

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 14 – November 5, 2010

**Summary**

- In response to an Action Letter from Dr. S. Percy Ivy of the National Cancer Institute (NCI) dated October 1, 2010 with a follow-up letter dated October 15, 2010, concerning the carboplatin, Section 7.0 has been revised. Section 7.0 contains a revision to the AUC-based dosing of carboplatin in patients, not to exceed 125 ml/min.
- Per NCI, the Secondary AML/MDS Report Form will no longer be used. Therefore, Sections 10 and 18 have been revised accordingly.
- Administrative/editorial changes.

**Accrual to this trial may continue, but the measures to assure patient safety must be put in place immediately. The safety measures should be implemented while your local IRB approval is being obtained.**

**Patients already on study who have tolerated their carboplatin dose should not have their dose modified (unless they are experiencing toxicity that requires dose modification per the protocol. As this is a change to enhance patient safety (by providing maximal allowed carboplatin doses), physicians should use the new instructions for newly enrolled patients even if the treatment starts before this addendum is approved by your local IRB.**

**Determination of the level of IRB review for this addendum (expedited versus full board review) is at the discretion of your local IRB.**

**Replacement pages are included. Please incorporate into the protocol and keep this addendum with your protocol.**

**Title Page** Updated to reflect Addendum 14 and revised NCI version date.

**Protocol Resource Page**

Page 2: **Lisa M. Finstuen** replaces ~~Rachael M. Meyers~~ as the NCCTG *Research Base* Quality Assurance Specialist.

The Research Base Data Management Specialist contact information has been removed (Vicki Bryhn). Please contact the NCCTG Research Base Quality Assurance Specialist (QAS) for technical questions regarding electronic form entry.

**Index**

Page 3: Appendix V has been deleted as this worksheet is no longer being used and the information contained in this appendix has been moved to Section 7.42.

**Section 7.0**

Page 21:

**Protocol Treatment**

Section 7.42, footnote 3, has been revised due to the Action Letter dated October 1, 2010 and follow-up letter dated October 15, 2010 from Percy Ivy regarding changes to the Calvert formula calculation as follows:

**CrCl is the creatinine clearance— use Appendix V (Carboplatin Dosing Worksheet) for the dose calculation for each cycle of therapy. Dosed using Calvert Formula with Cockcroft & Gault Equation Calvert Formula: CBDCA dose (mg) = target AUC x (GFR + 25). Note: The glomerular filtration rate (GFR) used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min. Therefore, for newly enrolled patients, the maximum carboplatin dose for this study is 900 mg. For the purposes of this protocol, the GFR is considered to be equivalent to the creatinine clearance (CrCl) and can be measured or calculated (Note: When concerned about patient safety in a given patient, measure GFR. The CrCl is calculated by the method of Cockcroft & Gault (CrCl[mL/min] = [140 – age] x actual body weight [kg] divided by plasma Cr [mg/dL x 72 x [0.85 if female or 1.0 if male])). Note: A correction factor is NOT to be used to calculate carboplatin doses based on the IDMS serum creatinine.**

**Section 10.0**

Pages 29/31:

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

With the removal of the Secondary AML/MDS Report Form, a new fourth bullet beneath the tables in Sections 10.21 and 10.22 have been added as follows for clarification:

- **SECONDARY MALIGNANCIES (defined as “cancer caused by treatment for a previous malignancy,” e.g., treatment with radiation or chemotherapy) are to be reported through AdEERS, as noted in Section 10.23. Secondary malignancies are not considered metastasis of the initial neoplasm. Secondary malignancy is unrelated to the first cancer that was treated, and may occur months or even years after initial treatment.**

**Note: Second Primary malignancy (malignancy not due to prior treatment) should not be reported through AdEERS.**

Page 30:

The first bullet under the “Additional Instructions...” section in Section 10.21 has been revised to reflect updated notification instructions as follows:

- **In the rare event when Internet connectivity is disrupted, a report may be prepared using the Adverse Event Expedited Report—Single Agent or Multiple Agents paper template (available on the CTEP Home Page at <http://ctep.cancer.gov>). Refer to CTEP, NCI Guidelines: Adverse Event Reporting Requirements for back-up submission instructions. When internet connectivity is interrupted, a 24-hour notification is made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, an AE report submitted on a paper template or a 24-hour notification that is called in, must be entered into electronic AdEERS by the original submitter of the report at the site. In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-**

**7497, or 301-897-7402 for CIP studies. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP website and will NO LONGER be accepted.**

Page 31: The last column for the “Secondary AML/MDS” section in Section 10.23 has been revised due to the removal of the Secondary AML/MDS Report Form as follows:

Reporting for this event required during and after completion of study treatment **via AdEERS.**

**Through December 31, 2010, continue using CTCAE v3.0: Report Myelodysplasia as “Blood/Bone Marrow – Other (Specify, \_\_\_\_\_).”**

**Beginning January 1, 2011, AdEERS will only accept CTCAE v4.0 for this study. Report these events using “Neoplasms benign, malignant and unspecified (including cysts and polyps)” and including the appropriate adverse event:**

- **Leukemia secondary or oncology chemotherapy OR**
- **Myelodysplastic syndrome OR**
- **Treatment related secondary malignancy**

~~Submit the NCI/CTEP Secondary AML/MDS Report form within 15 days via fax or mail to the NCCTG SAE Coordinator, NCCTG Operations Office, 200 First Street SW, Rochester, MN 55905, Fax (507)284-9628. The Operations Office will submit to NCI.~~

**Section 18.0** **Records and Data Collection Procedures**

Page 54: With the removal of the Secondary AML/MDS Report form, the row that references this form has been deleted.

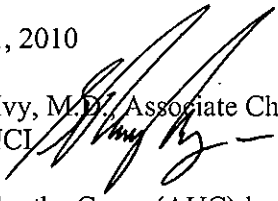
**Appendix V** **Carboplatin Dosing Worksheet**

Page 1: This appendix has been deleted as this worksheet is no longer being used. Information contained in this appendix has been moved to Section 7.42.



**ACTION LETTER FOR PROTOCOLS  
SPONSORED BY THE NATIONAL CANCER INSTITUTE  
THAT USE CARBOPLATIN**

**DATE:** October 1, 2010

**FROM:** S. Percy Ivy, M.D., Associate Chief, Senior Investigator, Investigational Drug Branch, CTEP, DCTD, NCI 

**SUBJECT:** Area Under the Curve (AUC)-based Dosing of Carboplatin Using IDMS-measured Serum Creatinine

**TO:** Investigators Performing NCI-Sponsored Clinical Trials That Include Carboplatin (NSC 241240)

The purpose of this letter is to alert investigators of a modification of area under the curve (AUC)-based dosing of carboplatin (NSC 241240) in studies sponsored by the Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI). See the accompanying list of all NCI/CTEP trials that are affected by this Action Letter.

Since this information represents a change in the AUC-based dosing of carboplatin in patients, an appropriate amendment must be reviewed and approved by NCI/CTEP as well as by the Institutional Review Board (IRB) of record for the study. However, **physicians should use the new method for carboplatin dose determination at the patient's next treatment even if that is before protocol or IRB approval.**

**Amendments are due to the Protocol and Information Office (PIO) at [PIO@CTEP.NCI.NIH.GOV](mailto:PIO@CTEP.NCI.NIH.GOV) by 5 PM ET on November 12, 2010** or as required based on protocol status (see the *Specific Instructions on Amendment Preparation Based on Protocol Status* section). The cover letter for the submitted amendment should state that it is being submitted in response to an Action Letter from S. Percy Ivy, MD (301-496-1196; [ivyp@ctep.nci.nih.gov](mailto:ivyp@ctep.nci.nih.gov)). Failure to respond in a timely fashion may result in suspension of the Principal Investigator or permanent study closure.

Serum creatinine is used as a surrogate for renal function. Carboplatin dosing using the Calvert formula is based on renal function determined by measured or estimated glomerular filtration rate (GFR). During the last 2 years, the National Institute for Standards and Technology (NIST) has standardized the measurement of serum creatinine using Isotope Dilution Mass Spectrometry (IDMS). By December 31, 2010, all clinical chemistry laboratories in the United States of America (USA) will have switched to the IDMS measurement, and reagents for older methodologies will no longer be available. Older methods were not standardized and led to widely variable creatinine measurements and poor performance of calculated GFR estimations, particularly in patients with low normal or extremely low serum creatinine measurements. There is no correlation between older methods for creatinine determination and the IDMS method. Therefore, IDMS creatinine values cannot be converted for use in formulas for calculating GFR and thus the AUC values that are used for carboplatin dosing described in the Food and Drug Administration (FDA)-approved labeling for this drug. The use of a correction factor in calculating the carboplatin dose based on IDMS-measured serum creatinine has led to an overestimation of the carboplatin dose administered and may result in enhanced drug-related toxicity for patients with near normal renal function receiving this chemotherapeutic drug for treatment of their malignancy. **Since the IDMS serum creatinine measurement method has been in use, an increase in the incidence of**

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expected carboplatin-related adverse events for some NCI/CTEP-sponsored studies has been reported.

In view of the potential seriousness of these expected adverse events, NCI/CTEP is requiring that all principal investigators for the specified protocols do the following:

- 1) Distribute this letter to all participating investigators and IRBs. The principal investigator or lead organization (e.g., coordinating center or group operations office) also needs to forward a copy of the e-mail or other rapid traceable communication (e.g., fax with return requested) to [PIO@CTEP.NCI.NIH.GOV](mailto:PIO@CTEP.NCI.NIH.GOV) within 7 calendar days of the date of this letter. Failure to comply within the 7-day timeframe may result in the temporary suspension of the principal investigator and enrollment of patients to the study.
- 2) Amend the protocol to assure that a correction factor is **NOT** used to calculate carboplatin doses based on IDMS serum creatinine.
- 3) Amend the protocol to assure that your protocol using carboplatin has a maximum dose for carboplatin based on the target AUC **OR** mandate measured GFR for patients with serum creatinine below the lower limit of normal.
- 4) If your study uses the Calvert formula for calculation of carboplatin dose, amend the patient treatment and drug administration section of the protocol to assure that your protocol using carboplatin applies the following formula to determine the maximum administered carboplatin dose\*. GFR may be measured or calculated using a standard formula.

**Calvert Formula**

Total Dose (mg) = (target AUC) X (GFR + 25)

**NOTE: the GFR used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min.**

**Maximum carboplatin dose (mg) = target AUC(mg•min/mL)•150 mL/min.**

\*The maximum carboplatin dose should not exceed target AUC(mg•min/mL)•150 mL/min, but it may be less. Many trials have a target carboplatin AUC of 6 which would result in a maximum dose of 900 mg. Highly specific settings like bone marrow transplant or pediatric studies may target a higher AUC.

- 5) For NCI/CTEP-sponsored studies with international participants that may or may not be using IDMS serum creatinine measurements, please use the same dosing instructions outlined above in number 4.
- 6) When concerned about safety in a specific patient, **measure GFR.**
- 7) Accrual to this trial may continue, but the measures to assure patient safety must be put in place immediately. The safety measures should be implemented while IRB and NCI/CTEP approval is obtained.

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Patients currently on study should continue on study and may be informed of the rationale for the possible change in their dosing of carboplatin.

- 8) Patients currently on study should continue to be monitored for the known adverse events associated with the administration of carboplatin as outlined in the package insert that can be found on the manufacturer's website.
- 9) Dose modifications should occur as outlined in the protocol document. Each patient should be thoroughly evaluated, closely monitored and supported as clinically appropriate.
- 10) Adverse event reporting should continue as outlined in the protocol document.
- 11) Submit all amendments to the protocol and informed consent form to NCI/CTEP by 5:00 pm ET on November 12, 2010. The amendment cover letter must state "This amendment is in response to an Action Letter from S. Percy Ivy, MD". Failure to comply within this timeframe may result in the temporary suspension of the principal investigator and permanent study closure.

Please submit the amendment, the change memo, and the cover letter to the PIO at [PIO@CTEP.NCI.NIH.GOV](mailto:PIO@CTEP.NCI.NIH.GOV).

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**ACTION LETTER GENERAL INSTRUCTIONS**

1. **Distribute this Action Letter to all participating investigators and IRBs within 2 working days.** For Cooperative Group studies, please follow instructions from Group Operations office. For sites participating in the NCI Central-IRB (CIRB) Initiative, NCI/CTEP has provided a copy of this Action Letter to the CIRB if the Action Letter affects any studies under CIRB review.
2. **Save a copy of the Action Letter for your records.**

**INSTRUCTIONS FOR PREPARATION OF AN AMENDMENT IN RESPONSE TO THIS ACTION LETTER**

**General Instructions on Amendment Preparation:**

- Instructions regarding the due date for an amendment and where to send it are included on the first page of the Action Letter. If any of the NCI-required changes are not applicable for your trial (i.e., already appear in your protocol), note this in your Change Memo.

**Specific Instructions on Amendment Preparation Based on Protocol Status:**

1. **Trials with a current NCI/CTEP status of Active**
  - Review and follow **ALL** the instructions outlined in this Action Letter.
  - You may include additional non-Action Letter related changes (any type) in your amendment response; however, this may delay amendment approval and thus, re-activation of your trial.
  - **If an amendment is required by a specific date and it is not submitted by the required submission date, NCI/CTEP will suspend accrual to your trial and may suspend the principal investigator and/or close your trial permanently (i.e., administratively complete).**
2. **Trials with a current NCI/CTEP status of Closed to Accrual or Temporarily Closed to Accrual**
  - Review and follow **ALL** the instructions outlined in this Action Letter.
  - You may include additional non-Action Letter related changes (any type) in your amendment response; however, this may delay amendment approval.
  - **If an amendment is required by a specific date and it is not submitted by the required submission date, NCI/CTEP will suspend accrual to your trial and may suspend the principal investigator and/or close your trial permanently (i.e., administratively complete) unless you explicitly request and are granted a waiver to delay submission of the amendment (may be applicable for trials temporarily closed to accrual when other protocol changes are pending).**
3. **Trials with a current status of Approved or Temporarily Closed to Accrual and Treatment**
  - The protocol must be revised as per the instructions outlined in the Action Letter in the next revised protocol draft submitted to NCI/CTEP. The protocol amendment must be submitted and approved by NCI/CTEP before the trial can be activated or re-opened.
  - You may include additional non-Action Letter related changes (any type) in your amendment response.

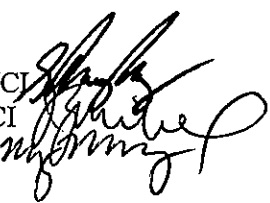
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4. Trials with a current NCI/CTEP status of In Review
  - The protocol must be revised as per the instructions outlined in the Action Letter. These changes must be included in the next revised protocol draft submitted to NCI/CTEP. The protocol will not be approved until these changes are made.
  - You may include additional non-Action Letter related changes (any type) in your revision response.
  
5. Trials with a current NCI/CTEP status of Closed to Accrual and Treatment or Complete
  - This information is being sent for informational purposes only. You may follow local IRB or Operations Office procedures and requirements.



**FOLLOW- UP for  
ACTION LETTER FOR PROTOCOLS  
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THAT USE CARBOPLATIN**

**DATE:** 15 October 2010

**FROM:** S. Percy Ivy, M.D., Associate Chief, IDB, CTEP, DCTD, NCI  
James Zwiebel, MD, Branch Chief, IDB, CTEP, DCTD, NCI  
Meg Mooney, MD, Branch Chief, CIB, CTEP, DCTD, NCI 

**SUBJECT:** Area Under the Curve (AUC)-based Dosing of Carboplatin Using IDMS-measured Serum Creatinine

**TO:** Investigators Performing NCI-Sponsored Clinical Trials that Include Carboplatin (NSC 241240)

**This follow-up is in response to queries regarding the original (October 1, 2010) Action Letter and includes additional information NCI/CTEP has received since issuing the original Action Letter. The new or additional information is bolded.**

The purpose of this letter is to alert investigators of a modification of Area Under the Curve (AUC)-based dosing of carboplatin (NSC 241240) in studies sponsored by the Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI). See the accompanying list of all NCI/CTEP trials that are affected by this Action Letter.

Since this information represents a change in the AUC-based dosing of carboplatin in patients, an appropriate amendment must be reviewed and approved by NCI/CTEP as well as by the Institutional Review Board (IRB) of record for the study. **Physicians should use the instructions for carboplatin dose determination described below ONLY for patients initiating treatment. Patients already on study who have tolerated their carboplatin dose should not have their dose modified (unless they are experiencing toxicity that requires dose modification per protocol). As this is a change to enhance patient safety (by providing maximal allowed carboplatin doses), physicians should use the new instructions described below even if the treatment starts before the study amendment is approved.**

Amendments are due to the Protocol and Information Office (PIO) at [PIO@CTEP.NCI.NIH.GOV](mailto:PIO@CTEP.NCI.NIH.GOV) by 5 PM ET on **November 12, 2010** or as required based on protocol status (see the *Specific Instructions on Amendment Preparation Based on Protocol Status* section). The cover letter for the submitted amendment should state that it is being submitted in response to an Action Letter from S. Percy Ivy, MD (301-496-1196; [ivyp@ctep.nci.nih.gov](mailto:ivyp@ctep.nci.nih.gov)). Failure to respond in a timely fashion may result in suspension of the Principal Investigator or permanent study closure.

During the last several years, the National Institute for Standards and Technology (NIST) has standardized the measurement of serum creatinine using Isotope Dilution Mass Spectrometry (IDMS). By December 31, 2010, all clinical chemistry laboratories in the United States of America (USA) will have switched to the IDMS measurement and reagents for older methodologies will no longer be available. Older methods were not standardized and lead to variable creatinine measurements. **Due to this**

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variability, the use of a single correction factor to convert IDMS creatinine values to “non-IDMS” creatinine values will not work across all labs and institutions.

The IDMS method, in general, generates a lower creatinine value than older methods in patients with normal renal function. In addition, the IDMS method is more likely to generate creatinine levels that are below the lower limit of normal. Serum creatinine is used to estimate glomerular filtration rate (GFR). Measurement of serum creatinine by the IDMS method could result in an overestimation of GFR in some patients with normal renal function. If the total carboplatin dose is calculated based on an estimated GFR using an IDMS-measured serum creatinine and the Calvert formula, carboplatin dosing could be higher than desired and could result in increased toxicity.

In view of the potential for an increase in serious expected adverse events, NCI/CTEP is requiring that all principal investigators for the specified protocols do the following:

- 1) Distribute this letter to all participating investigators and IRBs. The principal investigator or lead organization (e.g., coordinating center or group operations office) also needs to forward a copy of the e-mail or other rapid traceable communication (e.g., fax with return requested) to [PIO@CTEP.NCI.NIH.GOV](mailto:PIO@CTEP.NCI.NIH.GOV) within 7 calendar days of the date of this letter. Failure to comply within the 7-day timeframe may result in the temporary suspension of the principal investigator and enrollment of patients to the study.
- 2) **Remove any language in protocols indicating that conversion of IDMS creatinine levels to “non-IDMS” values should be performed. No standard correction factor has been adequately validated. Amend the protocol to assure that a correction factor is NOT used to calculate carboplatin doses based on modifications of IDMS serum creatinine measurement.**
- 3) The initial dose of carboplatin may be calculated using an estimated GFR or a measured GFR. The current label for carboplatin provides safe dosing instructions that are based on measured GFR. Provided that direct GFR measurements are made to assess renal function, carboplatin can be safely dosed according to the instructions described in the label.
- 4) If the initial carboplatin dose is based on an estimated GFR, amend the protocol to assure that your protocol uses a dose not to exceed the maximum dose for carboplatin based on the target AUC. Once the initial dose of carboplatin is calculated it does not need to be recalculated for subsequent cycles unless the patient is experiencing toxicity and requires dose modification to a lower dose of carboplatin.

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- 5) If your study employs the Calvert formula using an estimated GFR for calculation of the initial carboplatin dose, amend the patient treatment and drug administration section of the protocol to assure that your protocol applies the following instructions to determine the maximum administered carboplatin dose\*. The maximum administered carboplatin dose calculation below applies if serum creatinine is used in the formula for estimating GFR.

**Calvert Formula**

**Total Dose (mg) = (target AUC) X (GFR + 25)**

**NOTE: the GFR used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min, such that**

Maximum carboplatin dose (mg) = target AUC(mg•min/mL) • 150 mL/min.

\*The maximum carboplatin dose should not exceed target AUC(mg•min/mL)•150 mL/min. For example, if a trial utilizes a target carboplatin AUC of 6, the maximum dose would be 900 mg. Highly specific settings like bone marrow transplant or pediatric studies may target a higher AUC.

<b>Maximum AUC-based Carboplatin Dose</b>	
<b>AUC</b>	<b>Maximum Carboplatin Dose</b>
<b>6</b>	<b>900 mg</b>
<b>5</b>	<b>750 mg</b>
<b>4</b>	<b>600 mg</b>

- 6) For U.S. sites that have not yet implemented the IDMS serum creatinine measurement, or international sites that may or may not be using IDMS serum creatinine measurements, please use the same dosing instructions outlined above in Point number 5.
- 7) For specific patients, e.g. those with low muscle mass, direct measurement of GFR may be preferable to an estimation of GFR. In patients with an abnormally low serum creatinine, estimate GFR using a minimum creatinine level of 0.6 mg/dL, or cap the estimated GFR at 125 mL/minute as described in Point number 5.
- 8) Accrual to this trial may continue, but the measures to assure patient safety must be put in place immediately. The safety measures should be implemented while IRB and NCI/CTEP approval is obtained.

Patients currently on study should continue on study and may be informed of the rationale for the possible change in their dosing of carboplatin.

Patients currently on study who are not experiencing toxicity should continue on their current dose of carboplatin.

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- 9) Patients currently on study should continue to be monitored for the known adverse events associated with the administration of carboplatin as outlined in the package insert that can be found on the manufacturer's web site.
  
- 10) Dose modifications should occur as outlined in the protocol document. Each patient should be thoroughly evaluated, closely monitored and supported as clinically appropriate.
  
- 11) Adverse event reporting should continue as outlined in the protocol document.
  
- 12) Submit all amendments to the protocol and informed consent form to NCI/CTEP by 5:00 pm ET on November 12, 2010. The amendment cover letter must state "This amendment is in response to the memo from Dr. S. Percy Ivy, MD." Failure to comply within this timeframe may result in the temporary suspension of the principal investigator and enrollment to the study.

Please submit the amendment, the change memo, and the cover letter to the PIO at [PIO@CTEP.NCI.NIH.GOV](mailto:PIO@CTEP.NCI.NIH.GOV).

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**Specific Instructions on Amendment Preparation Based on Protocol Status:**

1. Trials with a current NCI/CTEP status of Active
  - Review and follow **ALL** the instructions outlined in this Action Letter.
  - You may include additional non-Action Letter related changes (any type) in your amendment response; however, this may delay amendment approval and thus, re-activation of your trial.
  - **If an amendment is required by a specific date and it is not submitted by the required submission date**, NCI/CTEP will suspend accrual to your trial and may suspend the principal investigator and/or close your trial permanently (i.e., administratively complete).
2. Trials with a current NCI/CTEP status of Closed to Accrual or Temporarily Closed to Accrual
  - Review and follow **ALL** the instructions outlined in this Action Letter.
  - You may include additional non-Action Letter related changes (any type) in your amendment response; however, this may delay amendment approval.
  - **If an amendment is required by a specific date and it is not submitted by the required submission date**, NCI/CTEP will suspend accrual to your trial and may suspend the principal investigator and/or close your trial permanently (i.e., administratively complete) unless you explicitly request and are granted a waiver to delay submission of the amendment (may be applicable for trials temporarily closed to accrual when other protocol changes are pending).
3. Trials with a current status of Approved or Temporarily Closed to Accrual and Treatment
  - The protocol must be revised as per the instructions outlined in the Action Letter in the next revised protocol draft submitted to NCI/CTEP. The protocol amendment must be submitted and approved by NCI/CTEP before the trial can be activated or re-opened.
  - You may include additional non-Action Letter related changes (any type) in your amendment response.

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4. Trials with a current NCI/CTEP status of **In Review**
  - The protocol must be revised as per the instructions outlined in the Action Letter. These changes must be included in the next revised protocol draft submitted to NCI/CTEP. The protocol will not be approved until these changes are made.
  - You may include additional non-Action Letter related changes (any type) in your revision response.
  
5. Trials with a current NCI/CTEP status of **Closed to Accrual and Treatment or Complete**
  - This information is being sent for informational purposes only. You may follow local IRB or Operations Office procedures and requirements.

## North Central Cancer Treatment Group

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

*For any communications regarding this protocol,  
please call the protocol resource person on the following page.*

Study Chair: Alex A. Adjei, M.D., Ph.D. (Research Base)\*  
Roswell Park Cancer Institute  
Elm & Carlton Streets  
Buffalo, NY 14263  
507/284- 9265  
507/284-5280 (FAX)  
[alex.adjei@roswellpark.org](mailto:alex.adjei@roswellpark.org)

Kendrith M. Rowland, Jr., M.D. (NCCTG)

Study Cochairs: Steven E. Schild, M.D. (Research Base)  
Jann N. Sarkaria, M.D. (Research Base)  
Larry Past, M.D. (Radiation Oncology)  
Marie-Christine Aubry, M.D (Pathology – Research Base) √  
Mitchel D. Bauman M.D. – (Pathology) √

Laboratory co-chair: Ricardo Lloyd, M.D., Ph.D.  
Mayo Clinic  
200 First Street, SW  
Rochester, MN 55905  
E-mail: [Lloyd.Ricardo@mayo.edu](mailto:Lloyd.Ricardo@mayo.edu)

Statistician: Nathan R. Foster, M.S. √

**DCTD Supplied Investigational Agents: PS-341 (NSC #681239)**

**\*Investigator having NCI responsibility for this protocol:**

√Study contributor not responsible for patient care.

<b>Document History</b>	<b>(Effective Date)</b>	<b>Document History</b>	<b>(Effective Date)</b>
Activation	September 17, 2004	Addendum 7	June 8, 2007
Addendum 1	February 11, 2005	Addendum 8	January 18, 2008
Update 1	February 11, 2005	Addendum 9	June 13, 2008
Addendum 2	July 29, 2005	Addendum 10	August 29, 2008
Addendum 3	March 17, 2006	Addendum 11	February 20, 2009
Addendum 4	August 18, 2006	Addendum 12	October 9, 2009
Addendum 5	February 2, 2007	Addendum 13	April 16, 2010
Addendum 6	June 8, 2007	Addendum 14	November 5, 2010

**Study Participants    Date Activated**

Entire NCCTG    September 17, 2004

NCI Version Date: October 28, 2010

Protocol Resources

	<b>Questions:</b>	<b>Contact Name:</b>
Add 1, 9, 12,13, 14	Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, forms completion	Lisa M. Finstuen NCCTG <i>Research Base</i> Quality Assurance Specialist Phone: 507/284-1328 Fax: 507/284-1902 E-mail: <a href="mailto:finstuen.lisa@mayo.edu">finstuen.lisa@mayo.edu</a>
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Add 1 10	Forms completion and submission	Christine E. Rogers, B.S. NCCTG Member Clinical Research Associate Phone: 217/383-3394
Add 1,2,8	Protocol document, consent form, Regulatory issues	Alicia L. Elsing NCCTG <i>Research Base</i> Research Protocol Specialist Phone: 507/538-3893 Fax: 507/284-5280 E-mail: <a href="mailto:elsing.alicia@mayo.edu">elsing.alicia@mayo.edu</a>
Add 3,5,8, 9,10	Paraffin-embedded Tissue Pathology	Jennifer S Mentlick NCCTG <i>Research Base</i> Pathology Coordinator Phone: 507/293-3928 Fax: 507/284-9628 E-mail: <a href="mailto:mentlick.jennifer@mayo.edu">mentlick.jennifer@mayo.edu</a>
Add 5,9,12	Non-paraffin Biospecimens	Roxann M. Neumann, RN, BSN, jCCRP NCCTG Biospecimen Resource Manager Phone: 507/538-0602 Fax: 507/266-0824 E-mail: <a href="mailto:neumann.roxann@mayo.edu">neumann.roxann@mayo.edu</a>
Add 3  Add 14	Adverse Events	Pat McNamara NCCTG <i>Research Base</i> AdEERS Coordinator Phone: 507/266-3028 Fax: 507/284-9628 E-mail: <a href="mailto:mcnamara.patricia@mayo.edu">mcnamara.patricia@mayo.edu</a>
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\* No waivers of eligibility per NCI

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7.4 Phase II Component - After the recommended maximum tolerated dose (MTD) has been determined, patients will continue to be enrolled from the whole NCCTG membership.

7.41 Pretreatment medication prior to Taxol

Add 1  
Update 1

Agent	Dose	Route	Day
DXM	10-20 mg	IV or PO	IF PO, begin within 12 hours prior to chemotherapy with route and dosing left to physician's discretion
BEN and RANIT or CIMET or FAMOT	25-50 mg	IV	30 minutes Pretaxol
	50 mg		
	300 mg		
	20 mg		
Bactrim	1 tablet BID twice a week	oral	Continuously during treatment

7.42 Treatment schedule - Use actual weight or estimated dry weight if fluid retention.

Add 1, 12

Add 1, 12  
Update 1

Agent <sup>1</sup>	Dose	Route	Day	Chemo ReRx	RT
PS-341	1.2 mg/m <sup>2</sup>	IV push into the side arm of a running IV of normal saline at 100 mL/hr	Days 1, 4, 8, 11	Q 3 weeks <sup>2</sup>	Total dose of 6,000 cGy given in 30 daily (except weekends) fractions of 200 cGy each, starting on Day 1 (total of 6 weeks or 2 cycles)
TAXOL	175 mg/m <sup>2</sup>	IV over 3 hours	Day 2		
CBDCA <sup>3</sup>	AUC=6	IV over 30 minutes after TAXOL			

Add 1

Update 1  
Add 14

1. Treatment should begin on a Monday or Tuesday.
2. For a maximum of 2 cycles.
3. Dosed using Calvert Formula with Cockcroft & Gault Equation Calvert Formula: CBDCA dose (mg) = target AUC x (GFR + 25). Note: The glomerular filtration rate (GFR) used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min. Therefore, for newly enrolled patients, the maximum carboplatin dose for this study is 900 mg. For the purposes of this protocol, the GFR is considered to be equivalent to the creatinine clearance (CrCl) and can be measured or calculated (Note: When concerned about patient safety in a given patient, measure GFR. The CrCl is calculated by the method of Cockcroft & Gault (CrCl[mL/min] = [140 – age) x actual body weight [kg] divided by plasma Cr [mg/dL x 72 x [0.85 if female or 1.0 if male]). Note: A correction factor is NOT to be used to calculate carboplatin doses based on the IDMS serum creatinine.

7.43 Treatment by a local medical doctor is not allowed.

Add 2

10.21 Phase 1 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days<sup>1</sup> of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 <sup>2</sup>
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unexpected and Expected
<b>Unrelated Unlikely</b>	Not Required	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	24-Hour; 3 Calendar Days
<b>Possible Probable Definite</b>	Not Required	7 Calendar Days	Not Required	24-Hour; 3 Calendar Days	24-Hour; 3 Calendar Days	7 Calendar Days	Not Required	24-Hour; 3 Calendar Days

<sup>1</sup> Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under an IND require reporting as follows:  
 AdEERS 24-hour notification followed by complete report within 3 calendar days for:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 4 unexpected events
- Grade 5 expected events and unexpected events

<sup>2</sup> Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see additional instructions and/or exceptions below under section entitled "Additional Instructions or Exceptions."  
 March 2005

**Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.**

- Expedited AE reporting timelines defined:
  - "24 hours; 3 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 3 calendar days of the initial 24-hour report.
  - "7 calendar days" - A complete AdEERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disability/incapacity, congenital anomaly, or birth defect must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- SECONDARY MALIGNANCIES (defined as "cancer caused by treatment for a previous malignancy," e.g., treatment with radiation or chemotherapy) are to be reported through AdEERS, as noted in Section 10.22. Secondary malignancies are not considered metastasis of the initial neoplasm. Secondary malignancy is unrelated to the first cancer that was treated, and may occur months or even years after initial treatment.

Add 14

Note: Second Primary malignancy (malignancy not due to prior treatment) should not be reported through AdEERS.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

**Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase I Trials Utilizing an Agent Under a CTEP IND:**

- In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497, or 301-897-7402 for CIP studies. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP website and will NO LONGER be accepted.
- Refer to Section 10.23 of this protocol for additional expedited reporting requirements.

10.22 Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days<sup>1</sup> of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 <sup>2</sup>	Grades 4 & 5 <sup>2</sup>
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unexpected	Expected
<b>Unrelated Unlikely</b>	Not Required	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days
<b>Possible Probable Definite</b>	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days	7 Calendar Days	Not Required	24-Hour; 3 Calendar Days	7 Calendar Days

<sup>1</sup> Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:  
 AdEERS 24-hour notification followed by complete report within 3 calendar days for:  
 • Grade 4 and Grade 5 unexpected events  
 AdEERS 7 calendar day report:  
 • Grade 3 unexpected events with hospitalization or prolongation of hospitalization  
 • Grade 5 expected events

<sup>2</sup> Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see additional instructions and/or exceptions below under section entitled "Additional Instructions or Exceptions."  
 March 2005

**Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.**

- Expedited AE reporting timelines defined:
  - "24 hours; 3 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 3 calendar days of the initial 24-hour report.
  - "7 calendar days" - A complete AdEERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disability/incapacity, congenital anomaly, or birth defect must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- SECONDARY MALIGNANCIES (defined as “cancer caused by treatment for a previous malignancy,” e.g., treatment with radiation or chemotherapy) are to be reported through AdEERS, as noted in Section 10.22. Secondary malignancies are not considered metastasis of the initial neoplasm. Secondary malignancy is unrelated to the first cancer that was treated, and may occur months or even years after initial treatment.

Add 14

Note: Second Primary malignancy (malignancy not due to prior treatment) should not be reported through AdEERS.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

**Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND:**

- In the rare event when Internet connectivity is disrupted, a report may be prepared using the Adverse Event Expedited Report – Single Agent or Multiple Agents paper template (available on the CTEP Home Page at <http://ctep.cancer.gov>). Refer to CTEP, NCI Guidelines: Adverse Event Reporting Requirements for back-up submission instructions. When internet connectivity is interrupted, a 24-hour notification is made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, an AE report submitted on a paper template or a 24-hour notification that is called in, must be entered into electronic AdEERS by the original submitter of the report at the site.
- Refer to Section 10.23 of this protocol for additional expedited reporting requirements.

Add 2

10.23 Other Required Expedited Reporting

Add 14

<u>EVENT TYPE</u>	<u>REPORTING PROCEDURE</u>
Secondary AML/MDS	<p>Reporting for this event required during and after completion of study treatment via AdEERS.</p> <p>Through December 31, 2010, continue using CTCAE v3.0: Report Myelodysplasia as “Blood/Bone Marrow – Other (Specify, _____).”</p> <p>Beginning January 1, 2011, AdEERS will only accept CTCAE v4.0 for this study. Report these events using “Neoplasms benign, malignant and unspecified (including cysts and polyps)” <i>and including the appropriate adverse event:</i></p> <ul style="list-style-type: none"> <li>- Leukemia secondary or oncology chemotherapy OR</li> <li>- Myelodysplastic syndrome OR</li> <li>- Treatment related secondary malignancy</li> </ul>
Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report	<p>If an AdEERS report has been submitted, this form does not need to be submitted.</p> <p>Enter into the remote data entry system within 5 working days of notification.</p>

Add 4

Add 3

**18.0 Records and Data Collection Procedures**

18.1 Submission Timetable

A  
d  
d  
3

A  
d  
d  
1  
3

A  
d  
d  
1  
4

A  
d  
d  
1  
3

Forms	Active-Monitoring Phase (Compliance with Test Schedule)					Event-Monitoring Phase <sup>2</sup> (Completion of Active-Monitoring Phase)				At Each Occurrence			
	Initial Material	Pathology Review	Follow-up material			q. 3 months until PD <sup>2</sup>	At PD <sup>2</sup>	After PD <sup>5</sup>	Death	ADR/AER	New Primary	Grade 4 or 5 Non-AER Reportable Events/Hospitalization	Late Adverse Event
	≤2 weeks after registration	≤30 days after registration	At cycle 1 Evaluation (Cycle 1 = first 3 weeks)	At cycle 2 evaluation (Cycle 2 = last 3 weeks of chemo-RT + 4-week post-RT eval)	Observation								
On-Study Form	X												
Baseline Adverse Events/Symptoms Form	X												
OP and Path Reports	X												
Measurement Form	X		X	X	X <sup>4</sup>								
Pathology Materials (See Section 17.0)		X											
Specimen Submission (See Section 14.0)		X											
RT Material <sup>1</sup>				X									
Event-Monitoring Form						X	X	X	X	X		X	
Evaluation/Treatment Form			X	X	X <sup>4</sup>								
Dose-Limiting Toxicity Reporting Form			X <sup>3</sup>	X <sup>3</sup>									
Nadir/Adverse Event Form			X	X	X <sup>4</sup>								
End of Active Treatment Form				X									
ADR/AER (See Section 10.0)									X				
Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form											X		
CTEP Report Variables Form	X												
<p>1. For patients who do not receive any scheduled radiation therapy, submit a radiation therapy reporting form with the reason radiation was not given. For patients who receive partial or complete radiation therapy, submit the following within two weeks after the last day of radiation:</p> <p>a. RT reporting form. b. Daily treatment records. c. Dosimetry calculations, monitor unit calculations, and isodose curves.</p> <p>d. Copies of representative simulation films of all treated fields. e. Copies of representative port films of all treated fields.</p> <p>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.</p> <p>2. If a patient is still alive after 5 years after registration, no further follow-up is required.</p>						<p>3. Required if ≥ grade 4 hematologic, ≥ grade 3 esophagitis, ≥ grade 3 pneumonitis, or ≥ grade 4 nonhematologic other than esophagitis, pneumonitis, dyspnea, or radiation dermatitis.</p> <p>4. During observation, patients will be followed at 3 months post-RT, q 3 months for 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.</p> <p>5. After PD, q3 months for 1 year post-registration and then q6 months for a maximum of 5 years post-registration.</p>							