

North Central Cancer Treatment Group

N0626: Phase II Randomized Study Pemetrexed With Sorafenib versus Pemetrexed Alone as Second-line Therapy in Patients With Advanced Non-Small Cell Lung Cancer

Addendum 6 – March 13, 2009

**Summary**

- Administrative/editorial changes.

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

**Title page** Updated to reflect Addendum 6 and revised NCI version date.

**Protocol Resources**

Page 2: The title for Sarah Hanson has been revised as follows:  
NCCTG Research Base Quality Control Assurance Specialist

The title for Alicia Elsing has been revised as follows:  
NCCTG *Research Base* **Research Protocol Specialist** Development Coordinator

**Section 8.0** **Dosage Modification Based on Adverse Events**

Pages 28-29: Dose re-escalation is not allowed in this study; therefore, footnote #1 has been deleted in Section 8.3 and remaining footnotes renumbered. As a result of the deletion of footnote #1, all references to the footnotes in the tables have been renumbered.

**Section 14.0** **Body Fluid Biospecimens**

Page 40: The first sentence in Section 14.251 has been updated as follows:  
Verify ALL sections of the Blood Specimen Submission Form, ~~MCLCT MML~~ Requisition Form, and specimen collection labels are completed and filled in correctly.

Page 41: Sections 14.254, 14.255, and 14.256 have been updated as follows:  
14.254 Ship specimens via Priority Overnight service, **Monday-Friday ONLY**, to Mayo ~~Central Laboratory for Clinical Trials~~ **Medical Laboratories (MCLCT MML)**. **Do not send samples on weekends or holidays.**

14.255 Use kit mailing labels for shipment to ~~MCLCT MML~~.

14.256 ~~MCLCT MML~~ will receive the samples and forward specimens ~~within two hours of accessioning~~ **immediately** to the NCCTG Research Base Biospecimen Accessioning and Processing (BAP) laboratory, Stabile 13-10A, Attention: BAP Supervisor.

**Section 16.0**

Pages 61-

**Statistical Considerations and Methodology**

The first paragraph for “Study Overview” in Section 16.1 has been revised for clarification as follows:

Study Overview: This randomized phase II study is designed to compare the progression-free survival (PFS) of pemetrexed and sorafenib (experimental arm) versus pemetrexed alone (standard treatment arm) as second line treatment among patients with advanced NSCLC (Stage IIIB with pleural effusions or IV) using a one-stage design **with a stopping rule for futility**. ~~The reason there will not be a formal interim or stage 1 analysis is because pemetrexed alone is considered the standard of care and we do not believe the addition of sorafenib will adversely affect the efficacy.~~ Patients will be randomized between pemetrexed alone and the combination of pemetrexed with sorafenib in a 1:1 fashion. The first 6 patients enrolled on Arm A (pemetrexed + sorafenib) that will be assessed for tolerability of this regimen, will be included in all efficacy analyses, if there is no need to reduce the dose of sorafenib. If, however, the sorafenib dose does need to be reduced based on the evaluation of the first 6 patients on Arm A, these first 6 patients will not be included in the efficacy analyses. See Section 7.22 for the details of this tolerability assessment.

The first paragraph for “Sample Size” in Section 16.1 has been revised for clarification as follows:

Sample Size: ~~Forty seven evaluable patients will be accrued to each arm of this study. A total of 94 patients (47 on each arm) will provide 82% power to compare the overall PFS for Arm A versus Arm B using a one sided log rank test with  $\alpha=.05$  with uniform enrollment for 15 months and a 3 month follow up period. This sample size calculation assumes the 6 month PFS for Arm A is 20% and the 6 month PFS for Arm B is 42%. The assumption of 42% PFS at 6 months is derived from the recently conducted phase III trial (38) where the median PFS for second line treatment for advanced NSCLC using pemetrexed alone was approximately 3 months which provides a 3 month PFS estimate of approximately 50% at 3 months. We assume that we will not have significant loss to follow up as historically NCCTG trials lost to follow up rates have been <1%.~~

**The primary goal of this trial is to compare the experimental arm (Arm B) to the standard arm (Arm A), where the alternative hypothesis is that the experimental arm has improved PFS compared to the standard arm. We will enter 47 evaluable patients to each arm of the study using a 1:1 randomization scheme. The primary analysis will be a comparison of Arm A to Arm B using a one-sided log-rank test between the 2 Kaplan-Meier curves. This analysis will take place after an approximate 15-month accrual period and after 73 total deaths and/or progressions have occurred (which should happen after around 3 months of follow-up in all evaluable patients). Additionally, we assume a constant accrual rate over the course of the study and that we will not have a significant lost to follow-up issue, as historically NCCTG trials lost to follow-up rates have been <1%. A sample size of 47 patients per arm (94 total) provides 82% power to detect an improvement in**

**median progression-free survival from 3.0 to 5.5 months (a hazard ratio of 1.82) using a 1-sided log-rank test at a significance level of 0.05. All patients meeting the eligibility criteria, who started treatment will be considered evaluable for the primary endpoint. If a patient is still alive 5 years after registration, no further follow-up is required.**

Page 62:

A new paragraph “Stopping Rule for Futility” has been added in Section 16.1 for clarification as follows:

**Stopping Rule for Futility: At the time that half of the expected number of deaths and/or progressions have occurred across both arms combined (i.e., around 37 deaths and/or progressions), we will compare the PFS between the 2 treatment arms. If the 1-sided Log-Rank test p-value is > 0.50 for the comparison of Arm A to Arm B, where the alternative hypothesis is that the experimental arm has improved PFS compared to the standard arm, we will stop the trial early and conclude that the experimental arm does not have improved PFS (49)..**

The “Over Accrual” paragraph in Section 16.1 has been revised as follows:

**Over Accrual: If more than the target number of patients is accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making; however, they will be included in the final analyses, described below. If more than the target number of patients are accrued, the additional patients will be used to evaluate the primary endpoint and will be included in final point estimates and confidence intervals, but will not be used for the adverse event stopping rule in the first 20 patients.**

Page 63:

Section 16.21 has been revised for clarification as follows:

The primary goal of this trial is to compare the PFS of the experimental arm (Arm A) to the control arm (Arm B). We will enter 47 evaluable patients to each arm for the study using a 1:1 randomization scheme. The primary analysis will be a comparison of Arm A to Arm B using a one-sided log-rank test. ~~The analysis will take place after a minimum of 3 months of follow up (for the last patient enrolled).~~ **This final analysis will take place after an approximate 15-month accrual period and after 73 total deaths and/or progressions have occurred (which should happen after around 3 months of follow-up in all evaluable patients).** All patients meeting the eligibility criteria, who started treatment, will be considered evaluable for this endpoint.

### **Section 17.0**

Page 66-68:

#### **Pathology Considerations/Tissue Biospecimens**

Section 17.21 has been revised for clarification purposes and to make this requirement consistent with standard of care as follows:

ALL original diagnostic slides used to make the diagnosis of Stage IV or Stage IIIB non-squamous cell histologic type of NSCLC should be clearly labeled and forwarded ≤30 days after registration for central review. ~~If the original slides cannot be released, slides from the same tumor block used to make the diagnosis are acceptable. If the slides from the metastatic diagnosis are not available, slides from the original Stage IV or Stage IIIB non-squamous cell histologic type of NSCLC diagnosis will be accepted.~~ **If the slides from the metastatic diagnosis are not available, slides from the original primary tumor will be accepted.**

The following text has been added for clarification to the address in Sections 17.252, 17.26, and 17.37:

NCCTG Operations Office  
Attn: PC Office (**Study N0626**)  
RO\_FF\_03\_24-CC/NW Clinic  
200 First Street SW  
Rochester, MN 55905

**Section 18.0**

Page 70:

**Records and Data Collection Procedures**

Reference to Section 17.35 has been corrected to read Section 17.33 for “Tissue Specimen Submission Form.”

Due to the title update for the Quality Assurance Specialist, reference to the QCS in footnote #2 has been revised to reflect QAS.

**Section 20.0**

Page 75:

**References**

Due to the revisions in Section 16.0, reference #49 is newly added as follows:

**Wieand S, Schroeder G, O’Fallon JR: Stopping when the experimental regimen does not appear to help. Statistics in Medicine 13: 1453-1458, 1994.**

**Appendix V**

Page 2:

**Research Base Instructions for (BAP) Shared Resource**

The first sentence under footnote #3 has been updated as follows:

For “Before tx, cycle 1, day 1” samples, plasma and DNA will be isolated from one EDTA tube using the protocols entitled “Plasma collection from whole blood samples” and “Extracting Samples on the AutoPure-LSGen”, respectively.