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 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)**. 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**

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 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.

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.

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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.

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.