

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 3 – June 27, 2008

Summary

- As a result of the safety analysis, information has been added to Section 1.0 and Section 3.0 has been modified to exclude patients with squamous cell carcinoma. Section 3.0 has also been modified to exclude prior exposure to other VEGF inhibitors (except bevacizumab) because of potential shared mechanism of action/resistance with sorafenib.
- Section 7.0 has been updated with dosage clarifications.
- Section 8.0 has been modified to clarify dose modifications.
- Section 12.0 has been modified to capture prior bevacizumab therapy.
- The stopping rule for Section 16.0 has been revised to include Arm B at the request of the Data Safety Monitoring Board (DSMB).
- Sections 1.0, 2.0, and 14.0 have been modified to remove pharmacokinetic analyses as the intracellular polyglutamate assay has not been developed.
- 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 3 and revised NCI version date.

Dr. Adjei's phone number has been updated.

Protocol Resource Page

Page 2: **Sarah Hanson** replaces ~~Rachael Meyers~~ as NCCTG Research Base Quality Control Specialist.

Helen Tollefson has been removed as NCCTG Research Base Pathology Coordinator.

The fax number for Jacqueline Lafky has been updated as follows:
(507) ~~284-8105~~ **266-0824**

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Page 3: The title for Appendix V has been revised as follows:
Research Base Instructions for Biospecimen Processing in the Biospecimens Accessioning and Processing (BAP) ~~Laboratory~~ **Shared Resource**

Section 1.0**Background**

Page 11:

A typographical error has been corrected in the second sentence of Section 1.7 as follows:

It also inhibits dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyl transferase (~~GARTF~~ **GARFT**), a folate-dependent enzyme involved in purine synthesis.

Page 12:

The first paragraph of Section 1.9a has been revised for clarification as follows:

The NCCTG lung committee is embarking on a correlative laboratory project to evaluate the pharmacogenomics of pemetrexed in NSCLC. To this end, we are collecting blood samples in a series of studies involving pemetrexed in lung cancer. Extracted DNA will be genotyped for single nucleotide polymorphisms (SNPs) in candidate genes **as listed in Section 14.4211 such as TYMS** (thymidylate synthase), DHFR (dihydrofolate reductase), FOLR1 (folate receptor 1), FPGS (folypolyglutamate synthase), GART (phosphoribosylglycinamide formyltransferase), SLC19A1 (reduced folate carrier, **also known as RFC-1**) and ABCC5 (ATP-binding cassette subfamily C, member 5, **also known as MRP5**)...

Page 13:

The fourth paragraph of Section 1.9a has been revised as follows to remove reference of the intracellular polyglutamate assay as this has not yet been developed:

All identified SNPs selected at frequencies of greater than 5%, functionally important SNPs and identified haplotype-tagged SNPs will be correlated ~~primarily with intracellular content of pemetrexed polyglutamates and secondarily to~~ toxicity/efficacy.

Section 1.9c is newly added as follows to reflect safety analysis information

1.9c Summary of Safety Analysis on first 6 Arm A patients

Two of the first 6 Arm A patients had DLT's. Both had squamous cell histology. Of the 2 patients with DLT's one patient had a grade 3 fatigue (and received nearly the full cycle dose), another patient had a grade 4 neutropenia that resolved within 7 days, with no fever, but also had a grade 3 lipase, and only received 50% of the sorafenib dose for the cycle. There were no DLT's in the first 5 patients with non-squamous histology. Since all the patients with DLT's had squamous cell histology, and there is emerging data that pemetrexed may be less effective in patients with squamous cell lung cancer, it was decided to maintain the dose of sorafenib at 400 mg BID, but exclude patients with squamous cell histology.

Section 2.0**Goals**

Page 14:

Section 2.3 has been revised to remove Section 2.31 as the as the intracellular polyglutamate assay has not yet been developed. The remaining sections have been renumbered.

~~2.31 — To evaluate the intracellular content of pemetrexed polyglutamates as a measure of activity of pemetrexed transport and activation enzymes.~~

New Section 2.31 has been revised as follows to delete reference to the intracellular polyglutamate assay as this has not yet been developed:

...gene expression levels with ~~intracellular levels of pemetrexed polyglutamates,~~ toxicity and/or efficacy of pemetrexed.

Section 3.0**Patient Eligibility**

Page 15:

Section 3.12 has been revised as follows to exclude patients with squamous cell carcinoma:

- 3.12 Histologic or cytologic confirmation of Stage IV ~~NSCLC~~ or Stage IIIB **non-squamous cell histologic type of NSCLC** (symptomatic pleural effusions should be drained prior to registration).
- Mixed histology allowed if all components consistent with NSCLC. Patients whose tumors have squamous cell histology/feature are **NOT** eligible.

Page 16:

Section 3.19h has been moved to contraindications and re-worded for clarification as follows:

~~3.19h Previously received drugs targeting vascular endothelial growth factor (VEGF) or VEGF receptor as long as the patient has not previously received sorafenib treatment. **Note: Prior therapy with bevacizumab is allowed.**~~

Page 18:

Section 3.29k has been newly added as the risk moved from required characteristics to contraindications and re-worded for clarification:

3.29k Prior therapy with agents that target VEGF, VEGF receptor or VEGF receptor tyrosine kinase inhibitors. Exception: Prior therapy with bevacizumab is allowed.

Section 4.0**Test Schedule**

Page 19:

The last two rows in the first column (Tests and procedures) have been revised for clarification to add the word "Mandatory."

Page 20:

Footnote #6 has been revised as follows due to the intracellular polyglutamate assay not yet being developed:

Three 10 mL samples in EDTA tubes of whole blood ~~and one 10 mL sample in sodium heparin tube (processed into plasma and red blood cells at the participating sites)~~ drawn prior to treatment and 24 hours post-treatment of cycle 1 ~~mandatory~~. See Section 14.2. Kits are required for this collection.

Section 6.0**Registration/Randomization Procedures**

Page 21:

The first paragraph and section bullet item have been updated to reflect that the ~~Registration/Randomization Center~~ is now known as the **Registration Office**.

Section 7.0**Protocol Treatment**

Pages 23-24:

Section 7.2 has been revised for clarification as follows:

Patients will continue treatment until PD, unacceptable toxicity, patient refusal to continue, or alternate treatment. Treatment will then be discontinued, and the patient will be observed 28-42 days and then will go to event monitoring (see Section 18.0).

Sections 7.21 and 7.22 have been revised as follows to reflect dosage clarifications:

- 7.21 **Arm A:** Delay the first dose of pemetrexed until the patient has taken folic acid for at least 5 of the 7 days immediately preceding the first dose of pemetrexed and until the vitamin B₁₂ injection has been administered.

~~Sorafenib is supplied as 200-mg tablets. Sorafenib will be given orally, 2 tablets (400 mg total) twice a day. A cycle constitutes 21 days. Patients are to swallow the tablets whole with approximately 250 ml (8 oz.) of water, each morning and evening (i.e., 12 hours apart). Tablets may be taken with or without food. Should not be taken with grapefruit/grapefruit juice.~~

Agent	Dose	Route	Day	ReRx Cycle = 21 days
Pemetrexed ^{*,†,‡}	500 mg/m ²	IV in 100 ml NS over 10 minutes	1	Every 21 days (±7 days)
Sorafenib	400-800 mg/day** (2 tablets)	Oral** twice a day^{***}	1-21	

* Creatinine clearance **must** be ≥ 45 mL/min before **any** pemetrexed is given using the Cockcroft-Gault formula (see Section 3.15).

** **Sorafenib is supplied as 200-mg tablets. Sorafenib will be given orally, 2 tablets (400 mg) twice a day for a total of 800 mg/day. A cycle constitutes 21 days. Patients are to swallow the tablets whole with approximately 250 ml (8 oz.) of water, each morning and evening (i.e., 12 hours apart). Tablets should be taken on an empty stomach. Should not be taken with grapefruit/grapefruit juice. Patients will take their pills at home. The patient will be asked to complete a pill diary (Appendix IV). The diary should be returned at the next scheduled visit. If any daily doses are missed, they will not be made up. The cycle length remains 3 weeks despite missed doses.**

‡ NSAID patients: See Section 9.9a and 9.9b.

† Clinically significant effusions must be drained prior to treatment (e.g., symptomatic pleural or peritoneal effusion). If patient is asymptomatic but the effusion volume is approximated to be >500 mL or produces measurable objective changes related to the effusion (e.g. echocardiographic ventricular compression, hypoxia on pulse oximetry, etc.), effusion should be drained. However, if, in the investigator's opinion, the effusion represents progression of disease, the patient should be discontinued from study therapy.

~~*** Patients will take their pills at home. The patient will be asked to complete a pill diary (Appendix IV). The diary should be returned at the next scheduled visit. If any daily doses are missed, they will not be made up. The cycle length remains 3 weeks despite missed doses.~~

7.22 The first 6 patients treated on Arm A will be evaluated weekly during the first cycle of treatment. The study will be closed to accrual/randomization until all 6 patients on Arm A have completed evaluation for dose-limiting toxicities (DLTs). **This part of the trial is complete as of Addendum 3. See Section 1.9c for a summary of the safety analysis conducted on the first 6 patients treated on Arm A.**

Page 25: Section 7.24 has been revised for clarification as follows:
7.24 Treatment by an LMD (**local medical doctor**) is not allowed. Treatment can only be done at the NCCTG accruing institution. Treatment will be administered on an outpatient basis.

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

Page 28: The following revisions have been made to the second table in Section 8.3:

- Reference to Footnote #1 has been deleted from the last column in the first, fourth, sixth, and eighth sections as Footnote #1 does not apply to pemetrexed.
- Reference to Footnote #3 has been added and reference to Footnote #6 has been deleted from the last column in the eighth section as Footnote #6 does not exist.

Section 12.0 **Descriptive Factors**

Page 38: Section 12.2 is newly added in order to capture prior therapy with bevacizumab:
12.2 Prior therapy with bevacizumab: Yes vs. no.

Section 14.0 **Body Fluid Biospecimens**

Page 40: Section 14.22 has been updated as follows:
All samples must be collected and shipped Monday-~~Thursday~~ **Friday** ONLY.

The table in Section 14.24 has been revised to delete the “Heparin (dark green)” row as the intracellular polyglutamate assay has not yet been developed. Footnote #2 has also been deleted.

Section 14.251 has been corrected to delete “NCCTG” in both the first and second sentences.

Page 41: The opening statement and first bullet in Section 14.253 have been deleted as follows due to the intracellular polyglutamate assay not yet being developed.
~~14.253 Ship specimens as follows:~~

- ~~• Cycle 1, day 1 pre-treatment and post-treatment specimens will be shipped in a dual-temperature shipping container. Place the refrigerated EDTA tubes with a solidly frozen cold pack (see kit instructions for proper packing of blood and cold pack to avoid freezing of specimen) in one compartment and place the frozen plasma and RBC samples with dry ice in the other compartment of the dual-temperature shipping container.~~

The first sentence in Section 14.254 has been updated to reflect that specimens are now allowed to be shipped Monday-**Friday** only.

Page 42: The sixth paragraph of Section 14.41 has been revised as follows due to the intracellular polyglutamate assay not yet being developed:

The identified haplotype-tagged SNPs will be correlated primarily with intracellular content of pemetrexed polyglutamates and secondarily to toxicity/efficacy.

Section 14.41 has been deleted as follows to remove pharmacokinetic analyses as the intracellular polyglutamate assay has not been developed:

~~14.41 Pharmacokinetic analysis~~

~~Pharmacokinetic analysis of plasma pemetrexed concentration-time data will be performed using non-compartmental methods (WinNonlin Professional Version 3.1; Pharsight 1999). The maximum plasma concentration (C_{max}) and the corresponding sampling time (t_{max}) will be interpreted from observed individual concentration and sampling time data. The area under the plasma concentration-time curve (AUC_{0-t}) and the area under the first moment curve ($AUMC_{0-t}$) will be calculated by the log-linear trapezoidal method. The apparent elimination rate constant ($\lambda_{z,t}$) will be determined from the slope of the linear regression over the terminal log-linear portion of the concentration-time curve. From this, the apparent elimination half-life ($t_{1/2}$) will be calculated as $\ln(2)/\lambda_{z,t}$ and plasma clearance (CL) and steady-state volume of distribution (V_{ss}) will be estimated. Estimates of $AUC_{(0-t)}$ and $AUMC_{(0-t)}$ will be extrapolated to infinite time.~~

Page 43: Section 14.421 has been deleted as follows to remove pharmacokinetic analyses as the intracellular polyglutamate assay has not been developed:

~~Intracellular polyglutamate assay for pemetrexed will utilize an HPLC-based method, which is currently being optimized (cellular aliquots of plasma and red blood cells samples drawn in Na heparin tubes).~~

Pages 42-44: Due to the deletion of Sections 14.41 and 14.421, all remaining sections have been renumbered.

Page 43: Section 14.4211 has been revised for clarification as follows:

DNA will be extracted and genotyped for known polymorphisms in genes involved in the transport, activation, inactivation and mechanism of action/resistance of pemetrexed. The genes of interest are:

- Reduced folate carrier (*RFC-1*, *SLC19A1*)
- MRP5 (*ABCC5*)
- Folate receptor α (*FOLR1*)
- ~~BCRP~~
- *FPGS*
- Methylenetetrahydrofolate reductase (*MTHFR*)
- ~~Methionine synthase~~
- **5-methyltetrahydrofolate-homocysteine methyltransferase (*MTRR*) reductase (methionine synthase)**
- Methylthioadenosine phosphorylase (*MTAP*)
- ~~TS~~ Thymidylate synthase (*TYMS*)
- DHFR

- GARFT (*GART*)
- **Gamma Glutamyl hydrolase (*GGH*)**

Page 44: Section 14.422 has been revised for clarification as follows:
 ...templates for real-time qPCR. The second strand cDNA from each sample (stored at -80°C) will be amplified by fluorescent-based kinetic PCR with gene-specific primers using the above mentioned I-Cycler iQ™ Real Time PCR Detection System (BioRad; Hercules, CA). Circulating cells will be ~~detected~~ **using tested for genes specified in Section 14.4211. RCF-1, MRP, folate receptor, BCRP, FPGS, methylenetetrahydrofolate reductase, methionine synthase, methylthioadenosine phosphorylase, TS, DHFR, GARFT (pemetrexed), PDGFR, C-kit, and VEGFR.** Oligonucleotides of the specific amplicons will be used in the real-time PCR assays to generate standard curves to allow for quantification of gene expression. The presence of β -actin mRNA will be used as an endogenous control in the samples to normalize the gene expression. Results will be expressed as gene copies/ng β -actin...

Section 15.0 Drug Information

Page 46: The first paragraph in Section 15.11 has been clarified as follows:
 Table 4 shows the percent of patients experiencing treatment-emergent adverse events that were reported in ~~at least 10% of~~ patients who received sorafenib in TARGET Trial. CTCAE Grade 3 treatment-emergent adverse events were reported in 31% of patients receiving sorafenib compared to 22% of patients receiving placebo. CTCAE Grade 4 treatment-emergent adverse events were reported in 7% of patients receiving sorafenib compared to 6% of patients receiving placebo.

Page 56: The following statement has been added to Section 15.2 to inform the memberships how to obtain the investigator brochure for Pemetrexed:
 15.2 Pemetrexed (pemetrexed disodium, Alimta® MTA)

- **Investigator brochure available on NCCTG web site**

Section 16.0 Statistical Considerations and Methodology

Page 59: At the request of the DSMB, the stopping rule for Section 16.1 has been revised to include Arm B as follows:
Adverse Events Stopping Rule: If it is deemed necessary to reduce the dose of sorafenib after the evaluation of the first 6 patients, these 6 patients will not be included in the evaluation of the adverse event stopping rule. **The rule below applies to patients on both Arm A and B, where Arm A and B adverse events will be evaluated separately. Only those adverse events or early deaths that are possibly, probably, or definitely related to study treatment will count towards the stopping rule below. If any of the following occur, accrual to the study will be suspended to allow for a full review of the data:**

- If 3 or more of the first 20 **treated** patients ~~in Arm A~~ (or 15% of all patients after 20 are accrued) experience grade 4/5 non-hematologic adverse events. ~~that are probably, possibly, or definitely related to study treatment, OR~~
- **If the rate of death within the first 60 days exceeds 10%.**

- OR ~~If~~ 7 or more of the first 20 patients (or 35% of **all** patients after 20 are accrued) experience a grade 4 neutropenia. ~~accrual to the study will be suspended to allow for investigation.~~

Section 17.0 Pathology Considerations/Tissue Biospecimens

Page 63: The word “NCCTG” has been deleted from the second bullet in Section 17.32 and the first sentence of 17.35.

Appendix I Consent Form

Page 4-5: The fifth sentence in the second to the last paragraph under the “During the study” section has been revised for clarification as follows as this was not done at the time of Addendum 2:

Tablets ~~may~~ **should** be taken ~~with or~~ without food.

The Cycle 1 Group A and Cycle 1 Group B tables have been revised to reflect the correct amount of blood being drawn as follows:

1	<ul style="list-style-type: none"> • Dexamethasone by mouth twice a day. • Pemetrexed will be given into a vein in your arm over 10 minutes. • Research blood draw (about 3 2 tablespoons) before treatment starts.
2	<ul style="list-style-type: none"> • Dexamethasone by mouth twice a day. • Research blood draw 24 hours after pemetrexed treatment (about 3 2 tablespoons).

Appendix V

Pages 1-2: The instructions for blood sample submission have been revised as follows due to the intracellular polyglutamate assay has not been developed:

Research Base Instructions for Biospecimen Processing in the Biospecimens Accessioning and Processing (BAP) Shared Resource

Summary Table of Research Blood/Blood Products Being Received in BAP for N0626

Collection tube description and/or additive (color of tube top)	Volume to be collected per tube (number of tubes to be collected)	Blood product to be processed in BAP	Before tx, cycle 1, day 1	24 hours after cycle 1, day 1	Before tx, cycle 2, day 1	Before tx, cycle 3 and cycle 5, day 1	Further processing required by BAP?	Shipping conditions
Tube labeled "Plasma"	~3 mL (1)	Plasma	X	X			No	Frozen
Tube labeled "RBCs"	~3 mL (1)	RBCs ⁺	X	X			No	Frozen
EDTA (purple)	10 mL (2)	CTCs ² CTCs ¹	X	X	X		Yes	Refrigerate/ cold pack (DO NOT FREEZE)
EDTA (purple)	10 mL (1)	Plasma, DNA	X				Yes	Refrigerate/ cold pack (DO NOT FREEZE)
EDTA (purple)	10 mL (1)	Plasma, buffy coat		X	X	X	Yes	Refrigerate/ cold pack (DO NOT FREEZE)

⁺RBCs; Red blood cells

²¹ CTCs; Circulating tumor cells

Item #2 has also been deleted and all remaining sections renumbered.

~~Frozen plasma and RBC samples will be stored at -80°C until a box is filled. Once a box is filled, forward the frozen plasma and RBC samples to Dr. Matthew Ames' laboratory (Attention: Stephanie Safgren, 4-4303.)~~