blood draw accurately listed under “Within 72 hours before surgery” rather than with “Cycle 1/Day 1” to clarify the timing of the draw.

Appendices IA, IB, IC – Consent Forms

Pages 7-8: The risks for Sorafenib have been updated as follows due to the receipt of an updated version of the investigator brochure:

Likely (*events occurring greater than 20% of the time*) (*newly added due to IB review*)

- Skin rash/skin peeling
- Diarrhea
- Tiredness
- Hand-foot syndrome (**numbness, tingling, redness and/or discomfort** of the skin on the palm or the bottom of the foot that may affect daily activities) (*expanded wording*)
- **Anorexia (loss of appetite, not feeling hungry)** (*expanded wording and moved from Less Likely due to IB review*)

- **Dyspnea (difficulty breathing)** (previously in the CAEPR but not in the consents and moved to Likely due to IB review)
- **Pruritus (itching)** (expanded wording and moved from Less Likely due to IB review)
- ~~Decrease in blood counts which may lead to serious infection, tiredness, or bleeding~~ **Drop in the white blood cell count which could be connected with an increased risk of infections** (rewording and moved from Less Likely due to IB review)
- ~~Low blood phosphate~~ **Decreased risk of phosphorus in the blood (called hypophosphatemia)** (reworded and moved from Less Likely due to IB review)
- ~~Decrease in blood counts which may lead to serious infection, tiredness, or bleeding~~ **Decrease in platelet count which may result in bleeding, even potentially serious bleeding such as in the lungs, intestine, or brain** (rewording and moved from Less Likely due to IB review)
- **High blood pressure (may cause headaches or feeling hot, but if serious could cause strokes or other problems)** (moved from Less Likely due to IB review)
- **Hair loss (scalp or body)** (moved from Less Likely due to IB review)
- **Nausea and vomiting** (moved from Less Likely due to IB review)
- **Pain (in mouth, stomach [pain in the belly],) bone, headache** (bone and headache were previously in the CAEPR under “undetermined”), **or tumor** (mouth and tumor pain newly added and stomach pain moved from Less Likely due to IB review)
- **Possible increase in pancreas-associated enzymes of amylase and lipase** (was in the CAEPR but not in the consents and moved to Likely due to IB review)
- **Dehydration (loss of body fluids)** (moved from Less Likely due to IB review)
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Less Likely (events occurring less than or equal to 20% of the time) (newly added due to IB review)

- ~~Nausea and vomiting~~ (moved to Likely due to IB review)
- Flu-like symptoms (feeling achy, feverish)
- ~~High blood pressure (may cause headaches or feeling hot, but if serious could cause strokes or other problems)~~ (moved to Likely due to IB review)
- Sores in mouth and/or throat
- Nail changes
- ~~Allergic reactions~~ (moved to Rare but serious due to IB review)
- Lightning of skin color
- Inflammation of pancreas (**pancreatitis** - which can cause diabetes or other problems in the future) (expanded wording due to IB review)
- ~~Hair loss (scalp or body)~~ (moved to Likely due to IB review)
- Weight loss
- Muscle pain
- Decreased oxygen in blood
- ~~Loss of appetite, not feeling hungry~~ (moved to Likely due to IB review)
- Painful swallowing
- ~~Heartburn~~ (moved to Rare but serious due to IB review)
- Excess fluid in stomach
- Non-life-threatening skin cancer
- Fluid around lungs
- High blood sugar
- Constipation
- ~~Itching~~ (moved to Likely due to IB review)
- ~~Dehydration (loss of body fluids)~~ (moved to Likely due to IB review)
- ~~Intestinal gas~~ **Excessive amounts of air and gases in the stomach** (rewording due to IB review)
- ~~Low blood phosphate~~ (reworded and moved to Likely due to IB review)
- Chills and/or shaking chills

- Fever
- Dry skin
- Redness of the face
- Infection
- ~~Decrease in blood counts which may lead to serious infection, tiredness, or bleeding (broken into 3 entries with white blood cell count and platelets moved to Likely due to IB review)~~
- **Anemia (drop in the red blood cells in the blood, which may cause tiredness and shortness of breath)** (reworded from previous bulleted item due to IB review)
- Joint pain/**inflammation** (arthritis) (expanded wording due to IB review)
- Kidney failure (**as seen on blood tests**) (expanded wording due to IB review)
- **General lung damage (i.e., inflammation in lungs, collapsed lungs)** (expanded wording due to IB review)
- Bleeding in stomach, intestines, kidney or bladder, **brain, lungs, spleen** (previously in CAEPR under “undetermined” section but not in consents)
- Fever associated with a low white blood cell count
- Liver injury (as seen on blood tests)
- ~~Stomach/abdominal pain (pain in the belly)~~ (reworded and moved to Likely due to IB review)
- **Numbness or tingling in the nerves of the hands or feet** (was in the CAEPR but not in the consents)
- **Difficulty in initiating or maintaining an erection** (was in the CAEPR but not in the consents and moved from “undetermined” due to IB review)
- **Peeling rash** (newly added due to IB review)
- **Depression** (newly added due to IB review)
- **Ring in the ears** (newly added due to IB review)
- **Hoarseness** (newly added due to IB review)
- **Upset stomach** (newly added due to IB review)
- **Acne** (newly added due to IB review)
- **Weakness** (newly added due to IB review)
- **Decrease in amount of testosterone or other hormones the body makes which could lead to a decrease in sex drive, skin problems, menstrual cycles, or more** (newly added due to IB review)
- **Teeth and bone changes** (newly added due to IB review)
- **Severe lung damage** (previously in CAEPR but not in the consents)

Rare but serious (events occurring less than 3% of the time) (newly added due to IB review)

- Hole in the bowel which could happen even long after you have stopped taking sorafenib **and could be life threatening** (expanded wording due to IB review)
- **Allergic reactions, also known as hypersensitivity reactions** (expanded wording and moved from Less Likely due to IB review)
- **Heartburn** (moved from Less Likely due to IB review)
- **Decrease in salts in the blood such as sodium** (previously in CAEPR but not in consents and moved from “undetermined” due to IB review)
- **Heart attack** (previously in CAEPR but not in consents and moved from “undetermined” due to IB review)
- **Decrease in heart function or heart failure** (previously in CAEPR but not in consents and moved from “undetermined” due to IB review)
- **Severe life-threatening rash** (previously in CAEPR but not in consents and moved from “undetermined” due to IB review)
- **Prolonged blood clotting times** (previously in CAEPR but not in consents and moved from “undetermined” due to IB review)
- **Decrease in thyroid function, with symptoms of tiredness, sensitivity to cold, and slow metabolic rate** (newly added due to IB review)

- **Rare brain dysfunction (reversible posterior leukoencephalopathy syndrome [RPLS])** *(newly added due to IB review)*
- **Severe increases in blood pressure** *(newly added due to IB review)*
- **Persistent runny nose** *(newly added due to IB review)*
- **Decreases in liver function** *(newly added due to IB review)*
- **Enlargement of breast tissue in males** *(newly added due to IB review)*
- **If you are taking a blood thinner such as Coumadin or Warfarin, sorafenib 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.** *(newly added due to IB review)*

Also reported on sorafenib trials but with the relationship still undetermined *(this section previously in CAEPR, but not in consents)*

- **Tiny broken blood vessels under the skin** *(previously in CAEPR but not in consents)*
- **Bleeding in the brain, lungs, spleen** *(previously in CAEPR but not in consents)*
- **Abnormal slow bowel contraction** *(previously in CAEPR but not in consents)*
- **Swelling of the arms and legs** *(previously in CAEPR but not in consents)*
- **Abnormal change in brain function like anxiety, dizziness, altered consciousness (encephalopathy)** *(previously in CAEPR but not in consents)*
- **Eye problems (double vision, inflammation)** *(previously in CAEPR but not in consents)*
- **Voice changes** *(previously in CAEPR but not in consents)*
- **Blood clots** *(previously in CAEPR but not in consents)*

Pages 9-11: The risks for CCI-779 have been updated and separated into categories as follows due to the receipt of an updated version of the investigator brochure:

Side effects ~~possibly related to~~ of CCI-779:

Very Common side effects related to CCI-779: *(due to IB review)*

- ~~Changes to your blood cell counts that could make you more likely to have an infection, cause bleeding, or anemia. If the bleeding is severe you may need a blood transfusion.~~ *(reworded and broken down into 3 categories due to IB review– see 3 bulleted items that follow)*
- **Decreased red blood cell supply (anemia), which can cause fatigue, shortness of breath, and a possible need for red blood cell transfusions** *(rewording due to IB review)*
- **Decreased white blood cell supply (leucopenia) which can put you at risk for infection** *(rewording due to IB review)*
- **Decrease in the number of platelets in the blood, resulting in the potential for increased bleeding and decreased ability for clotting** *(rewording due to IB review)*
- Fever
- Not feeling hungry that may cause weight loss
- Changes in taste
- Stomach problems, such as diarrhea, feeling sick to your stomach or throwing up.
- Dry skin, mouth, eyes
- Sores in your mouth
- 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). *(expanded wording due to IB review)*

- Changes in liver function tests, **which may put you at risk for liver damage** (*expanded wording due to IB review*)
- High blood sugar, which can mimic the effects of diabetes (**great thirst, a dry mouth, and a need to urinate often**) (*expanded wording due to IB review*).
- Low blood phosphorus
- Cough
- Rash (**which may be severe**), including acne or severe itching (*expanded wording due to IB review*)
- Nail changes
- Fluid collection in arms and legs
- Not being able to sleep, **or abnormal wakefulness** (*expanded wording due to IB review*)
- Feeling tired and weak, **loss of energy** (*expanded wording due to IB review*)
- Low **or high** blood pressure (*previously in CAEPR but not in consents*)
- ~~Fainting~~ (*moved to “undetermined” due to CAEPR review*)
- **Pain, including** back, joints, **chest** (*previously in CAEPR but not in consents*), **or muscles** (*expanded wording due to IB review*)
- **Dehydration** (*previously in CAEPR but not in consents*)
- **Shortness of breath** (*previously in CAEPR but not in consents*)
- **Headache/head** (*previously in CAEPR but not in consents*)
- **Depression** (*previously in CAEPR but not in consents*)
- **Nose bleeds** (*previously in CAEPR but not in consents and moved from “undetermined” due to IB review*)
- **Chills/shaking** (*previously in CAEPR but not in consents and moved from “undetermined” due to IB review*)
- **Flu-like syndrome** (*previously in CAEPR but not in consents and moved from “undetermined” due to IB review*)
- **Infection** (*previously in CAEPR but not in consents and moved from “undetermined” due to IB review*)
- **Constipation (infrequent or difficulty in passing stools)** (*previously in CAEPR but not in consents and moved from “undetermined” due to IB review*)
- **Inflammation and sores in the GI tract** (*previously in CAEPR but not in the consent*)
- **Stuffy nose** (*newly added due to IB review*)
- **Hair loss** (*newly added due to IB review*)
- **Sweating** (*previously in CAEPR but not in consent and moved from “undetermined” due to IB review*)
- **Dizziness** (*newly added due to IB review*)
- **Inflammation of the throat** (*newly added due to IB review*)

Common side effects related to CCI-779: (newly added due to IB review)

- Decreased testosterone levels and loss of desire for sex
- Change in blood pH
- Low potassium level
- **Pale or reddened irregular, elevated patches of skin and severe itching, hives** (previously in the CAEPR but not in the consents)
- **Wide-spreading inflammation and/or rash that goes deep into the skin** (previously in the CAEPR but not in the consents)
- **Inflammation of the lungs** (previously in the CAEPR but not in the consents)
- **Abdominal pain** (previously in the CAEPR but not in the consents)
- **Collection of fluid in the body overall and/or in the facial area** (previously in the CAEPR but not in the consents and moved from “undetermined” due to IB review)
- **Infection in the bloodstream** (newly added due to IB review)
- **Lack or loss of memory, inability to remember past experiences** (previously in the CAEPR but not in the consents and moved from “undetermined” due to IB review)
- **Confusion** (previously in the CAEPR but not in the consents and moved from “undetermined” due to IB review)
- **Allergic reaction (hypersensitivity)** (newly added due to IB review)
- **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** (newly added due to IB review)
- **Collection of fluid or blood in the lungs** (previously in the CAEPR but not in the consent and moved from “undetermined” due to IB review)
- **Catheter infection** (newly added due to IB review)
- **Fungal yeast infection** (newly added due to IB review)
- **Urinary tract infection** (newly added due to IB review)
- **Increased sleepiness** (formerly in the CAEPR but not in the consents)
- **Conjunctivitis (infection around the eye, also called pink eye)** (newly added due to IB review)
- **Herpes simplex, which may cause sores in the mouth or on the lips, inflammation of the gums and throat, and genital herpes** (newly added due to IB review)
- **Herpes zoster, sometimes known as shingles, and results in a painful blistering red rash that is confined to one side of the body** (newly added due to IB review)
- **Inflammation of the tongue** (newly added due to IB review)
- **Mouth pain** (newly added due to IB review)
- **Increase in blood clotting** (newly added due to IB review)
- **Abnormal amount of protein in the blood that is needed for blood clotting** (previously in the CAEPR but not in the consent)
- **Abnormally low calcium in the blood stream, that can result in muscle cramps, abdominal cramps, spasms** (newly added 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 CAEPR and IB review)
- **Impotence (inability to have sex)** (previously in the CAEPR but not in the consent)
- **Changes in kidney function tests; kidney failure** (newly added due to CAEPR review)
- **Difficulty swallowing** (newly added due to current CAEPR review)
- **Higher acid levels in blood** (previously in the CAEPR but not in the consent)

Uncommon side effects related to CCI-779: *(newly added due to IB review)*

- 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.
- **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 recent adverse events as described in the Summary of Change box)*

Also reported side effects on CCI-779 trials but with the relationship still undetermined: *(previously in CAEPR but not in consents)*

- **High levels of calcium in the blood stream** *(previously in CAEPR but not in consents)*
- **Bleeding (GI, brain)** *(previously in CAEPR but not in consents)*
- **If you are taking a blood thinner such as Coumadin or Warfarin, sorafenib 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 but not in consents)*
- **Fluid around the heart** *(previously in CAEPR but not in consents)*
- **Inflammation of the pancreas, bladder** *(previously in CAEPR but not in consents)*
- **Frequent urination** *(previously in CAEPR but not in 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)*
- **Abnormally high potassium level** *(newly added due to current CAEPR review)*
- **High level 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** *(moved from Very Common due to 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)*