A Pilot Study Evaluating Pemetrexed in ECOG Performance Status 3 Patients with Stage IV Non-Squamous Non-Small Cell Lung Cancer
Comprehensive Cancer Center of Wake Forest University (CCCWFU)
CCCWFU # 62115

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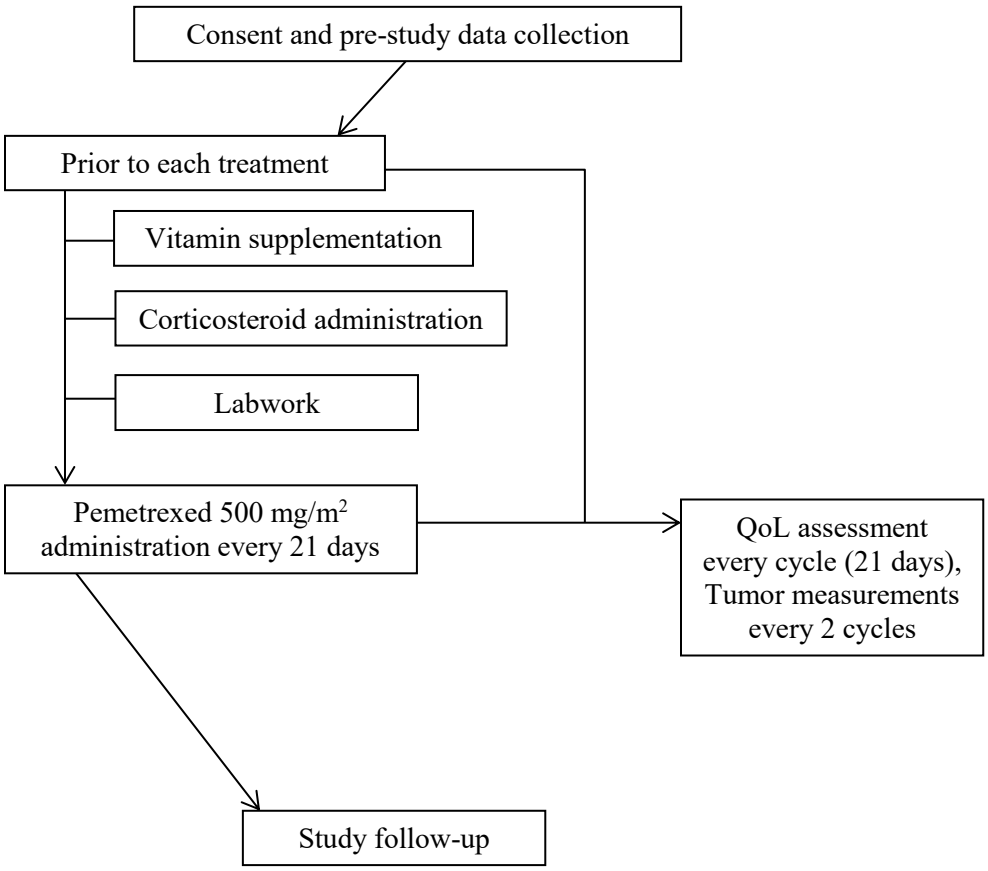
SCHEMA


Consent and pre-study data collection
Prior to each treatment
Vitamin supplementation
Corticosteroid administration
Labwork
Pemetrexed 500 mg/m2 administration every 21 days
QoL assessment every cycle (21 days), Tumor measurements every 2 cycles
Study follow-up

1.0 Introduction and Background

Lung cancer is the third most common cancer in both men and women and the leading cause of cancer death.[1] Only approximately 15% of lung cancer cases are diagnosed at the local stage, and 5-year relative survival rates for regional and distant metastases are a dismal 26.5% and 4%, respectively.[1] Systemic therapy is the predominant treatment for patients with advanced non-small cell lung cancer (NSCLC), based on clinical trials conducted over several decades that demonstrated improved survival and quality of life.[2-4] However, current National Comprehensive Cancer Network (NCCN) guidelines for patients with Stage IV non-squamous NSCLC and a performance status (PS) of 3 or 4 is best supportive care. Restricting treatment based on performance status is largely based on toxicity data from historic chemotherapy trials,[5-8] and previous studies have limited use of the chemotherapy pemetrexed to patients with PS 0 to 2. Given the relatively mild toxicity profile of pemetrexed,[9, 10] the ability to mitigate side effects with folic acid and vitamin B12 supplementation,[11] and the reported benefit of single agent pemetrexed in elderly patients with good performance status,[12, 13] further study of its effectiveness and tolerability is warranted in patients with a PS of 3.

PS is considered an important prognostic factor for patients with advanced NSCLC.[5-8] The ECOG 1594 trial randomly assigned patients to one of four platinum-based double-agent chemotherapy regimens: 1) paclitaxel (135 mg/m^2) over 24 hours with cisplatin (75 mg/m^2) on a 21-day cycle; 2) cisplatin (100 mg/m^2) with gemcitabine (1 g/m^2) on Days 1, 8, and 15 on a 28-day cycle; 3) cisplatin (75 mg/m^2) with docetaxel (75 mg/m^2) on a 21-day cycle; and 4) paclitaxel (225 mg/m^2) over 3 hours with carboplatin (area under the curve, 6).[14] The Data Monitoring Committee observed an excessive rate of adverse events among the patients with a PS of 2 and recommended discontinuation of enrollment of patients with a PS of 2. This observation contributed to many cooperative groups excluding patients with a PS of 2 from trials that included platinum-based therapy. A subsequent analysis of this trial revealed that patients with a PS of 2 had a poor prognosis, but the overall rate of treatment-related toxicity was similar among patients with a PS of 2 compared with patients with a PS of 0 or 1. Patients with a PS of 2 compared with patients with a PS of 0 or 1 experienced a higher rate of adverse events, but this was because of a higher rate of disease-related adverse events.

Pemetrexed is a multitargeted antifolate agent that has been approved for use in locally advanced or metastatic non-squamous non-small cell lung cancer as initial treatment in combination with cisplatin, as maintenance treatment of patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy, and after prior chemotherapy as a single-agent.[10] The primary adverse effect of pemetrexed, myelosuppression, presents as neutropenia and thrombocytopenia and is the dose-limiting toxicity of the drug. Elevated pretreatment levels of plasma homocysteine (a marker of folate deficiency) has been shown to be predictive of severe myelosuppression, while a high pretreatment level of methylmalonic acid (a marker of vitamin B12 deficiency) is an independent predictor of severe diarrhea and mucositis.[11] It has been reported that supplementation with folic acid and vitamin B12 substantially reduces pemetrexed-related toxicity without reducing efficacy.[11] In Scagliotti et al's Phase III, the key hematologic grade 3 or 4 drug-related toxicities for cisplatin/pemetrexed were significantly lower than those in cisplatin/gemcitabine

(neutropenia: 15% versus 27%, anemia: 6% versus 10%, and thrombocytopenia: 4% versus 13%, respectively; *P*<0.001).[15] Drug-related grade 3 or 4 febrile neutropenia (1% versus 4%, respectively; *P*<0.002) and alopecia (all grades, 12% versus 21%, respectively; *P*<0.001) were also significantly lower.[15]

Clinical trials evaluating use of pemetrexed in patients with NSCLC and a PS ≥2 are limited to a study by Jung et al. that retrospectively examined pemetrexed use in 56 Korean patients with NSCLC and PS ≥2 who had relapsed or progressed after prior chemotherapy treatment.[16] Anemia was the most frequent adverse event (28.4%), followed by nausea (23%). Grade 3-4 hematologic toxicity occurred in 8.8% of cases. None of the patients required dose modifications due to toxicity. Non-squamous cell carcinoma histology was significantly associated with a superior response rate (P=0.045) and disease control rate (P=0.008). The median survival time and the median progression free survival (PFS) time were 6.11 months and 2.17 months, respectively. Studies considering advanced age are available, such as the randomized phase II trial by Gridelli et al. evaluating single-agent pemetrexed versus sequential pemetrexed/gemcitabine in patients with NSCLC and PS of 0 to 2 who were ineligible for platinum-based chemotherapy. This study found that single-agent pemetrexed demonstrated moderate activity and was well tolerated, regardless of advanced age.[13] Similarly, in a single-arm phase II study of pemetrexed in elderly (≥70 years old) Japanese patients with advanced non-squamous NSCLC demonstrated favorable antitumor activity and mild toxicity.[17] In an analysis of two randomized phase III trials evaluating the survival and safety of pemetrexed in elderly patients (<65 years and ≥65 years, and <70 years and ≥70 years) with nonsquamous NSCLC and PS 0-1, Gridelli et al found minimal variation in the hematologic toxicities between the age groups, and the majority of hematologic toxicity rates were low.[12]

The primary endpoint of this single arm pilot study is to evaluate the effect of single agent pemetrexed chemotherapy in ECOG Performance Status 3 patients with stage IV non-squamous histology non-small cell lung cancer. We hypothesize that patients with non-squamous histology NSCLC and ECOG PS 3 receiving single agent pemetrexed chemotherapy will have a prolonged time to progression compared to best supportive care alone and will have improved quality of life (QOL) as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire version 3.0 (EORTC QLQ-C30) and the corresponding lung cancer-specific module (QLQ-LC13).[18]

2.0 Objectives

2.1 Primary Objectives

2.1.1 To evaluate the effect of single agent pemetrexed on tumor progression in ECOG Performance Status 3 patients with Stage IV non-squamous histology non-small cell lung cancer in a single arm pilot study.

2.1.2 To evaluate the effect of single agent pemetrexed on quality of life in ECOG Performance Status 3 patients with Stage IV non-squamous histology non-small cell lung cancer in a single arm pilot study.

2.2 Secondary Objective

2.2.1 To evaluate toxicity associated with single agent pemetrexed on tumor progression in ECOG Performance Status 3 patients with Stage IV non-squamous histology non-small cell lung cancer in a single arm pilot study.

3.0 Patient Selection

3.1 Inclusion Criteria

3.1.1 Patients must have histologically confirmed Stage IV non-squamous histology non-small cell lung cancer

3.1.2 ECOG performance status of 3

3.1.3 Sensitizing *EGFR*, *ALK* and *ROS-1* mutations are either negative or unknown

3.1.4 Patients must have normal organ and marrow function as defined below:

- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL
- creatinine clearance ≥45 mL/min

3.1.5 The effects of pemetrexed on the developing human fetus are unknown. For this reason and because Pregnancy Category D agents are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.6 Ability to understand and the willingness to sign an IRB-approved informed consent document

3.1.7 Ability to understand and complete the EORTC QOL instruments

3.1.8 ≥18 years of age

3.2 Exclusion Criteria

3.2.1 Patients who have previously received chemotherapy for non-small cell lung cancer, or have received radiotherapy within 2 weeks prior to entering the study, or who have not recovered from adverse events due to treatment more than 2 weeks earlier.

3.2.2 Patients whose tumors are positive for the sensitizing *EGFR* mutation.

3.2.3 Patients whose tumors are positive for the sensitizing *ALK* fusion

3.2.4 Patients whose tumors are positive for the sensitizing *ROS-1* fusion

3.2.5 Patients may not be receiving any other investigational agents.

3.2.6 Patients with symptomatic or recurrent brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.7 Patients whose pathology has squamous cell features unless there is an unequivocal determination of non-squamous pathology.

3.2.8 History of allergic reactions attributed to compounds of similar chemical or biologic composition to pemetrexed.

3.2.9 Pregnant women are excluded from this study because pemetrexed is a Category D agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with pemetrexed, breastfeeding should be discontinued.

3.3 Inclusion of Women and Minorities

Men and women of all races and ethnicities who meet the above-described eligibility criteria are eligible to participate in this study.

The study consent form will also be provided in Spanish for Spanish-speaking participants. Based on CCCWFU population estimates for lung cancer patients, we expect approximately 40% of participants to be women. Translating this to our sample size estimate of 30 patients, we anticipate enrolling at least 12 women. Similarly, we expect approximately 4% of study participants to be Hispanic/Latino (N=1). We anticipate enrolling 18% Black or African American (N=5) patients. For other minority groups (American Indian, Asian) we anticipate enrolling approximately 4% (N=1) patient. Should we not meet or exceed these estimates, the PI will engage the Cancer Center Health Equity Advisory Group to discuss strategies to enhance recruitment in these target populations.

4.0 Registration Procedures

All patients entered on any CCCWFU trial, whether treatment, companion, or cancer control trial, **must** be registered with the CCCWFU Protocol Registrar or entered into ORIS Screening

Log within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

You must perform the following steps in order to ensure prompt registration of your patient:

1. Complete the Eligibility Checklist (Appendix A)
2. Complete the Protocol Registration Form (Appendix A)
3. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

   Contact Information:
   Protocol Registrar PHONE (336) 713-6767
   Protocol Registrar FAX (336) 713-6772
   Protocol Registrar E-MAIL (registra@wakehealth.edu)

   *Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.

4. Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

Note: If labs were performed at an outside institution, provide a printout of the results. Ensure that the most recent lab values are sent.

To complete the registration process, the Registrar will:

- assign a patient study number
- register the patient on the study

5.0 Study Outcomes and Study Measures

5.1 Primary Outcomes

5.1.1 Time to tumor progression in ECOG Performance Status 3 patients with Stage IV non-squamous histology non-small cell lung cancer receiving single agent pemetrexed

5.1.2 Quality of life metrics in accordance with the EORTC QLQ-C30 and QLQ-LC13 instruments and PS in ECOG Performance Status 3 patients with Stage IV non-squamous histology non-small cell lung cancer receiving single agent pemetrexed

5.2 Secondary Outcomes

5.2.1 Hematologic toxicity associated with single agent pemetrexed on tumor progression in ECOG Performance Status 3 patients with Stage IV non-squamous histology non-small cell lung cancer

5.2.2 Response rate in ECOG Performance Status 3 patients with Stage IV non-squamous histology non-small cell lung cancer receiving single agent pemetrexed

5.2.3 Overall survival in ECOG Performance Status 3 patients with Stage IV non-squamous histology non-small cell lung cancer receiving single agent pemetrexed

6.0 Treatment Plan

6.1 Study-Related Interventions

	Pre-Study[a]	Prior to each treatment[b]	At Each Treatment[c]	After treatment[d]	Follow-up
Informed consent	X				
Demographics	X				
Medical history	X				
Concurrent meds	X				
Physical exam	X				
Vital signs (HR, BP, RR, Temp)	X		X		
Height, Weight, BSA	X		X		
PS and QOL	X		X		
Tumor measurements[e]	X			X[l]	
CBC w/diff, platelets	X	X[k]		X[m]	
Serum chemistry[f]	X	X			
B-HCG[g]	X				
Folic acid supplementation[h]		X			
Vitamin B12 administration[i]		X		X[n]	
Corticosteroid administration[j]		X	X	X	
Adverse event evaluation	X		X		X

[a] Pre-study requirements listed in table must be completed **within** 21 days prior to registration. See Appendix E.
[b] See Appendix F. To be completed prior to each treatment administration.
[c] See Appendix G. To be completed for each treatment.
[d] See Appendix H.
[e] See Appendix I.
[f] BUN, creatinine, bilirubin, SGOT [AST], SGPT [ALT]; within 7 days prior to treatment.
[g] Serum pregnancy test (women of childbearing potential).
[h] Begin folic acid once daily at least 7 days before the first dose of pemetrexed. Continue folic acid during the full course of therapy and for 21 days after the last dose of pemetrexed.
[i] Administer vitamin B12 1 mg intramuscularly at least 7 days prior to the first dose of pemetrexed and at least every 3 cycles thereafter.
[j] Administer dexamethasone 4 mg by mouth twice daily the day before, the day of, and the day after pemetrexed administration
[k] Patients should not begin a new cycle of treatment unless the ANC is ≥1500 cells/mm^3, the platelet count is ≥100,000 cells/mm^3, and creatinine clearance is ≥45 mL/min within 7 days prior to treatment.
[l] Patients should be reevaluated for response every 6 weeks (+/- 2 weeks). In addition to a baseline scan, confirmatory scans should also be obtained 6 weeks following initial documentation of objective response. See Appendix I.
[m] 7-10 days after the first treatment administration
[n] Every 3 cycles

6.2 Treatment Administration

Treatment can be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 9.0. Appropriate dose modifications are described in Section 7.0. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen Description				
Agent	**Dose**	**Route**	**Schedule**	**Cycle Length**
Pemetrexed	500 mg/m^2 in 100 mL of 0.9% Sodium Chloride Injection (preservative free)	IV over 10 minutes	Day 1	21 days

6.2.1 Premedication regimen and concurrent medications

Vitamin Supplementation:
Administer folic acid 400 mcg to 1000 mcg orally once daily beginning at least 7 days before the first dose of pemetrexed. Continue folic acid during the full course of therapy and for 21 days after the last dose of pemetrexed.

Administer vitamin B12 1 mg intramuscularly at least 1 week prior to the first dose of pemetrexed and at least every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as treatment with pemetrexed.

Corticosteroids:
Administer dexamethasone 4 mg by mouth twice daily the day before, the day of, and the day after pemetrexed administration. As an alternative, the day of treatment dexamethasone may be administered as a single dose of 10 mg intravenously prior to administration of the chemotherapy.

6.2.2 Laboratory monitoring

A CBC should be performed 7-10 days after the first dose for the first cycle of pemetrexed treatment. Patients should be monitored for nadir and recovery. Patients should not begin a new cycle of treatment unless the ANC is ≥1500 cells/mm^3, the platelet count is ≥100,000 cells/mm^3, and creatinine clearance is ≥45 mL/min. Chemistry tests will be performed to evaluate renal and hepatic function prior to each treatment.

6.2.3 Performance status and QOL

ECOG performance status and QOL will be assessed at the start of every cycle (i.e. every 3 weeks). QOL will be assessed by the EORTC QLQ-C30 and QLQ-LC13.[18]

The EORTC QLQ-C30 is reportedly the most frequently used QOL instrument in lung cancer clinical trials.[19] The QLQ-30 is a 30-item multi-dimensional questionnaire designed for use in cancer populations.[18] It contains nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale, requested by 4-point Likert or visual analogue scales. Several single-item symptom measures are also included. The QLQ-LC13 is a lung cancer-specific module to be used in conjunction with the QLQ-30 and is 13 additional items. These questionnaires have been shown to be reliable and valid in over 60 languages, can be self- or interviewer-administered and take approximately 11 minutes to complete.[18, 19]

6.3 General Concomitant Medication and Supportive Care Guidelines

Patients should receive *full supportive care*, including transfusions of blood and blood products, erythropoietin, antibiotics, antiemetics, etc., as clinically indicated. Medications considered necessary for the patient's well-being may be given at the discretion of the investigator, i.e., chronic treatments for concomitant medical conditions, as well as agents required for life-threatening medical problems, etc. The reason(s) for treatment, dosage, and dates of treatment should be recorded on the flow sheets.

6.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), including hematologic or nonhematologic Grade 3 or 4 toxicity after 2 dose reductions or immediately if Grade 3 or 4 neurotoxicity is observed
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6.5 Duration of Follow Up

Patients will be followed for adverse events monitoring for a minimum of 30 days after the last study drug is administered or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Patients will be followed every 6 weeks until death for monitoring survival study endpoints.

7.0 Dosing Delays/Dose Modifications

Dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum nonhematologic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, patients should be retreated using the guidelines in Tables 1-3. Patients should be removed from study if they have not fully recovered with respect to treatment related toxicity more than 6 weeks after the last treatment, i.e. a >3 week delay.

Table 1: Dose reduction – Hematologic Toxicities

Nadir ANC<500 mm^3 and nadir platelets ≥50,000/mm^3	75% of previous dose
Nadir platelets <50,000/mm^3 without bleeding regardless of nadir ANC	75% of previous dose
Nadir platelets <50,000/mm^3 with bleeding[a] regardless of nadir ANC	50% of previous dose
[a]These criteria meet the CTC version 2.0 (NCI 1998) definition of ≥CTC Grade 2 bleeding	

If patients develop non-hematologic toxicities (excluding neurotoxicity) ≥Grade 3, treatment should be withheld until resolution to less than or equal to the patient's pre-therapy value. Treatment should be resumed according to guidelines in Table 2. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is experienced.

Table 2: Dose reduction – Nonhematologic toxicities[a,b]

Any Grade 3 or 4 toxicities except mucositis	75% of previous dose
Any diarrhea requiring hospitalization (irrespective of Grade) or Grade 3 or 4 diarrhea	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose
[a]NCI Common Toxicity Criteria [b]Excluding neurotoxicity (see Table 3)	

8.0 Measurement of Effect

8.1 Antitumor Effect

As part of normal medical care, patients should be reevaluated for response every 6 weeks. In addition to a baseline scan, confirmatory scans should also be obtained after approximately 6 weeks to monitor for disease progression. Scans will be done independently of the study, however data acquired from the scans will be used for research purpose to evaluate the effects of the product under investigation. For the purposes of this study, patients should be reevaluated for response every 6 weeks (+/- 2 weeks). In addition to a baseline scan, confirmatory scans should also be obtained 6 weeks (+/- 2 weeks) following initial documentation of objective response.

Response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1.[20]

8.1.1 Definitions

- Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with pemetrexed
- Inevaluable for objective response: When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.
    - If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would most likely happen in the case of PD.
- Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
    - 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; when CT scans have slice thickness >5 mm, the minimum size should be twice the slice thickness);
    - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
    - 20 mm by chest X-ray.
- Measurable lesions:
    - Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness is recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
    - Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by crosssectional

imaging techniques such as CT or MRI can be considered measurable if the soft tissue component meets the definition of measurability described above.
    - ‘Cystic lesions’ thought to represent cystic metastases can be considered measurable if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Non-measurable lesions: Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
    - Lesions with prior local treatment, such as those situated in a previously irradiated area or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.
- Target lesions: All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline.
    - Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, as well as their suitability for reproducible repeated measurements.
    - All measurements should be recorded in metric notation using calipers if clinically assessed.
    - A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters, which will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. If lymph nodes are to be included in the sum, only the short axis will contribute.
    - Lymph nodes identified as target lesions should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm on study. When lymph nodes are included as target lesions, the ‘sum’ of lesions may not be zero even if complete response criteria are met since a normal lymph node is defined as having a short axis of <10 mm.
    - Target lesions that become ‘too small to measure’: While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small. However, sometimes lesions or lymph nodes become so faint on a CT scan that the radiologist may not feel comfortable assigning an exact

measure and may report them as being 'too small to measure', in which case a default value of 5 mm should be assigned.
    - Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.
- Non-target lesions: All lesions (or sites of disease) not identified as target lesions, including pathological lymph nodes and all non-measurable lesions, should be identified as non-target lesions and be recorded at baseline. Measurements of these lesions are not required and they should be followed as 'present', 'absent' or in rare cases, 'unequivocal progression'.

8.1.2 Methods for Evaluation of Measurable Disease

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

- CT is the best currently available and reproducible method to measure lesions selected for response assessment. MRI is also acceptable in certain situations (e.g., for body scans but not for lung).
- Lesions on a chest X-ray may be considered measurable lesions if they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Clinical lesions will only be considered measurable when they are superficial and ≥10 mm in diameter as assessed using calipers. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- Ultrasound (US) should not be used to measure tumor lesions.
- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response.
- Cytology and histology can be used in rare cases (e.g., for evaluation of residual masses to differentiate between Partial Response and Complete Response or evaluation of new or enlarging effusions to differentiate between Progressive Disease and Response/Stable Disease).
- Use of endoscopy and laparoscopy is not advised. However, they can be used to confirm complete pathological response.

8.1.3 Response Criteria

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this may include the baseline sum). The sum must also demonstrate an absolute increase of at least 5 mm.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

8.1.4 Evaluation of Non-Target Lesions

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be non-pathological in size (<10 mm short axis).
- Non-CR / Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker levels above normal limits.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.
    - When patient has measurable disease: To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
    - When patient has only non-measurable disease: There is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied is to consider if the increase in overall disease burden based on change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large' or an increase in lymphangitic disease from localized to widespread.
- New lesions: The appearance of new malignant lesions denotes disease progression.
    - The finding of a new lesion should be unequivocal (i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor, especially when the patient's baseline lesions show partial or complete response).

- If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.
- A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and disease progression.
- It is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is PD based on a new lesion.
  - No FDG-PET at baseline and a positive FDG-PET at follow-up:
    - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
    - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
    - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

8.1.5 Evaluation of Best Overall Response

Appendix I provides a summary of the overall response status calculation at each time point for patients who have measurable and non-measurable (therefore non-target) disease at baseline.

8.1.6 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

8.1.7 Survival Outcomes

Progression-Free Survival is defined as the duration of time from the start of treatment to the time of progression, death, or date of last contact

Overall Survival is defined as the duration of time from the start of treatment to date of death or date of last contact.

9.0 Adverse Events List and Reporting Requirements

9.1 Adverse Event List for Pemetrexed

In clinical trials, the most common adverse reactions (incidence ≥20%) during therapy with pemetrexed as a single agent were fatigue, nausea, and anorexia.

Grade 3 or 4 adverse reactions:

Incidence 1% to 5%
Hematologic – anemia, leukopenia, neutropenia, thrombocytopenia
Hepatic – increased ALT
Gastrointestinal – nausea, anorexia, vomiting
General – fatigue

Incidence Less than 1%
Hepatic – increased AST
Gastrointestinal - stomatitis/pharyngitis

9.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only.

- **Attribution** of the AE:

- Definite – The AE **is clearly related** to the study treatment.
- Probable – The AE **is likely related** to the study treatment.

- Possible – The AE **may be related** to the study treatment.
- Unlikely – The AE **is doubtfully related** to the study treatment.
- Unrelated – The AE **is clearly NOT related** to the study treatment.

9.3 STRC SAE Reporting Requirements

The Safety and Toxicity Reporting Committee (STRC) is responsible for reviewing SAEs for CCCWFU Institutional studies as outlined in Appendix B. STRC currently requires that all unexpected 4 and all grade 5 SAEs on these trials be reported to them for review. All CCCWFU Clinical Research Management (CRM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for STRC reporting are responsible for informing a clinical member of the STRC as well as the entire committee via the email notification procedure of the occurrence of an SAE.

9.4 WFUHS IRB AE Reporting Requirements

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or

informed consent process/document in order to insure the safety, rights or welfare of research subjects.

10.0 Pharmaceutical Information

A list of the adverse events and potential risks associated with the pharmaceutical agent administered in this study can be found in Section 9.1.

10.1 Pharmaceutical Accountability

This drug is commercially available.

10.2 ALIMTA (Pemetrexed)

Product description: Pemetrexed disodium heptahydrate has the chemical name L-Glutamic acid, *N*-[4-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate. It is marketed by Lilly USA, LLC. ALIMTA is supplied as a sterile lyophilized powder for intravenous infusion available in single-dose vials. The product is a white to either light yellow or green-yellow lyophilized solid. Each 100-mg or 500-mg vial of ALIMTA contains pemetrexed disodium equivalent to 100 mg pemetrexed and 106 mg mannitol or 500 mg pemetrexed and 500 mg mannitol, respectively. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

Solution preparation: Reconstitute each 500-mg vial with 20 mL of 0.9% Sodium Chloride Injection (preservative free). Reconstitution gives a solution containing 25 mg/mL ALIMTA. Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in color from colorless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted ALIMTA solution is between 6.6 and 7.8. FURTHER DILUTION IS REQUIRED. Reconstituted ALIMTA solution must be further diluted into a solution of 0.9% Sodium Chloride Injection (preservative free), so that the total volume of solution is 100 ml. Reconstitution and further dilution prior to intravenous infusion is only recommended with 0.9% Sodium Chloride Injection (preservative free). ALIMTA is physically incompatible with diluents containing calcium, including Lactated Ringer's Injection, USP and Ringer's Injection, USP and therefore these should not be used. Coadministration of ALIMTA with other drugs and diluents has not been studied, and therefore is not recommended.

Storage requirements and Stability: Chemical and physical stability of reconstituted and infusion solutions of ALIMTA have been demonstrated for up to 24 hours following initial reconstitution, when stored refrigerated. When prepared as directed, reconstitution and infusion solutions of ALIMTA contain no antimicrobial preservatives. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Discard any unused portion.

Route of administration: ALIMTA is administered as an intravenous infusion over 10 minutes. .As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions of ALIMTA. The use of gloves is recommended. If a solution of ALIMTA contacts the skin, wash the skin immediately and thoroughly with soap and water. If ALIMTA contacts the mucous membranes, flush thoroughly with water. ALIMTA is compatible with standard polyvinyl chloride (PVC) administration sets and intravenous solution bags. ALIMTA is not a vesicant. There is no specific antidote for extravasation of ALIMTA. To date, there have been few reported cases of ALIMTA extravasation, which were not assessed as serious by the investigator. ALIMTA extravasation should be managed with local standard practice for extravasation as with other non-vesicants.

Drug interactions:

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Although ibuprofen (400 mg four times a day) can decrease the clearance of pemetrexed, it can be administered with ALIMTA in patients with normal renal function (creatinine clearance ≥80 mL/min). No dose adjustment of ALIMTA is needed with concomitant NSAIDs in patients with normal renal function. Caution should be used when administering NSAIDs concurrently with ALIMTA to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of 2 days before, the day of, and 2 days following administration of ALIMTA. In the absence of data regarding potential interaction between ALIMTA and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following ALIMTA administration. If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

Nephrotoxic Drugs

ALIMTA is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. Concomitant administration of nephrotoxic drugs could result in delayed clearance of ALIMTA. Concomitant administration of substances that are also tubularly secreted (e.g., probenecid) could potentially result in delayed clearance of ALIMTA.

Disposal: Unused portions of agent should be disposed of in accordance with general anticancer agent guidelines

11.0 Data Management

Informed consent document	ORIS
Protocol registration form	ORIS
Pre-study data collection form	REDCap
Pre-treatment data collection form	REDCap
Treatment data collection form	REDCap
Follow-up data collection form	REDCap
Tumor Measurement form	REDCap
Treatment Response form	REDCap

12.0 Statistical Considerations

12.1 Analysis of Primary Objectives

There are two primary objectives in this study: 1) To evaluate the effect of single agent pemetrexed on tumor progression in ECOG Performance Status 3 patients with Stage IV non-squamous histology non-small cell lung cancer and 2) To evaluate the effect of single agent pemetrexed on quality of life in ECOG Performance Status 3 patients with Stage IV non-squamous histology non-small cell lung cancer.

Both of these objectives will be examined using a pilot study of 30 patients. We now will describe the analytic strategy to address each aim.

Based on historic data, the median progression free survival time for comparable patients has ranged from 2.8 to 4.9 months.[17, 21-23] However, the patients in this protocol are likely to have a worse prognosis since their ECOG performance status is 3 whereas the patients in the references had better ECOG performance status. Therefore, one goal of this trial is to see whether there is evidence that the median progression free survival time in this group of treated patients could be 12 weeks (i.e., 2.8 months). In order to do this we will determine whether each patient has a progression (or dies) before or after 12 weeks. We will then construct a 95% exact (Clopper Pearson) confidence interval around the proportion with PFS greater than or equal to 12 weeks. If this confidence interval includes 50% then that would provide evidence that the therapy is potentially promising. However, if the upper bound of the confidence interval does not include 50% then this would indicate that the treatment may not be promising for patients since we could rule out the possibility that the median PFS is 12 weeks or longer. We have designed this study to enroll 30 patients. If 9 out of 30 do not have a progression (or dies) at 12 weeks (30%) then the upper bound of a 2-sided 95% confidence interval would not include 50%, however if 10 or more patients (out of 30) do not have progression (or dies) at 12 weeks then the upper bound would include 50% suggesting that the treatment is promising.

In addition to estimating this confidence interval we will construct a Kaplan Meier survival curve to describe the time to progression data.

For the quality of life outcome we wish to compare the pre-treatment with the post-treatment values over time. Quality of life will be assessed every 3-weeks during the trial and we anticipate examining each of these assessments. For the purposes of identifying a primary time point for comparison we will compare the 12 week QOL value with the baseline QOL value. Since some patients may not have a 12 week measure, but we will assess QOL at each treatment time (i.e. every three weeks) we can use a longitudinal mixed models analysis to look at QOL over the time course. This approach would handle missing data if the data is missing at random, which means that measured covariates can be used to predict whether missing data will occur. We believe that it is possible that patients who have worse baseline co-morbid conditions may be more likely to have a 12-week QOL missing, and thus we will use these characteristics in the longitudinal mixed model analysis to examine change in QOL over time adjusting for baseline covariates. Based on historic data, most patients eligible for this study would have worsening QOL over a 12 week period, thus we wish to determine whether QOL can remain stable or possibly improve. To do this we will calculate a paired t-test to see if the average change is more than 0 (worsening) versus a two-sided alternative that the difference is 0 or better.

It should be noted that since this is a pilot study, there is a possibility that one of the two primary comparisons (confidence interval calculation and QOL change) may not meet the criteria for success, however if there is evidence that the effects are trending in the correct direction (i..e, if the average change in 12 week QOL is 0 or positive (implying some improvement)) then this would provide evidence that the treatment regimen is possibly working and could possibly warrant further studies.

12.2 Analysis of Secondary Objectives

There are three secondary objectives in this protocol 1) to evaluate the toxicities associated with single agent pemetrexed on tumor progression in ECOG Performance Status 3 patients with Stage IV non-squamous histology non-small cell lung cancer (in particular we will examine neutropenia, thrombocytopenia and fatigue (although fatigue will also be captured as part of quality of life assessment), 2) to estimate the response rate in ECOG Performance Status 3 patients with Stage IV non-squamous histology non-small cell lung cancer receiving single agent pemetrexed and 3) to estimate the overall survival in ECOG Performance Status 3 patients with Stage IV non-squamous histology non-small cell lung cancer receiving single agent pemetrexed

For toxicities we will estimate the number and type of toxicities observed during this protocol focusing on unexpected grade 3 or higher toxicities. No formal statistical tests will be done on these estimates.

Response rate will be estimate every 6 weeks for patients and these estimates will be presented with confidence intervals as well.

Overall survival will be examined by estimating a Kaplan-Meier survival curve using all patients enrolled.

12.3 Power and Sample Size

Since this is an aggressive disease and patients enrolled will be at ECOG Performance Status 3, it is an expected that all patients will progress or die prior to the end of the follow-up therefore we anticipate that all 30 patients will provide data for the time until progression endpoint analysis. . Quality of life will be measured at each visit when treatment is administered so it is expected that all patients will have some follow-up assessments to be used in analyses.

As described above, the first analysis will consist of determining what proportion of patients are progression-free (and alive) at 12 weeks (yes/no). With a total of 30 patients, a two-sided 95% confidence interval (using the Clopper-Pearson exact calculation) will have a maximum width of 0.374 (i.e., +/- 0.187). Thus, if the observed proportion of patients who are progression free at 12 weeks is 50% then the lower bound of this interval will rule out 31.3% (or lower). Likewise, if 30% or fewer patients are progression free at 12 weeks then the upper bound of this confidence interval will rule out 50% and thus suggest that the median progression free survival for this treatment is less than 12 weeks.

We have a planned interim analysis to take place after the first 15 patients are enrolled and have had more than 12 weeks of follow-up. If 2 or fewer of these first 15 patients have a response (i..e progress by 12 weeks) then we will stop the trial since the upper bound of a 2-sided 99% exact confidence interval would rule out 50%.

Likewise, with 30 patients enrolled, we have 80% power to detect a change in QOL equal to 0.53 standard deviations using a paired t-test with alpha=0.05 (2-sided test).

As stated above, since this is a pilot study, it is possible that we may not observe statistical significance for these two aims, however if the point estimates for these aims are in the correct direction this will provide evidence that the therapy may be a promising alternative for patients and thus warrant further investigation. If this were to occur, the data from this trial would be used to provide preliminary estimates of what PFS rates may be expected and what change in QOL may be expected in a larger efficacy study.

12.4 Estimated Accrual Rate

We anticipate that there will be many patients eligible for this trial since this population does not have many treatment options, thus we expect 2-3 patients a month and accrual would be finished between 10-15 months.

12.5 Estimated Study Length

Since this is an aggressive disease we anticipate that within 1-year of follow-up of the last enrolled patient we will have sufficient data to perform all analyses. Thus, we anticipate that the length of this study will be between 22 and 27 months.

12.6 Interim Analysis Plan

As described above an interim analysis will take place after 15 patients have been enrolled and have sufficient follow-up to determine whether their progression free survival time is above 2.8 months or not.

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Appendix A – Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

ZIPCODE: ___ ___ ___ ___ ___

SEX: ☐ Male ☐ Female Ethnicity (choose one): ☐ Hispanic ☐Non-Hispanic

Race (choose all that apply): ☐ WHITE ☐BLACK ☐ ASIAN ☐ PACIFIC ISLANDER ☐ NATIVE AMERICAN

Height: ___ ___.___ inches Weight: ___ ___ ___.___lbs.(actual)

Surface Area: ___ ___.___m^2

Primary Diagnosis: _____

Stage at Diagnosis: _____

Date of Diagnosis: ___ ___ /___ ___/___ ___

ECOG Performance Status: ___ ___ ___

PROTOCOL INFORMATION

Date of Registration: ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent: ☐ YES ☐ NO

(consent must be signed prior to registration)

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by ORIS): ___ ___ ___ ___ ___ ___ ___ ___

Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday.

Completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-7136772 or registra@wakehealth.edu.

Appendix B – Subject Eligibility Checklist

IRB Protocol No.	**CCCWFU Protocol No.**
Study Title: A Phase II Study Evaluating Pemetrexed in ECOG Performance Status 3 Patients with Stage IV Non-Squamous Non-Small Cell Lung Cancer	
Principal Investigator: Stefan Grant, MD	

Inclusion Criteria (as outlined in study protocol)	**Criteria is met**	**Criteria is NOT met**	**Source Used to Confirm * (Please document dates and lab results)**
Histologically confirmed Stage IV non-squamous histology non-small cell lung cancer	☐	☐	
ECOG performance status of 3	☐	☐	
Sensitizing *EGFR, ALK* and *ROS-1* mutations are either negative or unknown	☐	☐	
Absolute neutrophil count ≥1,500/mcL	☐	☐	
Platelets ≥100,000/mcL	☐	☐	
Creatinine clearance ≥45 mL/min	☐	☐	
The effects of pemetrexed on the developing human fetus are unknown. For this reason and because Pregnancy Category D agents are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately	☐	☐	
Ability to understand and the willingness to sign an IRB-approved informed consent document	☐	☐	
Ability to understand and complete the EORTC QOL instruments	☐	☐	
>18 years of age	☐	☐	

Exclusion Criteria (as outlined in study protocol)	**Criteria NOT present**	**Criteria is present**	**Source Used to Confirm * (Please document dates and lab results)**
Chemotherapy for Stage IV non-small cell lung cancer or radiotherapy within 2 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 2 weeks earlier	☐	☐	
Tumors known to be positive for the sensitizing *EGFR* mutation, the sensitizing *ALK* fusion or the sensitizing *ROS-1* fusion	☐	☐	
Receiving any other investigational agents	☐	☐	
Symptomatic or recurrent brain metastases	☐	☐	
Patients whose pathology has squamous cell features unless there is an unequivocal determination of non-squamous pathology	☐	☐	
History of allergic reactions attributed to compounds of similar chemical or biologic composition to pemetrexed	☐	☐	
Pregnancy	☐	☐	

This subject is ☐ eligible / ☐ ineligible for participation in this study.

ORIS Assigned PID: _____

Signature of research professional confirming eligibility:_____ Date: _____

Signature of Treating Physician**: _____ Date: _____

**Principal Investigator signature can be obtained following registration if needed

Appendix C – Mandatory STRC SAE Reporting Guidelines

Mandatory Safety and Toxicity Review Committee (STRC; Previously CROC)
Serious Adverse Event (SAE) Notification Procedure

Mandatory STRC SAE Reporting Requirements – Revised 6/05/2012

This document describes STRC reporting and use of the electronic submission form that is submitted **for unexpected grade 4 and any grade 5 (death during protocol intervention) SAEs on CCCWFU Institutional interventional trial patients**. There are multiple entities that require reporting of SAEs. Each entity has different rules for what is reported, and how it is reported.

Rules used by other entities (Institutional Review Board (IRB), AdEERS, MedWatch, etc.) should NOT be used to evaluate whether an event should be reported to STRC. Only the rules for reporting described in this document should be considered.

As defined in the NCI summary IV reporting guidelines, **CCCWFU Institutional studies covered by these reporting requirements are defined as: In-house, internally reviewed trials, including those collaborative studies conducted with industry sponsorship in which the center is a primary contributor to the design, implementation, and monitoring of the trial, or participation in a multi-site trial initiated by an institutional investigator at another center.** Institutional trials are almost always authored by a researcher here at CCCWFU. Institutional protocols are labeled NCI Code="I" for Institutional on the protocol screen in ORIS. Cooperative group protocols are **not** considered Institutional, but Research Base trials **are** classified as Institutional.

The STRC is responsible for reviewing SAEs for CCCWFU Institutional studies, as defined above. STRC currently requires that unexpected grade 4 and all grade 5 SAEs on these trials be reported to them for review. All Clinical Research Management (CRM) staff members assisting a PI in documenting and reporting an SAE that qualifies for STRC reporting are responsible for informing a clinical member of the STRC by phone, followed by informing the entire committee via the required email notification.

THESE REPORTING REQUIREMENTS APPLY TO EVERYONE WORKING WITH CANCER CENTER INSTITUTIONAL PROTOCOLS.

What is considered an SAE under this mandatory procedure?
Any **unexpected grade 4** event not including routinely experienced events per protocol (e.g. myelosuppression) and **all grade 5 events** (death during protocol intervention) should be reported. The patient is considered "on-treatment" as defined in the protocol, which can extend days/weeks/months past the last date of actual protocol intervention.

Table 1: Summary of STRC Reporting Requirements for Institutional Pilot, Phase 1, Phase 2 and Phase 3 Interventional Trials						
	ADVERSE EVENT					
	Grade 1, Grade 2, Grade 3		**Grade 4**		**Grade 5**	
	Unexpected	**Expected**	**Unexpected**	**Expected**	**Unexpected**	**Expected**
Unrelated	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Unlikely	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Possible	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Probable	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Definite	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**

STRC reporting may not be appropriate for specific expected adverse events for protocols. In those situations the adverse events that will not require STRC reporting **must be specified in the text of the approved protocol.**

STRC notification responsibilities of the person handling the reporting/documenting of the SAE:

1. Make a phone call to the appropriate clinical member of the STRC as listed below (page if necessary)—see note 2 below
2. Submit the STRC Notification Form WITHIN 24 HOURS of first knowledge of the event. This form is found at either the ORIS main menu page or by going to http://ccc.wfubmc.edu/oris/strc.aspx.
   This will ensure that all persons that the event applies to will be notified; remember to file a copy of your confirmation. (Form instructions will walk you through the required fields, consult the help page for further instructions.)
3. Ensure that you document that the appropriate persons on the STRC has been contacted.
4. Follow up with/update the clinical member of STRC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

Elements needed to complete the electronic STRC form:

1. ORIS Patient ID (PID)
2. Name of STRC Clinician notified/Date/Time/Comments.
3. Grade of event.
4. Is this related to protocol intervention or treatment?
5. Is suspension of the protocol needed?
6. Is any change to consent or protocol needed?
7. Was the nature or severity of the event unexpected?
8. Date of the event.
9. Brief description of the event using approved CTC version terminology.

10. Date of last study dose before event.
11. Relevant tests/labs.
12. **Most importantly make sure that the Investigator assigns attribution to the reported event (grade) using the appropriate CTCAE version for the protocol.**

The Clinical Members of STRC to Notify by Phone or Page:

- **Bayard Powell, MD** – Director-at-Large, CCCWFU; Chair, PRC; Section Head, Hematology/Oncology. 6-7970 / 6-2701 / Pager 806-9308
- **Glenn Lesser, MD** – Hematology Oncology 6-9527 / 6-0256 / Pager 806-8397
- **Kathryn Greven, MD** – Vice Chair – Radiation Oncology. 3-3600 / Pager 806-8314
- **Marissa Howard-McNatt, MD** – General Surgery 6-0545 / 806-6438

Definition of Unavailable: As a general guideline if the first clinician that is contacted does not respond to the phone call or page within a reasonable amount of time, then initiate contact with their backup. Give the back-up a reasonable amount of time to respond to a phone call or page before contacting another member. This is a general guideline. You must use your best judgment as a clinical research professional given the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting your STRC notification form. The important criteria is that have taken reasonable steps to notify and document that you have initiated some type of contact to one or more of the clinical members of STRC.

STRC CLINICAN RESPONSIBILITY: It is the responsibility of the STRC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of STRC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made further communication directly with the investigator may be warranted. STRC reserves the right to agree with the investigator's assessment if STRC does not agree with the investigator STRC reserves the right to suspend the trial pending further investigation.

AMENDMENTS TO PREVIOUS REPORTS: If you are not able to supply all pertinent information with the initial submission, once the additional information is available **do not submit a new report**. Go to the original email that was received by STRC and others "reply to all" and entitle your email "**Amendment** for (list date of event and patient ID) this will avoid duplications of the same event. List the additional information which you are reporting.

Appendix D – Adverse Event Log

Adverse Event Description	Cycle of Toxicity Onset[A]	Start Date	Stop Date	AE Type	Grade (1-5) per CTC v. 4.0	Attribution	Dose Limiting Toxicity[A]	Serious	Action Taken	Treating Physician Initials/ Date
				☐Expected ☐Unexpected	☐Mild/1 ☐Moderate/2 ☐Severe/3 ☐Life-threatening/4 ☐Death/5	☐Related ☐Probably ☐Possible ☐Unlikely ☐Unrelated	☐Yes ☐No	☐No ☐Hospitalization ☐Disability ☐Birth Defect ☐Life-threatening ☐Death ☐Other: ________	☐None ☐Therapy Withheld ☐Therapy D/C ☐Therapy Adjusted ☐Other: ________ ☐N/A	
				☐Expected ☐Unexpected	☐Mild/1 ☐Moderate/2 ☐Severe/3 ☐Life-threatening/4 ☐Death/5	☐Related ☐Probably ☐Possible ☐Unlikely ☐Unrelated	☐Yes ☐No	☐No ☐Hospitalization ☐Disability ☐Birth Defect ☐Life-threatening ☐Death ☐Other: ________	☐None ☐Therapy Withheld ☐Therapy D/C ☐Therapy Adjusted ☐Other: ________ ☐N/A	
				☐Expected ☐Unexpected	☐Mild/1 ☐Moderate/2 ☐Severe/3 ☐Life-threatening/4 ☐Death/5	☐Related ☐Probably ☐Possible ☐Unlikely ☐Unrelated	☐Yes ☐No	☐No ☐Hospitalization ☐Disability ☐Birth Defect ☐Life-threatening ☐Death ☐Other: ________	☐None ☐Therapy Withheld ☐Therapy D/C ☐Therapy Adjusted ☐Other: ________ ☐N/A	

ORIS ID: _____ Date of Study Visit: __ __/__ __/__ __

Appendix E: Pre-Study

1. Medical history:_____
   _____
   _____
   _____
2. Concurrent medications:_____
   _____
   _____
   _____
3. Physical exam:_____
   _____
   _____
4. Vital signs:
   a. HR_____
   b. BP___/___
   c. RR____
   d. Temp____
5. CBC results:
   Date __ __ /__ __ / __ __

   a. WBC____
   b. RBC____
   c. Hemoglobin____
   d. Hematocrit____
   e. MCV____
   f. MCH____
   g. MCHC____
   h. RDW____
   i. Neutrophils____
   j. Lymphocytes____
   k. Monocytes____
   l. Eosinophils____
   m. Basophils____
   n. Platelets____
6. Serum chemistry results:
   Date __ __ /__ __ / __ __

   a. BUN____
   b. Creatinine____
   c. bilirubin____
   d. SGOT[AST] ____
   e. SGPT[ALT] ____
7. Documentation of negative pregnancy test for women of child-bearing potential?
   Yes ☐ No ☐ N/A ☐
   If N/A – Please give specific reason with dates:_____
8. QOL questionnaire administered
   a. EORTC QLQ-C30 Yes ☐ No ☐ Date: __ __ / __ __ / __ __
   b. EORTC QLQ-LC13 Yes ☐ No ☐ Date: __ __ / __ __ / __ __

ORIS ID: _____ Date of Study Visit: __ __/__ __/__ __

Cycle #:_____
Appendix F: Pre-Treatment

1. CBC results:
   Date __ __ /__ __ / __ __

   a. WBC____
   b. RBC____
   c. Hemoglobin____
   d. Hematocrit____
   e. MCV____
   f. MCH____
   g. MCHC____
   h. RDW____
   i. Neutrophils____
   j. Lymphocytes____
   k. Monocytes____
   l. Eosinophils____
   m. Basophils____
   n. Platelets____

2. Serum chemistry results:
   Date __ __ /__ __ / __ __

   a. BUN____
   b. Creatinine____
   c. bilirubin____
   d. SGOT[AST] ____
   e. SGPT[ALT] ____

3. (For 1st treatment only): Documentation of Folic Acid supplementation started at least 7 days before first dose of pemetrexed?
   Yes ☐ No ☐ NA (Not 1st cycle) ☐ Date started: __ __ / __ __ / __ __

4. (For 1st treatment only): Documentation of Vitamin B12 administration at least 7 days before first dose of pemetrexed?
   Yes ☐ No ☐ NA (Not 1st cycle) ☐ Date administered: __ __ / __ __ / __ __

5. Documentation of Corticosteroid administration the day before each dose of pemetrexed?
   Yes ☐ No ☐ Date administered: __ __ / __ __ / __ __

ORIS ID: _____ Date of Study Visit: __ __/__ __/__ __

Cycle #:_____
Appendix G: Day of Treatment

1. Vital signs:
   a. HR_____
   b. BP___/___
   c. RR____
   d. Temp____
   e. Height____
   f. Weight____
   g. Body Surface Area____

2. ECOG Performance Status_____

3. QOL questionnaire administered
   a. EORTC QLQ-C30 Yes ☐ No ☐
   b. EORTC QLQ-LC13 Yes ☐ No ☐

4. Documentation of Corticosteroid administration on the day of treatment with Pemetrexed?
   Yes ☐ No ☐ Date administered: __ __ / __ __ / __ __

5. Documentation of continued folic acid supplementation?
   Yes ☐ No☐

6. (Every 3 cycles): Documentation of Vitamin B12 administration?
   Yes ☐ No ☐ NA ☐ Date administered: __ __ / __ __ / __ __

ORIS ID: _____ Date of Study Visit: __ __/__ __/__ __

Cycle #:_____
Appendix H: Post-Treatment

1. CBC results: (For 1st treatment only)
   Date __ __ /__ __ / __ __

   a. WBC____
   b. RBC____
   c. Hemoglobin____
   d. Hematocrit____
   e. MCV____
   f. MCH____
   g. MCHC____
   h. RDW____
   i. Neutrophils____
   j. Lymphocytes____
   k. Monocytes____
   l. Eosinophils____
   m. Basophils____
   n. Platelets____

2. Documentation of Corticosteroid administration the day after treatment with Pemetrexed?
   Yes ☐ No ☐ Date administered: __ __ / __ __ / __ __

ORIS ID: _____ Date of Study Visit: __ __/__ __/__ __

Appendix I: Tumor Measurement Form

Instructions: Complete and submit this form as required by the protocol. Do not leave any entries blank. Enter -1 to indicate that an answer is unknown, unobtainable, not applicable or not done. Retain a copy for your records and submit original to the CCCWFU Data Management Center.

CCCWFU Study Number: _____ CCCWFU Patient ID: _____

Patient Name: _____ MRN: _____

WFUHS/Affiliate:

_____

(Specify)

LIST ALL TARGET AND NON-TARGET SITES TO BE USED FOR RESPONSE:

Date of Observation (mm/dd/yy)							
Cycle:							
TARGET LESIONS							
Response Status (CR, PR, SD, PD)							
List sites for response:	Means of Evaluation	Measurement	Measurement	Measurement	Measurement	Measurement	Measurement
1.							
2.							
3.							
4.							
5.							
6.							
7.							
8.							
9.							
10.							
Total sum of LD for all Target Lesions:							
NON-TARGET LESIONS							
Response Status (CR, Incomplete Response/SD, PD):							
List sites for response	Means of Evaluation	Measurement	Measurement	Measurement	Measurement	Measurement	Measurement
1.							
2.							
3.							
4.							
5.							
6.							
7.							
Observer Signature:							

ORIS ID: _____ Date of Study Visit: __ __/__ __/__ __

Appendix J: Response Criteria

Study Visit:
- ☐ Baseline
- ☐ Week 6 (± 1 week)
- ☐ Week 12 (± 1 week)
- ☐ Week 18 (± 1 week)
- ☐ Week 24 (± 1 week)
- ☐ Other visit: (please specify) _____

Evaluation of target lesions

☐ Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm

☐ Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD

☐ Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions (this may include the baseline sum). The sum must also demonstrate an absolute increase of at least 5 mm.

☐ Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

☐ Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

☐ Non-CR/Non-PD: Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.

☐ Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Although a clear progression of “non-target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair).

Treating Physician Signature: _____ Date: ___ ___ / ___ ___ / ___ ___

PI Signature: _____ Date: ___ ___ / ___ ___ / ___ ___

ORIS ID: _____ Date of Study Visit: __ __/__ __/__ __

BEST OVERALL Response Criteria

Study Visit:
- ☐ Baseline
- ☐ Week 6 (± 1 week)
- ☐ Week 12 (± 1 week)
- ☐ Week 18 (± 1 week)
- ☐ Week 24 (± 1 week)
- ☐ Other visit: (please specify) _____

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see section 9.4.1).

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

ORIS ID: _____ Date of Study Visit: __ __/__ __/__ __

☐ Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm

☐ Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD

☐ Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions (this may include the baseline sum). The sum must also demonstrate an absolute increase of at least 5 mm.

☐ Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment. In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

Confirmatory Measurement/Duration of Response

Confirmation: confirmatory scans should also be obtained 6 weeks following initial documentation of objective response.

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Treating Physician Signature: _____ Date: ___ ___ / ___ ___ / ___ ___

PI Signature: _____ Date: ___ ___ / ___ ___ / ___ ___

ORIS ID: _____ Date of Study Visit: __ __/__ __/__ __

Appendix K – Survival Data

ORIS Assigned PID:___ ___ ___ ___ ___ ___ ___ ___ ___

Visit Date: ____ / ____ / _____

Visit Interval:

_____ 6 Wks Post _____ 12 Wks Post _____ 18 Wks Post _____ 24 Wks Post

_____ 30 Wks Post _____ 36 Wks Post _____ 42 Wks Post _____ 48 Wks Post

_____ Other Wks Post

DATE OF LAST CONTACT: ____ / ____ / _____

DECEASED: Y____ N____

DATE OF DEATH: ____ / ____ / _____