

North Central Cancer Treatment Group

N0321: Phase I/II Study of PS-341 in Combination with Paclitaxel, Carboplatin, and Concurrent Thoracic Radiation Therapy for Non-small Cell Lung Cancer (NSCLC)

Addendum 7 – June 8, 2007

Summary

- The 10th edition of the investigator brochure dated December 15, 2006 for PS341 has been received. Therefore, the drug information section and the risks section of the consent forms have been revised accordingly.
- 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 Updated to reflect Addendum 7 and revised NCI version date.

Protocol Resource Page

Page 2: The title for Vicki Bryhn has been updated as follows:
NCCTG *Research Base* ~~Protocol-Administrative~~ **Data Management Specialist**

Section 15.0 Drug Information

Page 42: Due to the receipt of an updated investigator brochure (IB) for PS341, the following risks have been added at the bottom of Section 15.16:
Due to IB review: ...herpes zoster, pulmonary hypertension, lung diseases of unknown cause, death of cancer cells that occurs quickly and releases toxins, reversible posterior leukoencephalopathy syndrome

Appendices IA and IB Consent Forms

Pages 5-8: Due to the receipt of an updated IB for PS341, the “What are the risks of the study?” section of the consent form has been revised as follows:

Likely related side effects of PS-341 (events occurring greater than 20% of the time):

- Fatigue (feeling tired or weak); lethargy, malaise, **general discomfort** (*newly added due to IB review*)
- Loss of appetite
- Weight loss
- Nausea (feeling sick to your stomach)
- Vomiting (throwing up)
- Pain – abdominal, headache/head, bone, joints, **muscles** (*moved from Less Likely due to IB review*)
- Pain or swelling in the arms or legs
- Weakness caused by damage of the nerves
- Diarrhea
- Constipation (difficulty passing stool)
- Fever

- Lowering of the red blood cell count causing anemia
- Lowering of blood clotting cells with an increased risk of bleeding and may lead to life-threatening bleeding
- Lowering of the white blood cell counts with an increased risk of infection and even life-threatening infections
- Problems with the central nervous system (the brain and spinal cord) which controls mental activities, movements and nerves
- Dehydration – Loss of fluid in the body, may need to stay in the hospital
- **Painful sensations, numbness, tingling or weakness in the arms and legs (neuropathy), which may not get better after discontinuation of this drug** (*newly added wording due to IB review*)
- Feeling dizzy or lightheaded **and, uncommonly, fainting** (*moved from Less Likely due to IB review*). **You should not drive any vehicle or operate any dangerous tools or machinery if you experience these symptoms.** (*newly added wording due to IB review*)
- Anxiety
- Cough
- Shortness of breath
- Rash **with itching and redness. An uncommon risk is a severe, life-threatening or deadly rash with shedding of the skin and mouth sores.** (*additional wording due to IB review*)
- Low blood pressure
- Decrease in kidney function, kidney damage or failure
- Pneumonia
- Irritation in the stomach or intestinal tract, **or mouth, which can cause pain** (*newly added wording due to IB review*)
- **Trouble sleeping** (*moved from Less Likely due to IB review*)
- **Herpes zoster (shingles), which occasionally results in persistent local pain, can sometimes spread over large areas of the body and, uncommonly, can affect the brain** (*newly added due to IB review*)

Less likely related side effects of PS-341 (events occurring greater than 3% but less than 20% of the time):

- Runny, stuffy, or itchy nose
- Ringing or buzzing in the ears
- Drop in heart's ability to pump blood
- Fluid around the heart
- ~~Trouble sleeping~~ (*moved to Likely due to IB review*)
- Uncontrollable shaking and chills
- Redness in the face
- Bruising, bleeding, soreness or redness of the skin where the injection is given
- Itching
- Skin peeling
- Hives or welts on the skin
- Passing gas
- Heartburn
- Slowing of the small intestine causing stomach pain, bloating and cramping (ileus) **which can lead to obstructions and in very rare instances surgery** (*newly added wording due to IB review*)
- Sores in the lining of the throat

- Changes in taste
- Bleeding anywhere in the body (i.e., intestine, brain), **which may or may not be associated with low platelet counts and blood clotting changes. This bleeding may result in bloody diarrhea and/or bloody vomit. Your doctor may recommend preventative platelet transfusions to rescue the risk of bleeding.** *(newly added wording due to IB review)*
- Fever with low white blood cell count
- Infection (sinus, **bladder, throat, stomach, intestines, skin**) **which can be life-threatening and result in multi-organ failure or death. The infection could be caused by bacteria, virus, or fungus.** *(newly added wording due to IB review)*
- Swelling in the head and neck
- Abnormal tests of liver function. **Uncommon risks are hepatitis and liver failure in patients who had received multiple other medications and had other serious medical conditions.** *(newly added wording due to IB review)*
- High/low blood sugar, **if you are a diabetic and are taking oral anti-diabetic agents, you may require close monitoring of your blood sugar levels** *(newly added wording due to IB review)*
- Increase or decrease in critical salts from the blood including sodium, potassium, magnesium, phosphate, calcium
- Change in walking stride or function (walking with a limp)
- Mood changes (feeling agitated)
- ~~Fainting~~ *(moved to Likely due to IB review)*
- Dry eye syndrome
- Damage to the surface of the eye
- Double or blurred vision
- Pain in the back, chest, ~~muscles~~ *(moved to Likely due to IB review)*, throat, voice box, or nerves
- Hiccups
- Fluid around the lungs
- Potentially life-threatening allergic reaction to the medication
- Changes in heart rate or rhythm (**possibly with the feeling of confusion, lightheadedness, dizziness, fainting, shortness of breath, and/or chest discomfort**). **An uncommon risk is a potentially life-threatening abnormal heart rhythm.** *(newly added wording due to IB review)*
- New onset **or worsening** of heart failure (**which may appear as shortness of breath, swelling in the legs, and/or chest pain**) **or decreased heart function. If you have heart failure or other disease that put you at risk of developing heart failure, you should tell your doctor.** *(newly added wording due to IB review)*
- Sepsis (severe infection which could lead to multi-organ dysfunction or death)
- Inflammation of the pancreas
- Inflammation in the intestinal tract
- Severe nerve damage resulting in profound weakness, paralysis, confusion, or seizures
- **Symptoms of flu and other upper respiratory tract infections, such as chills, sore throat, and runny nose** *(newly added due to IB review)*

Rare but serious side effects of PS-341 (events occurring less than 3% of the time):

- Abnormal hole in the GI tract
- Difficulty with urinating
- Inflammation in the peripheral blood vessels with bleeding into the brain
- **Loss of hearing** (*previously in CAEPR under “undetermined” but category changed due to IB review*)
- **A syndrome called “reversible posterior leukoencephalopathy syndrome” (RPLS) that affects the brain and can cause headaches, visual changes, altered mental status, or seizures, but is reversible** (*newly added due to IB review*)
- **A death of the cancer cells that occurs so quickly that it can cause release of toxins and injure organs, such as the kidneys** (*newly added due to IB review*)
- **Severe, life-threatening, or deadly lung diseases of unknown cause which may include inflammation of and accumulation of fluid in the lungs. This problem has been seen most commonly in Japan. Other risk factors for this complication include co-administration of a drug called cytarabine and a drug called daunorubicin** (*newly added due to IB review*)
- **Elevated pressure in the lungs, called pulmonary hypertension, has also been reported. This can cause difficulty breathing and can be life-threatening. If you have new or worsening breathing problems, you should tell your doctor.** (*newly added due to IB review*)