

North Central Cancer Treatment Group

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

Addendum 9 – February 27, 2009

Summary

This addendum is in response to a special request from Dr. John Wright of the National Cancer Institute (NCI) dated December 30, 2008 concerning sorafenib. The drug information section and the risks section of the consent form have been updated to reflect current drug safety information.

Risk changes in this addendum have been determined by NCI to not significantly alter the risk-benefit profile for 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.

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 9 revised NCI version date.

Section 15.0 **Drug Information**
Pages 60-63: Due to the receipt of an updated CAEPR (version 2.2), Section 15.16 has been replaced in its entirety.

Appendices IA-IB-IC **Consent Form**

In order to reflect current drug safety information for sorafenib, the risks section of the consent form has been revised as follows:

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

- ~~Skin rash/skin peeling~~ **Rash/flaking or shedding of outer layer of skin** (*reworded*)
- Diarrhea
- **Fatigue/Tiredness** (*expanded wording*)
- ~~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)~~ **Inflammation of the skin on the palms of the hands or soles of the feet** (*reworded*)
- ~~Anorexia (Loss of appetite, not feeling hungry)~~ (*wording condensed*)
- ~~Dyspnea (difficulty breathing)~~ (*deleted*)
- ~~Pruritus (itching)~~ (*moved to Less Likely*)
- ~~Drop in the white blood cell count which could be connected with an increased risk of infections~~ (*moved to Less Likely and reworded*)
- ~~Decreased level of phosphorus in the blood (called hypophosphatemia)~~ **Low blood phosphate level** (*reworded*)
- ~~Decrease in platelet count which may result in bleeding, even potentially serious bleeding such as in the lungs, intestine, or brain~~ (*deleted*)
- ~~High blood pressure (may cause headaches or feeling hot, but if serious could cause strokes or other problems)~~ (*moved to Less Likely and wording condensed*)

- Hair loss (~~scalp or body~~) (*wording condensed*)
- Nausea and vomiting (*vomiting has moved to Less Likely*)
- Pain (~~in mouth, stomach [pain in the belly], bone, headache, or tumor~~) **Stomach ache** (*with the exception of stomach, the other pain risks have moved to Less Likely and reworded*)
- Possible increase in pancreas associated enzymes of amylase and lipase (*deleted*)
- Dehydration (~~loss of body fluids~~) (*deleted*)
- **Low levels of a blood protein called albumin** (*newly added*)

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

- Flu-like symptoms (~~feeling achy, feverish~~) (*deleted*)
- Sores in mouth and/or throat (*deleted*)
- Nail changes (*deleted*)
- ~~Lightning of skin color~~ (*deleted*)
- Inflammation of pancreas (~~pancreatitis – which can cause diabetes or other problems in the future~~) (*deleted*)
- Weight loss
- **Muscle Pain (such as joints, muscles, headache, legs, chest, back)** (*moved from Likely and wording expanded*)
- **Pain** (*newly added*)
- Decreased oxygen in blood in a red blood cell protein that carries oxygen in the body (*reworded*)
- Painful swallowing (*deleted*)
- Excess fluid in stomach (*deleted*)
- Non-life-threatening skin cancer (*deleted*)
- Fluid around lungs (*deleted*)
- High blood sugar
- **Low blood sugar** (*newly added*)
- Constipation
- Excessive amounts of air and gases in the stomach (*deleted*)
- Chills and/or shaking chills (*deleted*)
- Fever
- Dry skin
- Redness of the face (*deleted*)
- Infection **with or without a low white blood cell count** (*wording expanded*)
- Anemia (~~drop in the red blood cells in the blood, which may cause tiredness and shortness of breath~~) (*deleted*)
- Joint pain/inflammation (arthritis) (*joint pain combined above – arthritis has been deleted*)
- Kidney failure (~~as seen on blood tests~~) (*wording condensed*)
- General lung damage (~~i.e., inflammation in lungs, collapsed lungs~~) (*deleted*)
- Bleeding in stomach, intestines, kidney or bladder **the reproductive organs or urinary system such as the bladder or kidney** (*reworded*)
- Fever associated with a low white blood cell count
- Liver injury (~~as seen on blood tests~~) (*deleted*)
- Numbness or tingling in the nerves of the hands or feet **Nerve damage causing numbness, tingling, or burning** (*reworded*)
- Difficulty in initiating or maintaining an erection (*deleted*)
- Peeling rash (*moved to Likely and reworded*)
- Depression (*deleted*)
- Ringing in the ears (*deleted*)
- Hoarseness, **laryngitis, loss or change in voice** (*wording expanded*)
- Upset stomach (*moved to Likely and reworded*)

- Aene (*deleted*)
- Weakness (*deleted*)
- ~~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~~ (*deleted*)
- Teeth and bone changes (*deleted*)
- Severe lung damage (*deleted*)
- Itching (*moved from Likely*)
- High blood pressure (*moved from Likely*)
- Vomiting (*moved from Likely*)
- Allergic reactions, also known as hypersensitivity reactions (fever, chills, rash, itching) (*moved from Rare but serious*)
- Decreased total number of white blood cells (*moved from Likely*)
- Decreased number of a type of white blood cell (*newly added*)
- Decreased number of blood cells that help to clot blood (*moved from Rare but serious and reworded*)
- Difficulty sleeping or falling asleep (*newly added*)
- Painful inflammation and ulceration of the lining of the digestive tract (*newly added*)
- Bleeding in the digestive tract (*newly added*)
- Bleeding of the respiratory tract (*newly added*)
- Swelling of the arms and legs (*newly added*)
- Increased liver enzyme levels (*newly added*)
- Abnormal liver or bone enzyme level (*newly added*)
- Abnormal digestive enzyme level (*newly added*)
- High blood levels of a liver pigment indicative of abnormal liver function (*newly added*)
- Low blood calcium level (*newly added*)
- Abnormal level of fat-digesting enzyme (*newly added*)
- High blood potassium level (*newly added*)
- Low blood potassium level (*newly added*)
- Low blood sodium level (*moved from Rare but serious and reworded*)
- Dizziness (*newly added*)
- Cough (*newly added*)
- Shortness of breath (*newly added*)
- Formation of presence of a blood clot inside a blood vessel (*newly added*)

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

- ~~Hole in the bowel which could happen even long after you have stopped taking sorafenib and could be life threatening~~ **A hole somewhere in the intestinal tract from the esophagus to the anus** (*reworded*)
- Allergic reactions, also known as hypersensitivity reactions (*moved to Less Likely and wording condensed*)
- Heartburn (*deleted*)
- ~~Decrease in salts in the blood such as sodium~~ (*moved to Less Likely and reworded*)
- Heart attack
- ~~Decreased in heart function or heart failure~~ **blood supply to the heart** (*reworded*)
- Severe life threatening rash (*deleted*)
- Prolonged blood clotting times (*moved to Less Likely and reworded*)
- ~~Decrease in thyroid function, with symptoms of tiredness, sensitivity to cold, and slow metabolic rate~~ (*deleted*)
- ~~Rare brain dysfunction (reversible posterior leukoencephalopathy syndrome [RPLS])~~ (*deleted*)
- Severe increases in blood pressure (*deleted*)
- Persistent runny nose (*deleted*)
- ~~Decreases in liver function~~ (*deleted*)
- ~~Enlargement of breast tissue in males~~ (*deleted*)

- ~~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.~~
(deleted)
- **Decrease in the ability of the heart to pump blood** (newly added)
- **Bleeding into the brain or spinal cord** (newly added)
- **Syndrome caused by high blood pressure characterized by headache, confusion, seizures, and vision loss associated with imaging findings** (newly added)

Also reported on sorafenib trials but with the relationship still undetermined

- ~~Tiny broken blood vessels under the skin~~
- ~~Bleeding in the brain, lungs, spleen~~
- ~~Abnormal slow bowel contraction~~
- ~~Swelling of the arms and legs~~
- ~~Abnormal change in brain function like anxiety, dizziness, altered consciousness (encephalopathy)~~
- ~~Eye problems (double vision, inflammation)~~
- ~~Voice changes~~
- **Blood clots**