

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 3 – March 17, 2006

Summary

- Clarification made as to when patients will go to event monitoring has been made to the Schema, Section 13, and Section 18 of the protocol.
- Clarification made to the eligibility criteria (Section 3.0) that women of childbearing potential must have a negative pregnancy test within 7 days of registration.
- Clarification to the test schedule (Section 4.0) as to when the tumor measurement should be done.
- Definition of hematologic toxicity has been clarified in the protocol treatment section (Section 7.21).
- Clarification made to the Adverse Event (AE) Reporting and Monitoring (Section 10.12) to direct protocol personnel to the correct location of the CAEPR listing.
- The National Cancer Institute has requested that the Comprehensive Adverse Events and Potential Risks List (CAEPR) be included in all protocols that CTEP holds the IND. This listing has been incorporated into the drug information section (Section 15) of the protocol and will replace the existing “Reported Adverse Events and Potential Risks” section. Also, additional side effects have been identified in this CAEPR listing and have been added to the model consent form.
- Protocol resource personnel updates.
- 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: Reflects Addendum 3 and revised NCI version date.

Protocol Resource Page

- Page 2: Protocol resource personnel updates are reflected as follows:
- The NCCTG *Research Base* Protocol Development Coordinator’s name has been updated to reflect Janis **Wobschall** rather than Janis ~~Gjervik~~.
 - The fax number for the NCCTG *Research Base* Pathology Coordinator has been updated to reflect 507/284-~~1902~~ **9628**.
 - The fax number for the NCCTG *Research Base* AdEERS Coordinator has been updated to reflect 507/284-~~1902~~ **9628**.
 - The fax number for the NCCTG *Research Base* Protocol Administration Specialist has been updated to reflect 507/284-~~1902~~ **538-0906**.
 - The fax number for the NCCTG *Research Base* Radiation Quality Control Coordinator has been updated to reflect (507) ~~284-1902~~ **266-7240**.

Schema

Page 4:

Phase I Component

The following clarifications have been made:

- The box entitled “4 week post RT evaluation” now reads “4 week post RT evaluation (**part of cycle 2**)”
- The observation phase has been added to clarify when tumor measurement should be done.
- The box entitled “Event Monitoring” has been deleted from the treatment section as patients will not go to event monitoring unless they have disease progression or go off-study for another reason.
- Footnote * has been revised to read:
Cycle 1 length = ~~21 days~~ **3 weeks**
Cycle 2 length = **7 weeks (last 3 weeks of chemo/RT + 4-week post-RT evaluation)**

Schema

Page 5:

Phase II Component

The following clarifications have been made:

- The box entitled “4 week post RT evaluation” now reads “4 week post RT evaluation (**part of cycle 2**)”
- The box entitled “CR, PR, SD” has been deleted.
- The box entitled “Event Monitoring” has been deleted from the treatment section as patients will not go to event monitoring unless they have disease progression or go off-study for another reason.
- Footnote ** has been revised to read:
Cycle 1 length = ~~21 days~~ **3 weeks**
Cycle 2 length = **7 weeks (last 3 weeks of chemo/RT + 4-week post-RT evaluation)**

Section 3.0

Page 12:

Eligibility CriteriaSection 3.19d is newly added to reflect that women of childbearing potential must have a negative serum pregnancy test ≤ 7 days of registration.

Section 4.0 Test Schedule

Page 14: The following revisions have been made for clarification as follows:

Tests and procedures	≤21 days prior to registration	Wkly during RT	Prior to drug administration on day 2, cycle 2 of Taxol/ CBDCA each cycle	4 wks post RT (part of cycle 2)	Phase II patients CR, PR, SD Observation q3 months for up to 2 years from time of registration 3 months post-RT, q3 months for 1 year post-RT, and then q6 months for a maximum of 5 years from time of registration
History and exam, wt, PS	X	X		X	X
Height	X				
Rad Onc. consultation	X ¹				
Toxicity assessment ²		X	X	X	X
Hematology group: HgB, WBC, ANC, PLT	X	X	X	X	X
Chemistry group: (Alk Phos, SGOT, total or direct bilirubin, creatinine, glucose)	X		X		X
FEV1	X				
Tumor measurement ³	X ³			X ³	X ³
Serum pregnancy test ⁴	X				
Tissue blocks (Section 14.3)	X ⁵				

1. This is done in order to verify that a radiation oncologist has seen and confirmed that the patient is a suitable candidate for this study.
2. See Section 10.3 for detail.
3. ≤30 days prior to registration. A CT chest to include the liver and adrenals are required for baseline evaluation, 4 weeks following RT, 3 months following RT, and every 3 months after that for a maximum of 2 years during the observation phase.
4. For women of childbearing potential only. Must be done ≤7 days prior to registration.
5. **Submit ≤30 days after registration.**

Section 7.0**Protocol Treatment**

Page 19:

The following revisions have been made to Section 7.21 (Definitions of DLT) to clarify the definition of hematologic toxicity used in this trial as follows:

- Reference to footnote “*” has been added to the heading “Toxicity.”
- Under the “Toxicity” column, “Hematologic” now reads “Hematologic (ANC, PLT)**”
- Under the “Definition” column for “Hematologic,” the text now reads “Grade \geq 4 for ~~5~~ **8** days”
- Footnotes * and ** are newly added.

Section 10.0**Adverse Event (AE) Reporting and Monitoring**

Page 28:

The first bullet item in Section 10.12 has been revised for clarification in order to reflect the location of the CAEPR listing as follows:

Expected AEs for expedited reporting purposes are listed on the CTEP Agent Specific Adverse Event List (ASAEL), a component of the Comprehensive Adverse Events and Potential Risks List (CAEPR). ~~To access the CAEPR for an agent under a CTEP IND, contact the AdEERS MD Help Desk at adeersmd@tech-res.com.~~ **Refer to Section 15.0 to locate the CAEPR for the CTEP IND agent(s).**

Section 11.0**Treatment Evaluation Using RECIST Criteria²⁰**

Page 33:

Section 11.1 has been revised for consistency with Schema and Section 4.0 (Test Schedule) as follows:

Schedule of Evaluations: Patients should ideally be reevaluated ~~every~~ at 4 weeks post-RT, 3 months post-RT, ~~and then~~ every 3 months **for 1 year post-RT, and every 6 months** thereafter for a maximum of ~~2~~ **5** years **from time of registration** (see below).

Section 13.0**Treatment/Follow-up Decision at Evaluation of Patient**

Page 36:

Section 13.21 has been deleted as this is noted in Section 4.0 (Test Schedule) as follows:

~~Acute toxicity will be evaluated at 4 weeks following the completion of RT.~~

Page 36:

Section 13.21, previously Section 13.23 has been revised as follows as this is also stated in Section 4.0 (Test Schedule):

If patient goes off study due to refusal to continue participation or unacceptable toxicity, the patient will then go to event monitoring ~~and will be followed every 3 months until progression, then every 6 months up to 5 years from time of registration.~~

Page 37:

Section 13.22 has been deleted as this is a duplicate statement from what is reflected in Section 13.26 as follows:

~~Patients with progressive disease during treatment will go to event monitoring; specifically, patients will be followed every 6 months up to 5 years from time of registration.~~

Section 13.0**Treatment/Follow-up Decision at Evaluation of Patient (Con't)**

Pages 36-37:

Due to the deletion of Sections 13.21 and 13.22, all remaining sections have been renumbered.

Page 37:

The first sentence of Section 13.22, previously Section 13.24 has been revised for clarification as follows:

Patients who develop proven progression or metastasis after completion of therapy will go to event monitoring **per Section 18.0**.

Page 37:

Section 13.24, previously Section 13.26 has been revised for consistency with the Schema and Section 4.0 (Test Schedule) as follows:

~~Phase II component only~~ **Observation:** If the patient has achieved CR, PR, or SD, at the 4 week post-RT evaluation, the patient will be observed ~~every at 3 months for up to two years from time of registration and then will go to event monitoring post-RT, every 3 months for 1 year post-RT, and then every 6 months for up to 5 years from time of registration.~~ Patients may receive adjuvant treatment at the discretion of the treating Radiation Oncologist and Medical Oncologist. If a patient goes on to receive adjuvant treatment, the patient will then go to event monitoring and will be followed every 3 months until progression, then every 6 months up to 5 years from time of registration.

Page 37:

The last sentence of Section 13.25, previously Section 13.27 has been revised for clarification as follows:

Patients who go on to receive alternative therapy will go to event monitoring ~~and will be followed every 3 months until progression, then every 6 months for up to 5 years from time of registration~~ **per Section 18.0**.

Page 37:

The last sentence of Section 13.26 has been revised to reflect the correct section number referenced as follows:

A patient found to have a $V_{20} > 40\%$ (see Section 7.3553) will not be treated on this protocol and the patient will be regarded as ineligible and will be replaced.

Section 14.0**Translational/Pharmacologic Studies**

Page 37:

The heading has been revised to clarify that these studies are optional as follows:

Translational/Pharmacologic Studies **(Optional)**

Page 38:

Section 14.3 has been revised to reflect the current address for Helen Tollefson as follows:

NCCTG Operations Office
~~Plummer 4 NW Clinic 3-24~~
200 First Street SW
Rochester, MN 55905
ATTN: Helen Tollefson, ~~NCCTG Pathology Coordinator~~

Page 38:

The second paragraph under the bullet items in Section 14.3 has been revised for clarification as follows:

The blocks/slides will be forwarded by ~~the NCCTG Pathology Coordinator~~ **Helen Tollefson** to the TACMA Biospecimen Laboratory, Guggenheim 1034, Mayo Clinic Rochester.

Section 15.0**Drug Information**

Page 38:

The phone number for obtaining the investigator brochure has been updated in Section 15.1 as follows:

Phone: 301-~~496-5725~~ **594-2079**

Pages 39-42:

Section 15.16 has been replaced in its entirety due to the inclusion of the CAEPR listing at the request of the National Cancer Institute.

Pages 39-57:

Due to the inclusion of the CAEPR listing, repagination has occurred.

Section 17.0**Pathology Considerations for Quality Control**

Page 53:

Section 17.2, the address for the Iowa Oncology Research Association has been updated as follows:

Iowa Oncology Research Association, ~~1223 Center Street~~ **300 East Locust,**
Suite ~~49,~~ **350,** Des Moines, IA 50309-1016.

Section 18.0**Records and Data Collection Procedures**

Page 54:

The following revisions have been made to Section 18.1 for clarification as follows:

- The heading has been revised as follows as this study requires remote data entry “~~(All materials are forwarded to the NCCTG Operations Office unless otherwise indicated.)~~”
- Under the “Follow-up material” section, the heading for the first two columns have been revised to read “**at each cycle 1 evaluation (cycle 1 = first 3 weeks)**” and **At end-of-treatment cycle 2 evaluation (cycle 2 = last 3 weeks of chemo/RT + 4-week post-RT eval).**”
- Reference to footnote 4 has been added under the “Observation” column for the “Measurement Form,” the Evaluation/Treatment Form,” and the “Nadir/Adverse Event Form.”
- Under the “Event-Monitoring Phase” section, the heading for the third column has been revised to read “**After PD⁵ q-6 mos.²**”
- Reference to footnote 3 has been deleted from the column entitled “At cycle 1 evaluation” and moved to the column entitled “Observation” for the Measurement form and now references footnote 4.
- The following statement has been added to footnote 1 “**NOTE: All materials will be forwarded to the NCCTG Operations Office, Attn: Kathryn Scherger, RT Coordinator, NW Clinic 3-24, 200 First Street SW, Rochester, MN 55905.**”
- Footnote 3 has been deleted.
- Previous footnotes 4 and 5 have now become footnotes 3 and 4 respectively.
- Reference to footnote 4 from the columns entitled “At cycle 1 evaluation” and “At cycle 2 evaluation” have been revised to reference footnote 3 in the “Dose-Limiting Toxicity Reporting Form” row.
- Footnote 4 has been revised to read “**During observation, patients will be followed at 3 months post-RT, q 3 months for up to 2 years from time of registration 1 year post-RT, and then q 6 months for a maximum of 5 years post-registration.** After the observation phase, patients will go to event monitoring for a maximum follow-up time of 5 years from their registration date.
- Footnote 5 is newly added.

Appendix IA**Phase I Component Consent Form**

Page 1:

Under the “What will happen in this research study?” section, a new last sentence has been added to the second paragraph for clarification as follows:

If your disease has not gotten worse at the 4-week post radiation therapy evaluation, you will also have routine blood tests done 3 months after radiation therapy is done, then every 3 months for 1 year after radiation therapy, and then every 6 months for up to 5 years from the time you went on study.

Page 2:

Under the “What will happen in this research study?” section, a new section was added to the table on page 2 entitled “**After Treatment is Done and Disease is the Same or Better**” in order to clarify when follow-up tests will be done.

Page 6:

Under the “What are the risks of the study?” section for PS-341, the following side effects have been added under the “happened but unclear if these effects were from PS-341” section due to the inclusion of the CAEPR listing into the protocol: **runny or itchy nose; ringing or buzzing in the ears; fluid around the heart; uncontrollable shaking and chills; weight loss; redness of the face; itching; hives or welts on the skin; heartburn; high/low blood sugar; low magnesium levels in the blood; low phosphate levels in the blood; mood changes; fainting; dry eye syndrome; double or blurred vision; pain in the back, bones, chest, arms, legs, joints, voice box, or nerves; cough; hiccups; fluid around the lungs; fever; changes in taste; bleeding anywhere in the body; and infection.**

Appendix IB**Phase II Component Consent Form**

Page 1:

Under the “What will happen in this research study?” a new last sentence has been added to the second paragraph for clarification as follows:

If your disease has not gotten worse at the 4-week post radiation therapy evaluation, you will also have routine blood tests done 3 months after radiation therapy is done, then every 3 months for 1 year after radiation therapy, and then every 6 months for up to 5 years from the time you went on study.

Page 2:

Under the “What will happen in this research study?” the last section in the table was revised in order to clarify when follow-up tests will be done as follows:

3 months after radiation therapy, then every 3 months for up to 1 year after radiation therapy, and then every 6 months for up to 5 years from time of study registration

Page 6:

Under the “What are the risks of the study?” section for PS-341, the following side effects have been added under the “happened but unclear if these effects were from PS-341” section due to the inclusion of the CAEPR listing into the protocol: **runny or itchy nose; ringing or buzzing in the ears; fluid around the heart; uncontrollable shaking and chills; weight loss; redness of the face; itching; hives or welts on the skin; heartburn; high/low blood sugar; low magnesium levels in the blood; low phosphate levels in the blood; mood changes; fainting; dry eye syndrome; double or blurred vision; pain in the back, bones, chest, arms, legs, joints, voice box, or nerves; cough; hiccups; fluid around the lungs; fever; changes in taste; bleeding anywhere in the body; and infection.**