

North Central Cancer Treatment Group

N0821: A Phase II First-Line Study of a Combination of Pemetrexed, Carboplatin and Bevacizumab in Advanced Nonsquamous NSCLC Evaluating Efficacy and Tolerability in Elderly Patients (Age \geq 70 yrs) with Good Performance Status (PS $<$ 2)

Addendum 1 – May 1, 2009

Summary

- Revisions were made to Sections 1.0, 4.0, 8.0, 10.0, 9.0, 11.0, 12.0, and 16.0 at the request of Eli Lilly.
- The consent form has been revised for clarification purposes.
- Administrative/editorial.

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

Title page Has been updated to reflect Addendum 1 and current NCI version date.

Protocol Resource Page

Page 2: The title for Sarah L. Hanson has been updated to read “NCCTG *Research Base* Quality Control Assurance Specialist.”

Roxann M. Neumann, RN, BSN, CCRP replaces ~~Jaqueline M. Lafky~~ as the NCCTG *Research Base* Biospecimen Resource Manager.

Index

Page 3: The title for Section 11.0 has been updated to read “Treatment Evaluation **using RECIST Criteria.**”

Section 1.0 **Background**

Page 7: At the request of Eli Lilly, a new sentence has been added to the last paragraph of Section 1.22 as follows:

This result provided support to revise approval labeling of pemetrexed to current recommended used in nonsquamous NSCLC.

Section 3.0 **Patient Eligibility**

Page 12: Section 3.12 has been revised for clarification as follows:

Histologic or cytologic confirmation of ~~Stage IV~~ nonsquamous NSCLC. **Patient should have stage IV or stage IIIB disease or ~~Stage IIIB~~ nonsquamous NSCLC (AJCC TNM sixth edition [69]; symptomatic pleural effusions should be drained prior to registration).**

Page 13: In order to be consistent with the registration procedures, the following criteria has been added 3.19g as follows:

Willingness to enroll in N0392. Note: Participation in N0392 is mandatory for this study.

Section 4.0 **Test Schedule**

Pages 16-17:

For clarification purposes, footnote #9 has been revised as follows:

Use Cockcroft-Gault formula as indicated in section 3.16. For determining carboplatin dose: - use actual body weight if it is less than the ideal body weight in the Cockcroft-Gault formula to derive calculated creatinine clearance. **Use adjusted body weight (See Section 3.16) if actual body weight exceeds ideal body weight.**

At the request of Eli Lilly footnote #13 is newly added as follows:

Patients who discontinue treatment for reasons other than disease progression should continue to undergo routine tumor assessments every 6 weeks (± 7 days) until disease progression unless patient is removed from study (patient refusal to be monitored per protocol, alternate therapies, etc.).

Reference to footnote #13 has been placed in the “Upon treatment discontinuation” column for “Tumor assessment.”

Section 7.0 **Protocol Treatment**

Page 19:

For clarification purposes, the last sentence in Section 7.1 has been revised as follows:

For carboplatin dose using calvert equation, use ~~ideal~~ **adjusted** body weight (**See explanation in Section 7.12**).

Page 21:

For clarification purposes, the last statement in the third paragraph of Section 7.12 has been revised as follows

(See ~~S~~**section 3.16 and footnote 9 of the table in Section 4.0 in table 4**)

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

Page 22:

Under the “Based on Interval Adverse Events or At Time of Retreatment” section for “Blood/Bone Marrow.” The fourth row of the last column has been revised at the request of Eli Lilly as follows:

Hold until ANC ≥ 1500 and PLTS $\geq 100,000$, then \downarrow by **54%**.

Section 9.0 **Ancillary Treatment/Supportive Care**

Page 24:

At the request of Eli Lilly, Section 9.2 has been revised as follows:

Growth Factors: Colony-stimulating factors should not be used prophylactically to prevent granulocytopenia. The American Society of Clinical Oncology (ASCO) guidelines should be followed. Dose reductions are required for hematologic toxicity; patients should not receive prophylactic granulocyte colony-stimulating factor (G-CSF) in any cycle. Physicians may use G-CSF only for patients who have ANC $< 0.5 \times 10^9/L$, ongoing or history of neutropenic fever and documented infections while neutropenic. The duration of uncomplicated neutropenia before initiation of G-CSF treatment should be ≥ 3 days. The physician must discontinue G-CSF before the start of the next cycle of

chemotherapy. The protocol allows for the use of erythropoietin ~~erythropoiesis-stimulating agents (ESAs)~~ but not the use of products that stimulate thrombopoiesis. **ESAs are not indicated for treatment of cancer-related anemia in patients with solid tumors. Erythropoietic therapy may be considered for treatment of chemotherapy induced anemia for a hemoglobin <10 g/dL after the patient has been counseled about the risks and benefits of ESA use. Because recommendations on the use of ESAs are rapidly evolving, investigators should frequently refer to the NCCN, ASCO, and/or Centers for Medicare and Medicaid Services web sites for the latest guidelines.**

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

Page 27:

At the request of Eli Lilly, the following has been added to Section 10.21:

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements

- **The NCCTG SAE Coordinator will forward a copy of all AdEERS reports to:**
- **Eli Lilly: SAE reporting fax number (866-644-1697).**

Section 11.0 **Treatment Evaluation**

Page 30:

The title for Section 11.0 has been updated as follows:

Treatment Evaluation **using RECIST Criteria (35)**

Page 32:

The title for Section 11.4 has been updated as follows:

Measurement of Effect **(RECIST)³⁵**

Section 12.0 **Descriptive Factors**

Page 34:

For clarification purposes, Section 12.1 has been revised at the request of Eli Lilly as follows:

NSCLC Stage **(AJCC sixth edition, 2002)**: IIIB with pleural or pericardial effusion vs. IV.

Section 14.0 **Body Fluid Biospecimens**

Page 36:

The first sentence of Section 14.251 has been updated as follows:

Verify ALL sections of the Blood Specimen Submission Form (Forms Packet), ~~Blood Specimen~~ **MML** Requisition Form (provided in kit), and ~~the specimen collection labels are~~ **is** completed and filled in correctly.

Section 14.252 has been updated as follows:

~~The S~~specimens must be shipped the same day ~~they are~~ **it is** drawn.

Section 14.254 has been updated as follows:

Ship specimens via Priority Overnight service, Monday – Friday ONLY, to ~~the Biospecimen Accessioning and Processing (BAP) Shared Resource~~ **Mayo Medical Laboratories (MML)**. Do not send samples on weekends or holidays.

Section 14.255 has been updated as follows:

~~Use kit mailing labels provided in the kit for shipment to the BAP Shared Resource~~ **The MML kits will contain a smart shipper label affixed to the**

berry colored shipping boxes or a pre-filled airbill will be provided. Shipping costs will be covered by NCCTG if these kits are used for shipping specimens to MML.

Page 37: Section 14.256 is newly added as follows:

MML will receive the samples and immediately forward specimens to the NCCTG Research Base Biospecimens Accessioning and Processing (BAP) Shared Resource, Stable 13-10A, Attention: BAP Supervisor.

As a result of Section 14.256 being newly added, previous Section 14.256 now becomes 14.257 and has been updated as follows:

BAP will process **the** specimens according to Appendix VII instructions.

Section 16.0 Statistical Considerations and Methodology

Page 59: At the request of Eli Lilly, the following text has been added to Section 16.82:

The following secondary analyses will be performed overall, and if possible, separately for patients 70-74 years old versus those ≥75 years old to further explore the age differences in these endpoints.

Section 17.0 Pathology Considerations/Tissue Biospecimens

Pages 64-65: The addresses in Sections 17.252, 17.26, and 17.37 have been updated as follows:

NCCTG Operations Office
 Attn: PC Office (**Study N0821**)
 RO_FF_03_24-CC/NW Clinic
 200 First Street SW
 Rochester, MN 55905

The first bullet in Section 17.33 has been revised for clarification as follows:

Paraffin Embedded Tissue Blocks with Corresponding H&E Slide (~~or~~ **OR 6** Unstained, Uncharged Slides with Corresponding H&E Slide)

Section 20.0 References

Page 73: Due to the clarification made in Section 3.12, reference #69 is newly added as follows:

Greene FL, Page DL, eds. AJCC cancer staging manual (6th edition). Philadelphia, PA 2002; 168-170.

Appendix I Consent Form

Page 4: The following row has been added to both of the Cycle 1 and Future Cycles tables as this information was inadvertently omitted:

2	• Dexamethasone by mouth twice a day.
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Page 9: This study involves elderly patients only. Therefore, the Reproductive Risks section has been revised as follows:

You should not ~~become pregnant or~~ father a baby while on this study because the drugs in this study can affect an unborn baby. To take part in this study, women must be surgically sterile **or** postmenopausal, ~~or use a medically approved contraceptive regimen during and for 3 months after treatment.~~ Men must be

surgically sterile or use a medically approved contraceptive regimen during and for 3 months after treatment. Check with your health care provider about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

If ~~you or~~ your partners plan to become pregnant, becomes pregnant, misses a period, or thinks ~~you (or she) she~~ might be pregnant, you must tell the study doctor right away. All reports of pregnancy must be followed to get information about the pregnancy and delivery and the health of the infant. We will talk to you about ways for managing the pregnancy.

Page 8: The heading for the “Less Likely” risks for carboplatin has been corrected as follows:
Less likely (events that occur less than or equal to 20% of time) ~~Rare but serious side effects~~

Appendix VII Research Base Instructions for Biospecimen Processing in BAP Shared Resource

Page 1: The first sentence of item #2 has been updated as follows:
DNA will be isolated from **one** EDTA tube using the protocol entitled “Extracting Samples on the AutoPure LSGen”.