

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 4 – August 18, 2006

Summary

- Response is not the primary endpoint for this study. Therefore, measurable disease is not needed. As a result, the eligibility criteria (Section 3.0) has been revised accordingly.
- As a result of radiation therapy being part of this study, a radiation oncologist must confirm that the patient is a suitable candidate for this study. Therefore, the appropriate revisions have been made to the registration section (Section 6.0) of the protocol.
- An updated Comprehensive Adverse Events and Potential Risks List (CAEPR) for PS-341 (Version 2.0) has been received from the National Cancer Institute. This revised listing has replaced the existing listing in the drug information (Section 15.0) of the protocol and appropriate revisions have been made to the consent form.
- The RECIST criteria language has been updated to reflect the current template standard.
- 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: Reflects Addendum 4 and revised NCI version date.

Section 3.0 Patient Eligibility

Page 12: Response is not the primary endpoint for this study; therefore, measurable disease is not needed. As a result, Section 3.13 has been deleted.

~~Patients must have measurable disease as defined in Section 11.0 (Recist criteria).~~

Section 3.19a has been deleted as follows as this question is reflected in the registration section (Section 6.19) of the protocol:

~~Radiation oncologist has seen the patient and confirms the patient is a suitable candidate for this study.~~

Due to Sections 3.13 and 3.19a being deleted all remaining sections have been renumbered.

Section 6.0 Registration/Randomization Procedures

Page 15: Section 6.19 is newly added as follows as a result of a radiation oncologist being required to confirm that the patient is a suitable candidate for the study:

A radiation oncologist has seen the patient and confirms the patient is a suitable candidate for this study.

Section 10.0 Adverse Event (AE) Reporting and Monitoring

Page 31: Section 10.23 table has been administratively revised as follows to reflect that the other grade 4 or 5 events will now be entered through the remote data entry system:

<p>Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report</p>	<p>Complete a Notification Form: Grade 4 or 5 Non AER Reportable Events/Hospitalization Form within 5 working days.</p> <p>If an AdEERS report has been submitted, this form does not need to be submitted.</p> <p><i>Fax or mail to the NCCTG SAE Coordinator, NCCTG Operations Office, 200 First Street SW, Rochester, MN 55905, Fax (507)284-9628.</i></p> <p>Enter into the remote data entry system within 5 working days of notification.</p>
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Section 11.0 Treatment Evaluation Using RECIST Criteria²⁰

Pages 33-36: The following revisions have been made to this section to reflect current template language:

- The following sentence has been added to the second bullet in Section 11.31: **For patients having only lesions measuring at least 1 cm to less than 2 cm must use spiral CT imaging for both pre- and post-treatment tumor assessments.**
- The first bullet under 11.32 has been revised to read “Conventional CT and MRI **must** ~~should~~ be performed with cuts of 1.0 cm or less in slice thickness contiguously.”
- The first sentence of the second bullet under 11.32 has been revised to read “Spiral CT **must** ~~should~~ be performed using a 5 mm contiguous reconstruction algorithm.”
- A new third bullet has been added to Section 11.32 and reads “**Ultrasound (US) may be used to measure tumor lesions that are clinically not easily accessible.**”
- A new second bullet has been added to Section 11.33 and reads “**In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks (see Section 11.44).**”
- The last sentence in Section 11.42 has been revised to read “Measurements are not required, and these lesions should be followed **in accordance with Section 11.433** as ~~“present”~~ or ~~“absent.”~~”
- The first column under the second bullet in Section 11.433 now reads “~~Non~~ **Complete Response Stable Disease (Non-CR SD).**”
- A new sentence has been added to the second column under the third bullet in Section 11.433 and reads “**Although a clear progression of ‘non-target’ lesions only is exceptional, in such circumstances, the opinion of the treating physician will prevail, and the progression status will be confirmed at a later time by the study chair or a review panel.**”
- The second row in the table in Section 11.44 now reflects:

CR	Non-CR/Non-PDS	No	PR
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- The last sentence in Section 11.46 has been revised to read “Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration (~~a decline of performance status by 2 points, i.e., PS 0 to PS 2~~):”
- The following three bullets have been added to Section 11.46:
 - Weight loss >10% of body weight.
 - Worsening of tumor-related symptoms.
 - Decline in performance status of >1 level on ECOG scale.

Section 15.0 Drug Information

Pages 39-42: Section 15.16 has been replaced in its entirety with the updated CAEPR listing for PS-341.

Pages 41-58: Due to the inclusion of the updated CAEPR listing for PS-341, repagination has occurred.

Appendices IA and IB Consent Forms

Pages 5-7: Due to the receipt of an updated CAEPR listing, the following revisions have been made to the consent form:

~~More common~~ **Likely related** side effects

- Fatigue (feeling tired or weak)
- Loss of appetite
- Nausea (feeling sick to your stomach)
- Vomiting (throwing up)
- Diarrhea
- Constipation (difficulty passing stool)
- ~~Abdominal cramping or pain~~ (moved to “Less likely” category)
- ~~Slowing of the small intestine causing abdominal pain and bloating~~ (moved to “Less likely” category)
- Fever
- ~~Rash~~ (moved to “Less likely” category)
- Lowering of the blood cell counts with an increased risk of infection
- **Lowering of the red blood cell count causing Anemia** (~~low blood iron~~) or bleeding
- **Lowering of blood clotting cells with an increased risk of bleeding**
- Headache
- ~~Low blood pressure~~ (this is moving to the “Less likely” category)
- **Problems with the central nervous system (the brain and spinal cord) which controls mental activities, movements and nerves** (moved from “Unclear” category)
- Neurologic effects such as numbness, tingling or weakness in the arms and legs
- **Shortness of breath** (moved from “Unclear” category)
- ~~Inflammation of veins~~

The following “Less likely related side effects of PS-341” category is newly added and the side effects have been moved from the “unclear” category unless otherwise indicated:

Less likely related side effects of PS-341

- **Runny, stuffy, or itchy nose** (*underscored portion newly added*)
- **Ringing or buzzing in the ears**
- **Lowering of the white blood cell counts with an increased risk of infection** (*moved from more common category*)
- **Low blood pressure** (*moved from more common category*)
- **Drop in heart’s ability to pump blood** (*newly added*)
- **Fluid around the heart**
- **Trouble sleeping** (*newly added*)
- **Uncontrollable shaking and chills**
- **Weight loss**
- **Redness in the face**
- **Bruising, bleeding, soreness or redness of the skin where the injection is given** (*newly added*)
- **Itching**
- **Rash** (*moved from more common category*)
- **Hives or welts on the skin**
- **Loss of fluid in the body, may need to stay in the hospital** (*newly added*)
- **Passing gas** (*newly added*)
- **Heartburn**
- **Slowing of the small intestine causing stomach pain, bloating and cramping** (*moved from more common*)
- **Sores in the lining of the throat** (*newly added*)
- **Changes in taste**
- **Bleeding anywhere in the body**
- **Fever with low white blood cell count** (*underscored portion newly added*)
- **Infection (sinus)** (*underscored portion newly added*)
- **Swelling in the head and neck** (*newly added*)
- **Swelling in the arms or legs** (*newly added*)
- **Abnormal tests of liver function**
- **Decrease in kidney function, kidney damage or failure** (*underscored portion newly added*)
- **High/low blood sugar**
- **Low magnesium levels in the blood**
- **Low phosphate levels in the blood**
- **Change in walking stride or function** (*newly added*)
- **Feeling dizzy or lightheaded** (*newly added*)
- **Mood changes (feeling agitated)** (*underscored portion newly added*)
- **Weakness caused by damage of the nerves** (*newly added*)
- **Fainting**
- **Dry eye syndrome**
- **Damage to the surface of the eye** (*newly added*)

- **Double or blurred vision**
- **Pain in the back, bones, chest, arms, legs, joints, muscles, throat, voice box, stomach, or nerves** (*underscored portions newly added*)
- **Cough**
- **Hiccups**
- **Fluid around the lungs**

The following category is newly added:

Rare but serious side effects of PS-341

- **Abnormal hole in the GI tract**

Per NCI and most IRBs, including side effects that are undetermined to be related to a particular drug is not mandatory; therefore, the “Side effects still undetermined to be related to PS-341” have been deleted.