

North Central Cancer Treatment Group

N0626: Phase II Randomized Study Pemetrexed With Sorafenib versus Pemetrexed Alone as Second-line Therapy in Patients With Advanced Non-Small Cell Lung Cancer

Addendum 5 – 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 Addendum 5 and revised NCI version date.

**Section 15.0** **Drug Information**  
Pages 49-59: Section 15.12 has been added due to the Comprehensive Adverse Events and Potential Risks List (CAEPR) for sorafenib being inserted into the protocol and the following text has been deleted in Section 15.11:

~~The following additional drug-related adverse events and laboratory abnormalities were reported from clinical trials of NEXAVAR in 1286 cancer patients who received sorafenib as monotherapy (very common 10% or greater, common 1 to less than 10%, uncommon 0.1% to less than 1%):~~

~~Cardiovascular: Uncommon: hypertensive crisis, myocardial ischemia and/or infarction~~

~~Dermatologic: Very common: erythema Common: exfoliative dermatitis, acne, flushing Uncommon: folliculitis, eczema, erythema multiforme~~

~~Digestive: *Very common*: increased lipase, increased amylase *Common*: mucositis, stomatitis (including dry mouth and glossodynia), dyspepsia, dysphagia *Uncommon*: pancreatitis, gastrointestinal reflux, gastritis~~

~~Note that elevations in lipase are very common (41%, see below); a diagnosis of pancreatitis should not be made solely on the basis of abnormal laboratory values~~

~~General Disorders: *Very common*: asthenia, pain (including mouth pain, bone pain, and muscle pain) *Common*: decreased appetite, influenza like illness, pyrexia *Uncommon*: infection~~

~~Hematologic: *Very common*: leukopenia, lymphopenia *Common*: anemia, neutropenia, thrombocytopenia *Uncommon*: INR abnormal~~

~~Hypersensitivity: *Uncommon*: hypersensitivity reactions (including skin reactions and urticaria)~~

~~Metabolic and Nutritional: *Very common*: hypophosphatemia *Common*: transient increases in transaminases *Uncommon*: dehydration, hyponatremia, transient increases in alkaline phosphatase, increased bilirubin (including jaundice), hypothyroidism~~

~~Musculoskeletal: *Common*: arthralgia, myalgia~~

~~Nervous System and Psychiatric: *Common*: depression, *Uncommon* tinnitus~~

~~Reproductive: *Common*: erectile dysfunction *Uncommon*: gynecomastia~~

~~Respiratory: *Common*: hoarseness *Uncommon*: rhinorrhea, diffuse alveolar damage~~

~~In addition, the following medically significant adverse events were reported infrequently during clinical trials of sorafenib: cerebral hemorrhage, transient ischemic attack, cardiac failure, arrhythmia, thromboembolism, acute renal failure. For these events, the causal relationship to sorafenib has not been established.~~

~~For the most recent safety update, please refer to the current Nexavar® Prescribing Information.~~

Due to the inclusion of the CAEPR listing, all remaining sections have been renumbered. Repagination throughout the remainder of the document has also occurred.

**Appendix I**      **Consent Form**

Pages 7-8:      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~~ (combined with flaking skin below)
- ~~Dehydration~~ (deleted)
- **Fatigue or Tiredness** (expanded wording)
- ~~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)
- ~~Skin peeling~~ **Rash/flaking or shedding of outer layer of skin** (combined with skin rash above and reworded)
- ~~Anorexia (loss of appetite, not feeling hungry)~~ (wording condensed)
- ~~Dyspnea (difficult 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 risk 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~~ (moved to Less Likely)
- Hair loss
- Diarrhea
- Nausea, ~~vomiting~~ (moved to Less Likely)
- **Low levels of a blood protein called albumin** (newly added)
- ~~Pain (in mouth, stomach, bone, headache, or tumor pain)~~ **Stomach ache** (with the exception of stomach, the other risks have moved to Less Likely and reworded)
- ~~Possible increase in pancreas-associated enzymes of amylase and lipase~~ (deleted)

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

- ~~Anemia (drop in the red blood cells in the blood, which may cause tiredness and shortness of breath)~~ **Decrease in a red blood cell protein that carries oxygen in the body** (reworded)
- ~~Depression~~ (deleted)
- ~~Numbness or tingling in the nerves of the hands or feet~~ **Nerve damage causing numbness, tingling, or burning** (reworded)
- ~~ringing in the ears~~ (deleted)
- **Hoarseness, laryngitis, loss or change in voice** (expanded wording)
- Constipation
- ~~Mouth sores~~ (deleted)
- ~~Difficulty swallowing~~ (deleted)
- ~~Upset stomach~~ (deleted)
- Dry skin

- ~~Peeling rash~~ (*moved to Likely and reworded*)
- ~~Aene~~ (*deleted*)
- ~~Inflammation of the joints~~ (*deleted*)
- ~~Muscle pain~~ (*combined with pain category below*)
- ~~Difficulty in initiating or maintaining an erection~~ (*deleted*)
- ~~Weakness~~ (*deleted*)
- Fever
- ~~Flu like symptoms (fever, aching joints, etc.)~~ (*deleted*)
- ~~Decrease in Wweight loss~~ (*reworded*)
- ~~Increase in liver function test values~~ **Abnormal liver or bone enzyme levels** (*reworded*)
- ~~Decrease in kidney function as measured by blood tests~~ **Kidney failure** (*reworded*)
- ~~Decrease in amount of testosterone or other hormones the body makes which could lead to a decrease in sex drive, skin problems, menstrual cycles~~ (*deleted*)
- ~~Teeth and bone changes~~ (*deleted*)
- ~~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*)
- ~~Inflammation of the pancreas~~ (*deleted*)
- **High blood pressure** (*moved from Likely*)
- **Itching** (*moved from Likely and reworded*)
- **Decreased total number of white blood cells** (*moved from Likely and reworded*)
- **Decreased number of a type of white blood cell** (*newly added*)
- **Vomiting** (*moved from Likely*)
- **Pain (such as joints, muscles, headache, legs, chest, back)** (*moved from Likely and reworded*)
- **Pain**
- **Allergic reactions** (*moved from Rare but serious and condensed wording*)
- **Bleeding in the reproductive organs, or urinary system (such as the bladder or kidney)** (*newly added*)
- **Fever with dangerously low white blood cell count** (*newly added*)
- **Infection with or without a low white blood cell count** (*newly added*)
- **Abnormal digestive enzyme level** (*newly added*)
- **High blood levels of a liver pigment indicative of abnormal liver function** (*newly added*)
- **Abnormal level of fat-digesting enzyme** (*newly added*)
- **Decreased number of blood cells that help to clot blood** (*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*)
- **Increased liver enzymes** (*newly added*)
- **Low blood calcium level** (*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 or presence of a blood clot inside a blood vessel** (*newly added*)

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

- ~~Allergic reactions, also known as hypersensitivity reactions~~ (*moved to Less Likely and wording condensed*)
- ~~Decrease in thyroid function, with symptoms of tiredness, sensitivity to cold, and slow metabolic rate~~ (*deleted*)
- ~~Decrease in salts in the blood such as sodium~~ (*moved to Less Likely and reworded*)
- ~~Rare brain dysfunction (reversible posterior leukoencephalopathy syndrome)~~ (*deleted*)
- Heart attack
- ~~Decreased~~ **in heart function or heart failure blood supply to the heart** (*reworded*)
- ~~Severe increases in the blood pressure~~ (*deleted*)
- ~~Persistent runny nose~~ (*deleted*)
- ~~Heartburn~~ (*deleted*)
- **A Holes developing somewhere in the intestinal system which could be life-threatening tract from the esophagus to the anus** (*reworded*)
- ~~Decreases in liver function~~ (*deleted*)
- ~~Severe life threatening rash~~ (*deleted*)
- ~~Enlargement of breast tissue in males~~ (*deleted*)
- ~~Prolonged blood clotting times~~ (*deleted*)
- ~~If you are taking a blood thinner such as Coumadin or Warfarin BAY 43-9006 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*)
- ~~Inability to bear children (it is unknown for how long, it may last forever)~~ (*deleted*)
- **Decrease in the ability of the heart to pump blood** (*newly added*)
- **Bleeding into the brain or spinal cord**
- **Syndrome caused by high blood pressure characterized by headache, confusion, seizures, and vision loss associated with imaging findings** (*newly added*)