

North Central Cancer Treatment Group

N0776: Phase II Trial of Avastin® in Combination with Sorafenib in Recurrent Glioblastoma Multiforme

Addendum 6 – 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 5 revised NCI version date.

Section 15.0 **Drug Information**
Pages 37-40: Due to the receipt of an updated CAEPR (version 2.2), Section 15.12 has been replaced in its entirety.

Appendix I **Consent Form**
Pages 6-7: In order to reflect current drug safety information for sorafenib, the risks section of the consent form has been revised as follows:

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

- ~~Skin Rash~~ **Rash/flaking or shedding of outer layer of skin** (*wording expanded*)
- ~~Fatigue~~ **Fatigue/Tiredness** (*wording expanded*)
- ~~Hand and foot syndrome (numbness, tingling, redness, and/or discomfort of hands or feet that may affect activity of daily living.~~ **Inflammation of the skin on the palms of the hands or soles of the feet** (*reworded*)
- ~~Flaking or sloughing of skin~~ (*combined with rash above*)
- Diarrhea
- **Loss of appetite** (*moved from Less Likely and wording condensed – formerly “Anorexia [loss of appetite, not feeling hungry]”*)
- **Low blood phosphate level** (*moved from Less Likely and reworded – formerly “Decreased risk of phosphorus in the blood [called hypophosphatemia]”*)

- **Hair loss** (*moved from Less Likely*)
- **Nausea** (*moved from Less Likely*)
- **Stomach ache** (*moved from Less Likely*)
- **Low levels of a blood protein called albumin** (*moved from Less Likely*)

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

- Decrease in a ~~part of~~ red blood cells **protein** that carries oxygen in the body (*reworded*)
- ~~Condition of the nervous~~ **Nerve damage system** that causes numbness, tingling, **or** burning (*reworded*)
- Constipation
- ~~Difficulty swallowing~~ (*deleted*)
- Dry skin
- Fever
- ~~Flu-like symptoms (fever, aching joints, etc.)~~ (*deleted*)
- ~~Decrease in W~~ **weight loss** (*reworded*)
- Abnormal liver or bone enzyme levels
- Kidney failure
- ~~Chills/shaking chills~~ (*deleted*)
- ~~Excessive amounts of air and gases in the stomach~~ (*deleted*)
- High blood sugar
- **Low blood sugar** (*newly added*)
- ~~Fluid around the lungs~~ (*deleted*)
- ~~General lung damage, inflammation of the lung~~ (*deleted*)
- ~~Flushing of the skin~~ (*deleted*)
- ~~Pancreatitis~~ (*deleted*)
- ~~Heartburn~~ (*deleted*)
- ~~Hair loss~~ (*moved to Likely*)
- Allergic reactions, also known as hypersensitivity reactions (**fever, chills, rash, itching**) (*wording expanded*)
- ~~Dehydration~~ (*deleted*)
- ~~Anorexia (loss of appetite, not feeling hungry)~~ (*moved to Likely and wording condensed*)
- ~~Pruritus (Itching)~~ (*wording condensed*)
- ~~Drop in the~~ **Decreased total number of** white blood cells count which could be connected with an increased risk of infections (*reworded*)
- **Decreased number of a type of white blood cell** (*newly added*)
- ~~Decreased risk of phosphorus in the blood (called hypophosphatemia)~~ (*moved to Likely and 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
- ~~Nausea, V~~ **omiting** (*nausea moved to Likely*)
- **Pain such as** (~~in stomach, joints, or~~ **muscles, headache, legs, chest, back**) (*stomach moved to Likely and wording expanded*)
- **Pain** (*newly added*)
- ~~Non-threatening superficial skin cancer~~ (*deleted*)
- ~~Lightening of the skin~~ (*deleted*)
- ~~Nail changes~~ (*deleted*)
- ~~Fluid collection in the abdomen~~ (*deleted*)
- ~~Irritation or sores in the lining of the throat~~ (*deleted*)

- ~~Bleeding of areas such as the intestinal system, in the reproductive organs, and/or urinary system such as the bladder or kidney~~ (*reworded*)
- Fever **associated with a dangerously low white blood cell count** (*reworded*)
- Infection **with or without a low white blood cell count** (*wording expanded*)
- ~~Low levels of a blood protein called albumin~~ (*moved to Likely*)
- Abnormal digestive enzyme level
- ~~Abnormal level of bilirubin in the blood. Bilirubin is a bile pigment found in the liver~~ **High blood levels of a liver pigment indicative of abnormal liver function** (*reworded*)
- **Increased liver enzyme levels** (*newly added*)
- **Decreased number of blood cells that help to clot blood** (*newly added*)
- Abnormal blood level of fat-digesting enzyme
- ~~Decrease in oxygen supply to a tissue~~ (*deleted*)
- ~~Collection of air outside the lungs in the space surrounding the lungs~~ (*deleted*)
- ~~Elevation of blood tests such as blood elastase~~ (*deleted*)
- **Hoarseness, laryngitis, loss or change in voice** (*newly added*)
- **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*)
- **Low blood calcium level** (*newly added*)
- **High blood potassium level** (*newly added*)
- **Low blood potassium level** (*newly added*)
- **Low blood sodium level** (*newly added*)
- **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 2% of the time)

- ~~A Hholes developing somewhere in the intestinal system tract which could be life threatening from the esophagus to the anus~~ (*reworded*)
- **Heart attack** (*newly added*)
- **Decreased blood supply to the heart** (*newly added*)
- **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*)