

North Central Cancer Treatment Group

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

Addendum 4 – January 11, 2008

**Summary**

- Due to the toxicities that have been seen with the CCI-779 dose level 0 (25 mg), extensive discussions were held with the Cancer Therapy Evaluation Program of the National Cancer Institute and it was decided that an intermediate dose level should be added.
- The risk section of the consent form for CCI-779 has been updated in accordance with the investigator brochure Edition 11 dated February 2007.
- Editorial/administrative changes, which include (1) an editorial correction to a risk in the consent form for CCI-779 for the category “Also reported side effects on CCI-779 trials but with the relationship still undetermined;” (2) correction to the spelling of Sorafenib in assorted places in the protocol; and (3) duplication of side effects in the consent form for sorafenib corrected.

**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 4 and revised NCI version date.

**Section 1.0**

Page 16:

**Background**

Typographical error corrected in the second sentence of the third paragraph in Section 1.4 as follows:

As part of this biomarker initiative, phase II studies using combinations of the following agents: temsirolimus, erlotinib, bevacizumab, ~~sorafenib~~ **sorafenib** and tipifarnib, in glioma, melanoma and renal cell carcinoma will be providing tumor and blood specimens for a cross study analysis.

**Section 7.0**

Page 24:

**Protocol Treatment**

Section 7.12 has the following added to outline the additional dose level that has been added:

**An additional dose level (sorafenib 200 mg po bid and CCI-779 20 mg) was added as of Addendum 4. For this dose level and subsequent dose levels, a cohort of 6 consecutive patients will be enrolled. If, at any point, two DLTs are encountered within a dose level, the MTD has been exceeded and a subsequent cohort of 6 will be enrolled at the next lower dose. This modification was made as it is anticipated, based on current research, that dose level -1 will be a well-tolerated dose. By enrolling 6 patients consecutively, the time to evaluate the dose level will be minimized. Toxicity will be closely monitored and appropriate adjustments will be made if 2 DLTs are observed.**

*Anticipated dose level of both drugs*

<b>Dose Level/TAC**</b>	<b>Sorafenib dose</b>	<b>CCI-779 dose</b>
-3	200 bid	10
-2	200 bid	15
<b>-1</b>	200 bid	<b>20</b>
0*	200 bid	25
1	400 bid	25
2	400 bid	50
3	400 bid	75
4	400 bid	125
5	400 bid	175
6	400 bid	250

**Section 16.0**

Page 72:

**Statistical Considerations and Methodology**

Sections 16.21 and 16.22 have been modified to address the addition of the additional dose level:

- 16.21 **Study Design:** The cohorts-of-3+3 design **in combination with the cohorts of 6 design for dose levels -1, -2, and -3** as described in Section 7.1 will be used to assess acute toxicity of CCI-779 in combination with sorafenib. CCI-779 dose will be modified as outlined in section 7.1.
- 16.22 **Sample Size:** A minimum of 9 and maximum of 42 patients will enter Study 1 unless undue toxicity or other factors affect patient accrual. The sample size was determined by the dose escalation schedule in section 7.12. ~~and the cohorts of 3 + 3 design~~

**Appendices IA, IB, IC – Consent Forms**

- Page 7: A correction has been made under the “Likely” risks category for Sorafenib as follows:
- Decreased ~~risk level~~ of phosphorus in the blood (called hypophosphatemia)
- Page 8: Typographical error corrected under the “Rare but serious” category for Sorafenib as follows:
- If you are taking a blood thinner such as Coumadin or Warfarin, ~~sorafenib~~ **sorafenib** may change the amount of blood thinner in your blood.
- Page 7: An error occurred in Addendum 3 in which the side effects “bleeding in the brain, lungs, spleen” were added to both the “Less Likely...” and “Also reported...” categories for sorafenib. These will remain in the “Also reported...” category and deleted from the “Less Likely...” category.

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

Very Common side effects related to CCI-779 Likely (events occurring greater than 20% of the time):  
(reworded)

- 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
- Decrease in the number of platelets in the blood, resulting in the potential for increased bleeding and decreased ability for clotting
- 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)
- ~~Changes in liver function tests, which may put you at risk for liver damage~~ (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)
- ~~Low blood phosphorus~~ (moved to Less Likely)
- Cough
- Rash (which may be severe), including acne or severe itching
- Nail changes
- Fluid collection in arms and legs
- ~~Not being able to sleep, or abnormal wakefulness~~ (moved to Less Likely)
- Feeling tired and weak, loss of energy
- ~~Low or high blood pressure~~ (moved to Less Likely)
- Pain, including back, joints, chest, **abdomen** (moved from Less Likely), or muscles
- ~~Dehydration~~ (moved to Less Likely)
- Shortness of breath
- Headache/head
- ~~Depression~~ (moved to Less Likely)
- Nose bleeds
- Chills, shaking
- Flu-like syndrome
- Infection
- Constipation (infrequent or difficulty in passing stools)
- Inflammation and sores in the GI tract
- Stuffy nose
- ~~Hair loss~~ (moved to Rare but serious)
- Sweating
- ~~Dizziness~~ (moved to Less Likely)
- Inflammation of the throat

Common side effects related to CCI-779 Less Likely (events occurring less than or equal to 20% of the time): (reworded)

- 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
- Wide-spreading inflammation and/or rash that goes deep into the skin
- Inflammation of the lungs
- ~~Abdominal pain~~ (moved to Likely and included in the existing risk of “Pain, including back, joints, chest, or muscles)
- Collection of fluid in the body overall and/or in the facial area
- Infection in the bloodstream
- Lack or loss of memory, inability to remember past experiences
- Confusion
- **Dizziness** (moved from Likely)
- **Not being able to sleep, or abnormal wakefulness** (moved from Likely)
- **Depression** (moved from Likely)
- Allergic reaction (hypersensitivity)
- 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
- Collection of fluid or blood in the lungs
- Catheter infection
- Fungal yeast infection
- Urinary tract infection
- Increased sleepiness
- 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 blistery red rash that is confined to one side of the body
- Inflammation of the tongue
- Mouth pain
- Increase in blood clotting
- Abnormal amount of protein in the blood that is needed for blood clotting
- Abnormally low calcium in the blood stream that can result in muscle cramps, abdominal cramps, spasms
- **Low blood phosphorus** (moved from Likely)
- Increase in an enzyme that helps produce energy. An increased level may be a sign of cell damage
- **Changes in liver function tests, which may put you at risk for liver damage** (moved from Likely)
- **Low or high blood pressure** (moved from Likely)
- Impotence (inability to have sex)
- Changes in kidney function tests; kidney failure

- Difficulty swallowing
- Higher acid levels in blood
- **Dehydration** (*moved from Likely*)
- **Decreased or delayed wound healing** (*newly added*)

Uncommon side effects related to CCI-779 Rare but serious (events occurring less than 2-3% of the time): (*reworded*)

- 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.
- **Hair loss** (*moved from Likely*)
- 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.

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, ~~serafenib~~ **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 level
- 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

CCI-779 may cause active immunizations to be less effective. Thus, the use of live vaccines should be avoided while taking CCI-779.