

North Central Cancer Treatment Group

N0775: A Randomized Phase II Trial of Temozolomide (TMZ) and Avastin® or ABI-007/Carboplatin (CBDCA) and Avastin® in Patients with Unresectable Stage IV Malignant Melanoma

Addendum 12 – November 26, 2010

Summary

- Due to the optional tissue request the following sections have been revised: Sections 1.0, 17.0, 18.0, 20.0 and the consent form
- Contact information for Research Base Pathology Coordinator has been added for questions regarding “Paraffin-embedded tissue”.
- Contact information for Research Base Data Management Specialist has been removed
- 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 10.0 and 18.0 have been revised accordingly.

Patients currently 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 assure that measures be implemented immediately while local IRB approval is being obtained.

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

Replacement protocol is included. Please replace the current copy with the one attached. Please keep this addendum with your protocol.

Title Page Reflects the addition of Addendum 12 and revised NCI version date.

Protocol Resources

Page 2: The Research Base Data Management Specialist contact has been removed (Kathleen Welch). Please contact the NCCTG Research Base Quality Assurance Specialist (QAS) for technical questions regarding electronic form entry.

Contact information has been added for the Research Base Pathology Coordinator, as follows:

Paraffin-embedded tissue pathology	Christine R Maszk NCCTG Research Base Pathology Coordinator Phone : (507) 266-8919 Fax : (507) 284-9628 E-mail : maszk.christine@mayo.edu
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Section 1.0 Background

Page 10: Due to the optional tissue being requested the following paragraph has been added to Section 1.9d (references also added to Section 20.0):

Specific genetic mutations are becoming more of a mainstage as potential targets in the treatment of cancer, including malignant melanoma. Recent evidence suggests that approximately 40-60% of all melanomas have a mutation in the BRAF as part of the mitogen-activated protein (MAP) kinase pathway [44,45]. Approximately 90% of these BRAF mutations are reported to occur as a substitution of glutamic acid for valine at amino acid 600 (V600E). It is unknown whether carrying this particular mutation has any prognostic significance. However a recent report from Dummer et al, looked at patients who were either BRAF wild type or BRAF mutated and were treated with a combination of temozolomide and bevacizumab and their outcomes [46]. While this was a small study, the patients who were BRAF wild type had a statistically significant better overall survival (14.8 vs 9.2 months, ; p=0.02) ³. Based on this preliminary evidence we would propose testing tumor tissue from patients enrolled on this particular study for BRAF mutations and compare their outcomes to those who are BRAF wild type.

Because of large amount of text, repagination from this point forward has occurred.

Section 4.0 Test Schedule

Pages 15-16: The “**Optional Research tissue sample^R**” has been added as the 11th row due to the added pathology. An X has been placed in the “≤ 14 days prior to registration” column with an annotation to the new Footnote 13. The corresponding footnote is as follows:

13. Submit ≤30 days after re-consent.

Section 7.0 Protocol Treatment

Page 20: Section 7.26 has been revised due to the Action Letter dated October 1, 2010 from Percy Ivy regarding changes to the Calvert formula calculation. The following revisions have occurred:

The dose of CBDCA will be calculated by the formula of Calvert, et al. (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. As of October 1, 2010, the maximum carboplatin dose for patients is 750 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

creatinine clearance is calculated by the method of Cockcroft and Gault (CrCl [mL/min] = (140 - age) x actual body weight [Kg]/ plasma Cr [mg/dL] x 72 x [0.85 if female]).

Note: A correction factor is NOT to be used to calculate carboplatin doses based on the IDMS serum creatinine. ~~1. GFR = Glomerular filtration rate~~

Section 10.0

Pages 31-32

Adverse Event (AE) Reporting and Monitoring

: With the removal of the Secondary AML/MDS Report Form, a new third bullet beneath the table has been added for clarification in Section 10.21 as follows:

- **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.**

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

Page 32:

The final bullet point in Section 10.21 has been revised with current information regarding the AdEERS forms and contact information. Changes are as follows:

- **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. 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. ~~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>) and faxed to the NCCTG Operations Office at 507-284-9628. Once Internet connectivity is restored, an AE report submitted on a paper template or a 24-hour notification phoned in must be entered electronically into AdEERS by the original submitter at the site. Contact the NCCTG SAE Coordinator (as identified on the NCCTG Protocol Resources page) for additional back-up submission instructions.~~**

Revisions have occurred in Section 10.22 due to the removal of the AML/MDS Report Form in the “Secondary AML/MDS” row for clarification, as follows:

EVENT TYPE	REPORTING PROCEDURE
Secondary AML/MDS	<p>Reporting for this event required during and after completion of study treatment, via AdEERS using CTCAE v3.0: Report Myelodysplasia as “Blood/Bone Marrow - Myelodysplasia” and Leukemias as “Blood/Bone Marrow - Other (Specify, __)”.</p> <p>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.</p>

Section 17.0 Pathology Considerations/Tissue Biospecimens

Pages 63-65: Due to the optional tissue request the following information has been added in this section:

17.0 Pathology Considerations/Tissue Biospecimens: ~~None~~

17.1 Tissue Biospecimen Submission NOTE: Patients must have consented to submission of the optional tissue(s) listed in the following table.

17.11 Summary Table of Tissue Biospecimens for This Protocol

Type of tissue biospecimen to submit	Mandatory or optional	When to submit	Reason for submission (background/methodology section)	Where to find specific details for biospecimen submission
Formalin-fixed paraffin-embedded (FFPE) tissue blocks (OR unstained slides with corresponding H&E)	Optional*	≤30 days after reconsent	Correlative studies (Section 17.51)	Section 17.2

*Samples are optional but are strongly recommended

17.2 Paraffin Embedded Tissue Blocks/Slides

17.21 Submit one formalin fixed paraffin-embedded (FFPE) tumor tissue block with largest amount of invasive tumor (at least 1 cm of tumor for cases of surgical resection) from original surgery. A corresponding H&E slide for each submitted block must be provided to permit quality assessment of each tissue block.

17.22 The FFPE tissue block is preferred; however, if an institution is unable to provide a tissue block, cut (10) ten micron sections and mount on charged glass slides. Label the slides with NCCTG patient ID number, accession number, and order of sections. H&E stain every eighth slide (i.e., slides labeled 1, 10 etc.). These H&E slides will be reviewed centrally under the research base’s protocol for assessing tissue quality. The remaining unstained slides will be processed as described in 17.54. For samples containing less than 0.5 square millimeters of tumor tissue, multiple sections should be mounted onto each slide to ensure that the appropriate amount of tumor tissue is available. Ideally, each slide must have a minimum of 75% tumor tissue on the slide to be deemed adequate for study. Do not bake or place covers slips on the slides.

17.23 The following materials below are mandatory (unless indicated otherwise) and required for shipment:

- Paraffin embedded tissue blocks with corresponding H&E slide (OR 10 unstained slides with corresponding H&E(s)).
- NCCTG Research Tissue Submission Form
- Surgical Pathology Report
- Operative Report (*optional*)

Note: Please include the NCCTG patient ID number on all materials listed above.

- 17.24** The block/slides must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, NCCTG patient ID number, and patient initials.
- 17.25** N0775 Tissue specimens must be shipped ≤ 30 days after consent.
- 17.26** Verify that the appropriate sections of the Research Tissue Submission Form are completed and filled in correctly. Enter information from the Research Tissue Submission Form into the remote data entry system on the same day the specimen is submitted (see Forms Packet).
- 17.27** Ship all block/slide tissue specimens and accompanying materials to the NCCTG Research Base:
- NCCTG Operations Office**
Attn: PC Office (Study N0775)
RO_FF_03_24-CC/NW Clinic
200 First Street SW
Rochester, MN 55905
- 17.28** If a corresponding H&E wasn't submitted with the block/slides, the NCCTG Operations Office will request a slide to be processed (i.e., cut and H&E stained) from the tumor tissue block and forwarded to Dr. Lori Erickson, Mayo Clinic Rochester, to be reviewed under the research base's protocol for assessing tissue quality for the proposed correlative studies, unless the tumor size is too small. If the tumor tissue is too small, assessment of tissue quality will occur at the time the translational studies are performed.
- 17.3** Frozen Tumor Tissue None
- 17.4** Study Methodology and Storage Information
- 17.51** Submitted FFPE tumor tissue blocks/slides will be collected in order to assess correlation of responses of PCR done using the following primers and probe: B-RAF, 5'-CCTCACAGTAAAAATAGGTG-3' (forward), 5'-ATAGCCTCAATTCTTACCA-3' (reverse), 5'-CTACAGAGAAATCTCGAT-BHQ-1-3' (LNA), CTACAGTGAAATCTCG (PNA). The PCR assay will be done with an ABI 7900 real-time PCR Detection System (Applied Biosystems). Genomic DNA (20 ng) from serum is amplified using real-time PCR (ABI, 7900) in a 20- μ L reaction containing each PCR primer, LNA, PNA, deoxynucleotide triphosphate, MgCl₂, PCR buffer, and AmpliTaq Gold Polymerase (Applied Biosystems, Branchburg, NJ). Each PCR reaction is subjected to 55 cycles at 94°C for 60 s, 72°C for 50 s, 53°C for 50 s, and 72°C for 60 s. Each sample will be assayed in triplicate with appropriate positive and negative cell line and reagent controls.

- 17.52** The institutional pathologist will be notified by the NCCTG Operations Office (Pathology Coordinator) if the block may be depleted.
- 17.53** Blocks requested to accommodate individual patient management will be returned promptly upon request.
- 17.54** DNA will be extracted from FFPE tissue using Qiagen FFPE Tissue following manufacturer's instructions. This one step procedure renders PCR ready DNA.

Briefly, primers are designed to amplify exon 15 of the B-RAF gene, including the mutation hotspot (V600E). PNA (Biosynthesis, Inc.) is designed to clamp the hotspot on the wild-type (wt) template and block the wt template from being amplified by PCR. A fluorescence resonance energy transfer (FRET) dual-labeled LNA probe was designed and synthesized (Integrated DNA Technologies) to recognize and hybridize at V600E, specifically the T-to-A mutation, as this mutation is the most frequently seen mutation for B-RAF at this hotspot. A second FRET DNA probe is purchased from IDT (Integrated DNA Technologies) and synthesized using the adjacent sequences to the LNA probe, avoiding the hotspot, to amplify and estimate the total number of DNA templates, both wild type (V600E) and mutant (V600E), in the PCR reaction. Real-time quantitative PCR for mutation using both the PNA clamp and FRET LNA probe will be done in a separate reaction from the quantitative PCR for total number of templates using the FRET DNA probe. The same method used to identify B-RAF mutations will be applied to the SPARC UTR analysis. Evidence suggests that there may be differences in clinical outcomes in patients expressing some of these biomarkers. Outcomes of this analysis will be used to see if such biomarkers influence outcomes in patients treated while on this study.

B-RAF and SPARC UTR analysis will be completed by Dr. Daniel J. Knauer, Manager Biomarker Discovery, 1588 South Coast Drive, Costa Mesa, CA 92626; Telephone (657) 859-2108.

Section 18.0 Records and Data Collection Procedures

Page 66:

Due to the optional tissue being requested, "NCCTG Research Tissue Submission Form (See Section 17.0), all patients" has been added as a new form as the third row of the table, with an X in the first column (≤ 2 weeks after registration), with an annotation to the new Footnote 6. The corresponding footnote is as follows:

6. Submit ≤ 30 days after re-consent.

With the elimination of the Secondary AML/MDS Report form, the row "NCI/CTEP Secondary AML/MDS Report Form" has been removed from the table.

Section 20.0 References

Page 70:

References 44 – 46 have been newly added and are located in the text that was added in Section 1.9d.

Appendix I
Pages 13-15:**Consent Form**

Due to the optional tissue request the following revisions have occurred:

About Using Biological Samples for Research

This study also has laboratory tests that will be performed to study small samples of blood. A blood sample will be done by drawing some blood from a vein. The blood will be taken just before treatment starts, prior to each cycle during treatment and at the end of active treatment.

~~The blood will be sent to laboratories associated with NCCTG, where the tests will be done. These tests will be done in order to understand how your cancer responds to treatment. It is hoped that this will help investigators better understand your type of cancer. The results of these tests will not be sent to you or your study doctor and will not be used in planning your care. (moved below and reworded to include tissue)~~

These **blood** tests are for research purposes only and you will not have to pay for them. These research tests are mandatory. If you do not agree to having your blood drawn for research purpose, you will not be able to participate in the study.

We would also like to request some tumor tissue from your original surgery or biopsy. You will not have to have an additional surgery/biopsy for this “optional” request. If you do not agree to provide your tissue for research purposes, you are still able to participate in the study. Please read the information sheet provided to you called "How is Tissue Used for Research" to learn more about tissue research.

(Site instructions – The above referenced information sheet can be found on the NCCTG website <https://ncctg.mayo.edu/ncctg/forms/NonProtocolSpecificForms/>)

Please read the following statements and mark your choice:

I agree to provide a tissue sample(s) to: _____ laboratories associated with NCCTG, for research testing planned as part of this study.

Yes **No** Please initial here: _____ Date: _____

Your research blood and tissue will be sent to laboratories associated with NCCTG, where the tests will be done. These tests will be done in order to understand how your cancer responds to treatment. It is hoped that this will help investigators better understand your type of cancer.

If there is left over ~~sample~~ **blood and/or tissue**, we would like to keep those samples for future research. If you agree, the samples will be kept and may be used in research to learn more about cancer and other diseases. Your ~~blood~~ samples may be helpful for research testing. The research that may be done with your ~~blood~~ samples may not help you but might help other people who have cancer and other diseases in the future.

Reports about research done with your ~~blood~~ samples will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over blood **or tissue** samples for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your ~~blood~~ samples can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your **blood or tissue**. Then any ~~blood~~ samples that remain will no longer be used for research.

In the future, people who do research may need to know more about your health. While NCCTG may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes ~~blood~~ samples are used for genetic research (about diseases that are passed on in families). Even if your ~~blood~~ samples ~~is-are~~ used for this kind of research, the results will not be put in your health records.

Your ~~blood~~ samples will be used only for research and will not be sold. The research done with your ~~blood~~ samples may help to develop new products in the future.

Benefits

The benefits of research using blood **or tissue samples** include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number. No matter what you decide to do, it will not affect your care.

1. My blood sample(s) may be kept for use in research to learn about, prevent, or treat cancer.

Yes No Please initial here: _____ Date: _____

2. My blood sample(s) may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No Please initial here: _____ Date: _____

3. My tissue sample(s) may be kept for use in research to learn about, prevent, or treat cancer.

Yes No Please initial here: _____ Date: _____

4. My tissue sample(s) may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No Please initial here: _____ Date: _____

If you want your sample(s) destroyed at any time, write to the Secretary of the _____ Institutional Review Board _____.
 NCCTG has the right to end storage of the sample(s) without telling you.

The sample(s) will be the property of NCCTG. Outside researchers may one day ask for a part of your sample(s) for studies now or future studies.

How do outside researchers get the sample?

Researchers from universities, hospitals, and other health organizations do....

Please read the following statements and mark your choice:

1. I permit NCCTG to give my blood sample(s) to outside researchers:

Yes No Please initial here: _____ Date: _____

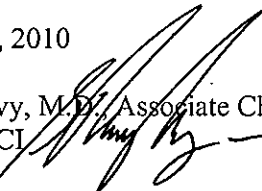
2. I permit NCCTG to give my tissue sample(s) to outside researchers:

Yes No Please initial here: _____ Date: _____



**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**

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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 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.

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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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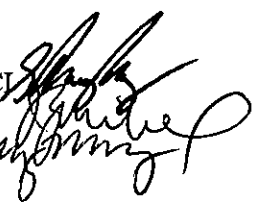
4. Trials with a current NCI/CTEP status of In Review
 - The protocol must be revised as per the instructions outlined in the Action Letter. These changes must be included in the next revised protocol draft submitted to NCI/CTEP. The protocol will not be approved until these changes are made.
 - You 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 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.

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 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.

Maximum AUC-based Carboplatin Dose	
AUC	Maximum Carboplatin Dose
6	900 mg
5	750 mg
4	600 mg

- 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.

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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.