A Phase II Study of Pemetrexed in Recurrent Cervical Adenocarcinomas

Protocol ID: CWG2014034 Pemetrexed - cervical

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I. Study Objectives

Primary Objective: Evaluate the antitumor efficacy, response rate, of pemetrexed in the treatment of recurrent cervical adenocarcinoma.

Secondary Objective: Evaluate PFS and OS for recurrent cervical adenocarcinomas treated with pemetrexed.

II. Background and Rationale

Cervical cancer is the third most common gynecologic malignancy occurring in the United States[1]. In the U.S. we can expect 12,340 cases of cervical cancer causing 4,030 deaths[1]. Cancer of the uterine cervix that has metastasized to or recurred at sites not amenable to treatment by surgery or radiation portends a grim prognosis. No potentially curative therapy yet exists. The focus of treatment has been palliation with chemotherapy.

Cervical adenocarcinomas (AC) have been found to have a poor prognosis compared to their squamous counterparts[2]. Cervical cancers have been increasing in absolute incidence and the US and have increase from 10%-12% of cervical cancers in the 1070s to 20% currently [1,2]. A study of early stage cervical cancers AC histology was associated with significantly decreased survival compared with SCC histology[2]. Multivariate analysis demonstrated AC histology to be an independent predictor of decreased survival in radiation therapy treated groups. They concluded that adenocarcinoma is an independent prognostic indicator of poor survival in early stage cervical cancer patients with intermediate and high risk factors, regardless of the type of adjuvant radiotherapy after radical hysterectomy. In a study of advanced stage cervical cancer 423 patients with stages IIB-IVA (141 ACA: 282 SCCA) were evaluated[3]. The overall complete responses (CR) between AC and SCCA were 86.5% and 94.7%, respectively (p=0.004). The 5-year overall survival rates of AC compared to SCCA were 59.9% and 61.7% respectively. They concluded that AC in locally advanced cervical cancer had poorer response rate from treatment and also used longer time to achieve CR than SCC.

Despite these observed disparities in survival between AC and squamous cell carcinomas (SCCA), cervical cancer patients with AC histology receive the same front-line treatment as those with SCC histology. Other cancer such as lung cancer have adopted different approached to the treatment of different histologies of cancer[4,5]. Pemetrexed has emerged in the treatment of nonsquamous NSCLC.[5]. Pemetrexed (LY231514, Eli Lilly and Company, Indianapolis, IN, USA) is an antifolate, antineoplastic agent that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication. In vitro studies have shown that pemetrexed inhibits thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase, all folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides[6]. Histology has emerged as a predictive factor for pemetrexed efficacy in non-small cell lung cancer (NSCLC)[5]. One study evaluated the differential efficacy of pemetrexed by histology in the second-line, first-line, and maintenance settings in the context of these three large phase III studies[5]. The analyses indicated the superior efficacy of pemetrexed in nonsquamous patients and a favorable safety profile compared with other standard treatment options. Thus, histology is predictive of the improved efficacy of pemetrexed in patients with nonsquamous NSCLC.

Pemetrexed has been evaluated in the treatment of recurrent cervical cancer in two Phase II trials[6,7]. Pemetrexed has shown modest activity in treatment of recurrent cervical cancers in these studies. Patients had a 15% response rate and up to 59% disease stabilization rate. Median progression free survival was 3.1 months and overall survival was 7.4 months. These studies

however, only had 22%(6)-25%(11) of patients having adenocarcinoma histology and response rate and survival were not segregated by histology. It is the objective of this study given the emergence and success of pemetrexed in the treatment of nonsquamous NSCLC to evaluate the efficacy of pemetrexed in the treatment of recurrent cervical adenocarcinomas.

III. Subject Eligibility

Inclusion criteria:

1. Patients must have had advanced or recurrent adenocarcinoma or adenosquamous cell carcinoma of the cervix with documented disease progression.
2. Patients must have had measurable disease defined as at least one lesion that could be accurately measured in at least one dimension, which must have been 20 mm when measured by conventional techniques including palpation, plain X-ray, CT, and MRI or 10 mm when measured by spiral CT.
3. 18 years of age or older
4. Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2 and a life expectancy >3 months.
5. Life expectancy $\geq$ 12 weeks
6. Participants must have measureable disease by RECIST criteria
7. Absolute neutrophil count $\geq$ 1500 mm^3, platelet count $\geq 100\times10^9$ L, hemoglobin $\geq$ 8.5 g/dL
8. Creatinine clearance $\geq$ 45 mL/min using the standard Cockcroft and Gault formula (below) or GFR measured by Tc99m-DPTA serum clearance method:
    a. Males: [140 - Age in years] × Actual Body Weight (kg) 72 × Serum Creatinine (mg/dL)
    b. Females: Estimated creatinine clearance for males × 0.85
9. Total bilirubin $\leq$ 2 mg/dL, AST/ALT $\leq$ 5 times the upper limit of normal range
10. At least 21 days from administration of chemotherapy
11. No remaining grade 2 or higher toxicity from prior cancer therapies unless judged to be clinically insignificant by the Principal Investigator
12. At least four (4) weeks from prior major surgery
13. Willingness to provide permission to access archived tumor samples and additional blood samples for evaluation of Foundation One Analysis where available Enterprise wide.
14. Women of child-bearing potential (i.e., women who are pre-menopausal or not surgically sterile) must be willing to use an acceptable contraceptive method (abstinence, oral contraceptive or double barrier method) for the duration of the study and for 30 days following the last dose of study drug, and must have a negative urine or serum pregnancy test within 2 weeks prior to beginning treatment on this trial.

Exclusion Criteria:

1. Uncontrolled cardiac disease, congestive heart failure, angina, arrhythmias or hypertension.
2. Myocardial infarction or unstable angina within 2 months of treatment.
3. Known human immunodeficiency virus (HIV) infection or chronic active Hepatitis B or C (patients are NOT required to be tested for the presence of such viruses prior to therapy on this protocol).
4. Active clinically serious infection > CTCAE (version 4.03) Grade 2.
5. Thrombotic or embolic events such as a cerebrovascular accident including transient ischemic attacks within the past 6 months.

6. Pulmonary hemorrhage/bleeding event ≥ CTCAE Grade 2 within 4 weeks of first dose of study drug.
7. Any other hemorrhage/bleeding event ≥ CTCAE Grade 3 within 4 weeks of first dose of study drug.
8. Serious non-healing wound, ulcer, or bone fracture.
9. Major surgery, open biopsy or significant traumatic injury within 4 weeks of first study drug.
10. Inability to complete informed consent process and adhere to the protocol treatment plan and follow-up requirements.
11. Concurrent severe illness such as active infection, or psychiatric illness/social situations that would limit safety and compliance with study requirements.

IV. Subject Registration and Documentation

A Study Inclusion/Exclusion Checklist will be completed for each subject and study eligibility will be verified by the Principal Investigator or Sub-investigator. Subjects must begin treatment within 28 days of all baseline studies. All original subject documents will be retained by the clinical research department.

Follow **Table 1. Schedule of Study Procedures** in the Appendix.

If a procedure or assessment has been completed as part of the standard routine care, and the procedure meets the protocol defined criteria and has been performed in the timeframe of the study, the test will not be required to be repeated, unless clinically indicated.

V. Treatment Protocols

Pemetrexed 500 mg/m2 will be administered on an outpatient basis on an every three week schedule. Pemetrexed will be administered as a 10 minutes intravenous (IV) infusion in (for 500-mg vial) 100 ml of saline via peripheral vein or central line on Day 1 of each 21 day cycle.

Premedication with dexamethasone will be per institutional guidelines.

On initiation of pemetrexed, on day one of first chemotherapy cycle, patients will begin taking folic acid at a dose of 350 to 600 mcg daily as well as receive an intramuscular injection of 1000 mcg of vitamin B12, with subsequent vitamin B12 injections given every 9 weeks while on study.

Dose Delay or Reduction

Prior to administration of a subsequent dose of pemetrexed, a subject must meet the following criteria:

- Any clinically significant pemetrexed-related toxicity must return to baseline or at least grade 1. Laboratory values should meet the parameters in the eligibility criteria unless specifically addressed in the dose delay/modification instructions in Table 2 or justification is provided by the investigator in the clinical chart.

In the event that the administration of pemetrexed was delayed for reasons of toxicity, the subject may receive subsequent administrations of pemetrexed at a reduced dose. The amount of dose reduction will be based on guidelines in Table 2 in the Appendix.

In the event of toxicity that necessitates a delay of more than 3 weeks, subjects may be removed from study.

Discontinuation of Protocol Treatment Administration

Pemetrexed will be discontinued in the event of any of the following:

- Clinically significant progressive disease after at least one (1) cycle of pemetrexed
- Unacceptable adverse event(s) considered secondary to pemetrexed despite appropriate therapy
- Delay of more than 4 weeks of pemetrexed administration
- Withdrawal of consent by the subject
- Lack of compliance by the subject
- Changes in the subject's medical condition that render further administration of pemetrexed unacceptable in the judgment of the Principal Investigator
- Termination of study by CTCA

Removal of Subject from Study

Subjects will be removed from further follow-up for any of the following reasons:

- Request by the subject to no longer be followed
- Completion of all study required follow-up and no plans for further administration of pemetrexed
- Death
- Termination of study by CTCA

Use of Anti-emetics and Supportive Care

The anti-emetic regimen will be dictated by NCCN guidelines for mild emetogenic chemotherapy. Steroids may be included in the anti-emetic regimen.

Supportive measures should be used as dictated by current standard of care at the CTCA.

Prohibited Concomitant Medications/Therapies

- Prophylactic use of growth factors such as G-CSF, GM-CSF, and erythropoietin unless treatment regimen meets the criteria for use (subjects receiving erythropoietin on a chronic basis at time of study entry may continue erythropoietin administration)
- Any other anti-cancer therapy including investigational therapies unless allowed at the time of study entry

VI. Study Drug

Pemetrexed is commercially available a listed on NCCN guidelines as an acceptable treatment for recurrent cervical cancer

VII. REGULATORY AND REPORTING REQUIREMENTS

The study will be conducted according to the principles of the Declaration of Helsinki (as Scotland 2000, as clarified in 2002), the International Conference on Harmonization Guidance on Good Clinical Practice and the requirements of all local regulatory authorities regarding the conduct of clinical trials and the protection of human subjects.

Adverse event reporting will be as per the current NCI criteria.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html).

VIII. Institutional Review Board (IRB)/Ethics Committee (EC)

Approval of this study will be obtained from an IRB/EC prior to enrolling subjects on study.

IX. Public Trial Registry

This study will be listed on a Public Trial Registry such as ClinicalTrials.gov shortly after receiving IRB approval.

X. Written Informed Consent

Consent forms must be in a language fully comprehensible to the prospective subject, otherwise the document must be translated into the subject's native language per institutional policy. Written, dated informed consent for the study must be obtained from all subjects before the start of any protocol specified procedures.

XI. Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Subject's individual identifying information will be kept as confidential as possible under local, state, and federal law. Data generated as a result of this study are to be available for inspection on request by the following:

- The Office for Human Research Protection (OHRP) in the U.S. Department of Health and Human Services
- Government agencies including the Food and Drug Administration (FDA)
- The sponsor's Human Research Protection Program (HRPP)
- Western Institutional Review Board (WIRB).

Western Regional Medical Center and Eastern Regional Medical Center may retain in its files copies of subject medical information required for auditing of case report forms (CRFs).

Individual subject identities will not be disclosed in any report or publication related to the study.

XII. Financial Disclosure

Investigators must be in compliance with the current FDA guidelines and regulations concerning financial disclosure.

XIII. Data Quality Assurance

Accurate, consistent, and reliable data will be ensured through the use Good Clinical Practices (GCP) guidelines regarding clinical data management practices and procedures.

All data will be collected using the data collection spreadsheet. Eastern Regional Medical Center will provide this collection spreadsheet to Dr. Farley when requested for data review.

XIV. Control of the Study Materials

The Inpatient Pharmacy will account for all standard of care medications. All medications are kept under lock in an inaccessible location while in storage. Since all drugs referenced in this protocol are standard of care medications, the standard hospital pharmacy record keeping will be completed.

XV. Adverse Events

Adverse Event (AE) Definition (using CTCAE version 4.03)

An AE is any untoward medical event that occurs to a subject following the start of study drug administration, whether or not the event is considered drug-related. Pre-existing conditions are not considered an AE unless the condition worsens by at least one grade following the start of study drug(s) administration.

Death due to disease progression occurring 31 days or more from the day of last study drug administration will not be reported as an AE or SAE.

Any drug related AE of grade 2 or higher should be followed for resolution until either 1) the start of subsequent anti-cancer therapy or 2) death.

Serious Adverse Event (SAE) Definition

An SAE is any AE that results in any of the following outcomes:

- Death
- A life-threatening experience
- An inpatient hospitalization or prolongation of an existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

An event that is not listed above but that requires intervention to prevent one of the outcomes listed above is also considered an SAE.

Elective hospitalizations that are not in response to an AE will not be considered an SAE.

Serious Adverse Event Reporting

All reportable SAEs must be reported to Western Regional Medical Center's Institutional Review Board (IRB) within 24 hours of the Investigator becoming aware of the SAE.

To report an SAE, sites will complete the IRB's required form and submit the form to Western Regional Medical Center's IRB via email, fax, or online portal.

All reportable SAEs will need to be submitted to HRPP as well.

Site must report all reportable SAEs that occur within 30 days after the last dose of pemetrexed treatment while on this study or until the subject receives additional cancer therapy.

Relationship to Pemetrexed

The relationship of an AE or SAE to pemetrexed will be classified using the following four (4) categories:

- Definitely related
- Likely related
- Unlikely related
- Definitely not related

XVI. Protocol Deviations

All protocol deviations will be noted in the subjects chart and also on WIRB's Promptly Reportable Information form. The site's PI or Sub-I (if PI is not available) will review the Promptly Reportable Information form to determine whether the deviation is reportable to the IRB. If the deviation is not reportable, he/she will need to ensure the appropriate box is checked and provide an explanation as to why the event is not reportable. All reportable deviations will need to be submitted to WIRB, Dr. Farley, and HRPP.

XVII. Statistical And Analytical Considerations

Determination of Sample Size

The sample size was based on the primary efficacy variable, tumor response. The historical rate for the tumor response is assumed to be 15%. Using a one-sided significance level of 0.05, power of 80%, and a tumor response rate of 40% for the pemetrexed treated patients, it was determined that a total of 30 patients would need to be enrolled in the study. The study may be stopped early for futility if no objective responses are seen before 8 patients have entered.

Analysis Datasets

The definitions of the analysis datasets are as follows:

- The Evaluable for Safety Population will consist of all subjects who receive at least one dose of pemetrexed
- The Evaluable for Efficacy Population will consist of all subjects who receive at least one dose of pemetrexed and who have had at least one post-baseline disease assessment

General Statistical Considerations

Statistical summaries for quantitative variables will include the sample size, mean, median, standard deviation, minimum, and maximum. For categorical variables summaries will include the number and percent of patients in each category observed. Unless otherwise noted, statistical significance will be declared if the two-sided p-value is ≤ 0.05.

Subject Disposition

Data tabulations will summarize the following subject numbers:

- Enrolled
- Received treatment
- Evaluable for safety and efficacy
- Who violate the protocol
- Who complete the protocol
- Who withdraw because of 1) adverse event(s), 2) disease progression, 3) physician's recommendation, or 4) withdrawal of consent

Subject Characteristics

Demographic characteristics of subjects will be summarized using descriptive statistics:

- Age
- Sex
- Ethnicity
- Performance status
- Prior therapies
- Tumor type

Efficacy Analysis

The evaluable for efficacy population will be used for efficacy analysis. Efficacy will be determined for each subject in the efficacy population for each of the following 4 outcomes:

The Primary Efficacy Variable

- Tumor Response: Subjects will be assigned one of the following categories based on the response criteria outlined in RECIST 1.1 as appropriate for each tumor type: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease. An objective response will be defined as either a CR or PR.

The Secondary Efficacy Variables

- Time to Response will be determined for subjects with an objective response only. Time to Response will be defined as the period of time from the date of first study drug administration until the first objective documentation of response (CR or PR).
- Duration of Response will be determined for subjects with an objective response only. Duration of Response will be defined as the period of time from the date of first objective response to the date of progression.
- Progression-Free Survival is defined as the period of time from the date of first study drug administration to the date that the subject is determined to have progressive disease or death due to any cause.

Criteria response evaluation and overall response rates will be summarized by proportions together with exact binomial 95% confidence intervals for each dose group. The tumor response rate for the pemetrexed treated patients will be compared with the historical rate of 15% using a one-sided z-test. Durations (time to response, duration of response, and progression-free survival) will be summarized by Kaplan- Meier methods. Median survival with 95% confidence intervals will be calculated and survival graphs will be presented for all Kaplan-Meier analyses.

Safety Analysis

All subjects who receive any amount of pemetrexed (Safety Population) will be included in the final summaries and listings of safety data.

Detailed information collected for each AE will include: description of the event, MedDRA coding including System Organ Class and Preferred Term, duration, whether the AE was serious, relationship to study drug, action taken, clinical outcome, and whether or not it was a DLT. Severity of the AEs will be graded according to the CTCAE version 4.03. Emphasis in the analysis will be placed on AEs classified as dose limiting. Frequencies of subjects experiencing at least one AE will be displayed by body system and preferred term according to MedDRA terminology. Summary

tables will present the number of subjects observed with AEs and corresponding percentages. The denominator used to calculate incidence percentages consists of subjects receiving at least one dose of study drug for each dose group. Within each table, the AEs will be categorized by MedDRA body system and preferred term. Additional subcategories will be based on event severity and relationship to study drug.

Deaths and other SAEs will be tabulated as well as described in detail.

Vital signs, including the change from baseline, will be summarized using descriptive statistics. The statistical significance of the mean change from baseline will be determined using a paired t-test.

Summary tables will be prepared to examine the distribution of laboratory measures over time. Shift tables may be provided to examine the distribution of laboratory toxicities.

XVIII. Specimen Collection

Mutation Analysis

Testing for mutations will be conducted on tumor tissue. Tissue biopsy is optional. If subjects do decide to have a tissue biopsy, they will not be charged for the procedure or the cost of the genetic testing. In addition, if the subjects have already had genetic testing done on their sample we can use the results from that test.

Specimens will be sent for Genetic Testing analysis for patients who respond to pemetrexed (patients are on treatment for at least 6 months).

XIX. Financial Responsibility

The medication pemetrexed and other standard chemotherapy agents are commercially available. The costs of treating cancer with these medications and any other treatments received, and the cost of treating any side effects from such treatments will be billed to the patient's health plan or insurance company. If medical care is needed as a result of injury while being in this study, medical care will be provided to the patient and the insurance company will be billed.

XX. References

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4. Patel JD, Socinski MA, Garon EB, et al: PointBreak: A Randomized Phase III Study of Pemetrexed Plus Carboplatin and Bevacizumab Followed by Maintenance Pemetrexed and Bevacizumab Versus Paclitaxel Plus Carboplatin and Bevacizumab Followed by Maintenance Bevacizumab in Patients With Stage IIIB or IV Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol, 2013

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6. Miller DS, Blessing JA, Bodurka DC, et al: Evaluation of pemetrexed (Alimta, LY231514) as second line chemotherapy in persistent or recurrent carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol 110:65-70, 2008

7. Lorusso D, Ferrandina G, Pignata S, et al: Evaluation of pemetrexed (Alimta, LY231514) as second-line chemotherapy in persistent or recurrent carcinoma of the cervix: the CERVIX 1 study of the MITO (Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies) Group. Ann Oncol 21:61-6, 2010

Appendix

Table 1. Schedule of Study Procedures

Parameter	Baseline	Cycle 1	Cycle 2	Cycle 3	Cycles 4+	Follow-up
Day of cycle	-28 to 1	1	1	1	1	
Informed consent	X					
Complete medical history, height	X					
Complete physical exam	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X
Vital signs (BP, HR, RR, temp) and weight	X	X	X	X	X	X
Review con meds, AEs	X	X	X	X	X	X
Disease status (baseline and prior to C3, C5, C7, C9, etc.)	X			X	(X)	(X)
Urinalysis	X					
Pregnancy test	(X)					
CBC with differential	X	X	X	X	X	X
Serum chemistries	X	X	X	X	X	X
Genetic Testing mutational analysis*						(X)
Pemetrexed administration		X	X	X	X	
Survival assessment						X

General

- Blood draws and vital signs are performed prior to dosing of pemetrexed
- Study visits and procedures may occur +/- 7 days of the day given unless otherwise indicated
- X – required event

- (X) – as indicated

Follow-up – Follow-up visit should occur 30 days (+/- 7 days) after last dose of pemetrexed

Cycle 2+ – Cycle 2 and subsequent cycles will start +/- 7 days of day 22 of the prior Cycle.

Disease status –All subjects should have their disease status monitored with at least a chest, abdominal, and pelvic CT and any other scans as appropriate for their disease. Scans completed within 28 days of start of treatment do not need to be repeated (for screening). Scans are performed at baseline and prior to Cycle 3, Cycle 5, Cycle 7, Cycle 9, etc.

CBC with differential – WBC, ANC, RBC, HGB, HCT, platelets, MCV, and differential. If completed within 3 days prior to start of C1D1 – no need to repeat

Serum chemistries – Sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, AST, ALT, total bilirubin, alkaline phosphatase, total protein, albumin. If completed within 3 days prior to start of C1D1 – no need to repeat.

***Genetic Analysis** – If subject consents to Genetic Analysis, Genetic Testing mutation status collected from tumor tissue of patients remaining on pemetrexed without progression for at least 6 months.

Table 2

Hematologic dose modifications for pemetrexed

Absolute Neutrophil Count (ANC) $\geq$1000/mm^3 and platelet count (PC) $\geq$100,000/mm^3	Maintain 100% of full dose
ANC <500/mm^3 and platelet count $\geq$ 50,000/mm^3	Administer 75% of full dose
Platelet count <50,000/mm^3 without bleeding regardless of ANC nadir	Administer 75% of full dose
Platelet count <50,000/mm^3 with bleeding (CTC G2) regardless of ANC nadir	Administer 50% of full dose

Non hematologic dose modifications for pemetrexed

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