Vitamin D, Leptin, Vitamin D Receptor Polymorphism, and Treatment-Related Morbidity in Ovarian, Primary Peritoneal and Fallopian Tube Cancer

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Investigational Product: Cholecalciferol (Vitamin D3, a fat soluble vitamin involved in many biologic processes).

Protocol Number: OU201612LH- Vitamin D Ovarian

This clinical trial will be conducted in compliance with the protocol, International Conference on Harmonization Good clinical Practice Guidelines E6 (ICH-GCP), other applicable regulatory requirements and with the Declaration of Helsinki and its amendments.

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1.0Hypothesis and Objectives

1.1 Specific hypotheses:

1.1.1Low serum 25(OH)D will be associated with increased treatment-related morbidity.

1.1.2 Repletion of 25(OH)D will be associated with an increase towards normal of serum leptin levels.

1.1.3 VDR *FokI* SNP polymorphism will be associated with lower circulating levels of 25(OH)D.

1.2 Objective(s)

1.2.1 Primary objective:

1.2.1.1 To assess treatment-related morbidity (including 30-day postoperative surgical morbidity and chemotherapy-related morbidity) and 1-year disease-free survival in patients with deficient serum 25(OH)D levels at the time of ovarian, primary peritoneal, or fallopian tube cancer diagnosis who did and did not receive vitamin D repletion.

1.2.2 Secondary objectives:

1.2.2.1 To describe serum 25(OH)D levels, serum leptin levels, and VDR *Fok*I SNP status among newly diagnosed ovarian, primary peritoneal, or fallopian tube cancer patients.

1.2.2.2 To determine the proportion of patients with ovarian, primary peritoneal, or fallopian tube cancer that have deficient vitamin D at diagnosis and have normal serum 25(OH)D after oral vitamin D supplementation during primary therapy.

1.2.2.3To identify potential relationships between serum 25(OH)D and serum leptin levels when controlling for BMI.

1.2.2.4To evaluate change of serum leptin levels with repletion of 25(OH)D in patients with low levels at the time of ovarian primary peritoneal, or fallopian tube cancer diagnosis.

1.3 Translational Research Objectives:

1.3.1 To evaluate VDR *FokI* SNP status relationship with serum 25(OH)D levels and treatment-related morbidity and cancer outcomes.

2.0Background Information. Rationale for selected approach and

trial design.

2.1 Overview of Ovarian Cancer

Ovarian cancer (including primary peritoneal and fallopian tube cancer) is the fifth leading cause of cancer-related deaths in women in the United States and the most lethal gynecologic cancer [1]. It was estimated that in 2016, more than 22,000 women will be diagnosed with ovarian cancer leading to more than 14,000 deaths [2]. The median age of diagnosis of women with ovarian cancer is 63, with increased comorbidities leading to treatment-related toxicities in older women [3]. The inability to receive adjuvant chemotherapy negatively impacts overall survival (OS). Number of cycles of chemotherapy also appears to be important. For example, elderly women who receive more than three chemotherapy cycles have been found to have improved OS [3]. Further study to identify factors to improve treatment tolerability and reduce treatment-related morbidity in ovarian cancer patients are warranted.

2.2 Vitamin D Deficiency in Cancer

Vitamin D has been well-studied due to its role in many important cellular pathways. Laboratory and observational studies suggest that it plays a role in many diseases such as autoimmune diseases, cardiovascular disease, diabetes, cancer risk and cancer survival. The correlation of low serum 25(OH)D with elevated risk for malignancy has been best studied in colorectal cancer [4]. Decreased levels of serum 25(OH)D have been correlated with increased risk of breast cancer in postmenopausal women. [5]. Women receiving chemotherapy and anti-hormonal therapy for breast cancer experience treatment-induced bone loss due to premature ovarian failure or direct cytotoxic effects of chemotherapy. This causes an increase in the osteoporosis and skeletal morbidity risk[6]. Similar effects can be estimated in ovarian cancer patients given that standard treatment requires surgical menopause as well as cytotoxic therapy in the majority of patients.

The majority of studies pertaining to vitamin D and ovarian cancer concern the association of low serum 25(OH)D with increased cancer risk. Limited study has been performed investigating the correlation of serum vitamin D and ovarian cancer prognosis or treatment-related morbidity. A study performed in Australia investigated serum 25(OH)D levels at the time of diagnosis of ovarian cancer in 670 women. They noted a significant association between higher circulating 25(OH)D concentrations and longer survival in women with ovarian cancer when adjusting for other clinical predictors of

survival [7]. Similarly, Walentowicz-Sadlecka et al. reported low serum 25(OH)D concentrations in women with ovarian cancer undergoing primary cytoreductive surgery to be associated with lower overall survival[8]. The impact of repletion of vitamin D in ovarian, primary peritoneal, or fallopian tube cancer patients has yet to be determined.

Findings from an unpublished study performed at the University of Oklahoma have shown an inverse correlation between low levels of serum vitamin D and treatment-related morbidity in women aged 65 years and older with ovarian cancer. More specifically, when comparing median serum 25(OH)D levels between patients who experienced chemotherapy delay ≥7days versus those who did not, lower mean 25(OH)D levels were significantly associated with chemotherapy delays (23.6 ng/dL, n=28 no delay versus 14.6 ng/dL, n=30 delay, p=.0112). (Figure 1)[9].

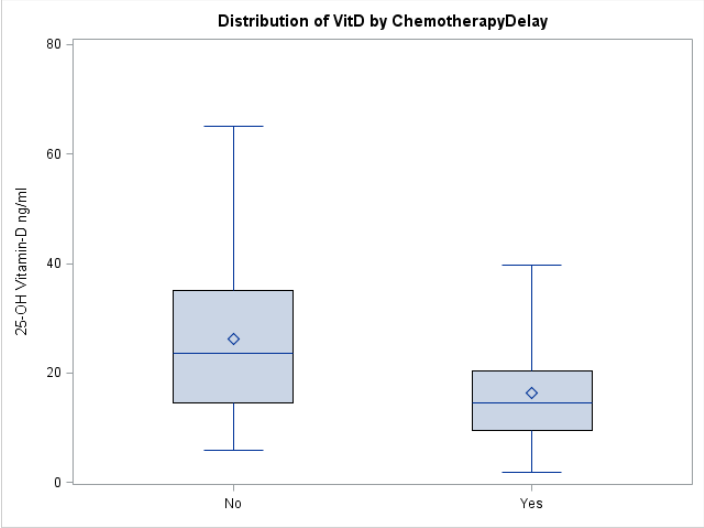


Figure 1. Serum 25(OH)D levels by chemotherapy delay status.
Delay (≥7 days) n=30, median 25(OH)D 14.6 ng/dL. No delay n=28, median 25(OH)D 23.6 ng/dL (p=0.0112).

To date, there have been no prospective or randomized controlled trials evaluating serum 25(OH)D and treatment-related risks in cancer patients. No data exists regarding the effect of repletion of vitamin D and prevention of ovarian cancer treatment-related morbidity. As previously mentioned, number of cycles of chemotherapy received appears to correlate with improved OS in women with ovarian cancer [3]. Given the findings of the above-mentioned study correlating low serum 25(OH)D levels and chemotherapy

delay, vitamin D represents a potentially modifiable factor that could improve treatment tolerance among women with ovarian cancer.

2.3 Leptin and Ovarian Cancer

Leptin is an adipokine that appears to stimulate growth of cancer cells while decreasing apoptosis [10]. Serum leptin levels have also been linked to elevated levels of pro-inflammatory cytokines in malignancy [11]. Retrospective analysis of data from NHANES III revealed an inverse relationship between serum leptin levels and cancer death in women[12]. In ovarian cancer, there is some data to show that lower leptin levels may be associated with increased initial tumor burden and subsequent increases in leptin may correlate with complete cytoreduction [13]. Further study is needed to better understand the role of leptin in ovarian cancer. Vitamin D receptors are involved in production of adipokines such as leptin; however, the response of serum leptin levels to repletion of vitamin D remains unclear [1]. Conflicting data exists between meta-analyses investigating changes in leptin following correction of vitamin D levels in humans [1]. This study aims to assess for potential relationships between serum 25(OH)D levels and leptin levels, including any changes that may occur during repletion of 25(OH)D.

Women with treatment-related morbidity often experience delays in treatment, changes in chemotherapeutic regimens and surgical or chemotherapy-related complications requiring hospitalization. Identifying modifiable risk factors among patients with ovarian cancer (including fallopian tube and primary peritoneal cancer) that can prevent treatment-related morbidity represents an important goal in the care of these women.

Safety:

Cholecalciferol is a generally safe and well-tolerated medication. Repletion of vitamin D is considered standard of care and will be undertaken utilizing current available guidelines[14].

Translational Research Background:

Vitamin D receptors (VDR) are extensively expressed in epithelial cells of both normal and tumor ovarian tissue. VDR functions as a transcriptional regulatory factor involved in decreasing cell proliferation and inhibition of apoptosis [15]. As such, this may carry implications for ovarian cancer tumorigenesis. The VDR rs2228570 (*FokI*) single nucleotide polymorphism (SNP) represents the most common and best studied SNP in the VDR gene leading to an alteration of VDR protein structure and decreased transcriptional activity as compared to the wild type [15, 16]. Meta-analyses of several small studies have associated *FokI* SNP with increased risk of ovarian cancer, [15, 16]. One such study performed a meta-analysis with pooled odds ratios and 95% confidence intervals to assess the associations between VDR polymorphisms (*Cdx*-2, *Fok*I, *Bsm*I, *Apa*I, and *Taq*I) and risk for breast and ovarian cancer. Only the *Fok*I SNP was found to be associated with increased risk of breast and ovarian cancers[17]. Currently, no data exists to correlate VDR SNP polymorphisms to circulating 25(OH)D levels at the time of diagnosis of ovarian cancer. There is limited data to suggest that in both prostate cancer and colorectal cancer, the homozygous VDR *FokI* SNP (prostate) and homozygous VDR *TaqI* SNP (colorectal) are associated both with increased risk of the respective malignancy and lower circulating 25(OH)D levels [18, 19].

3.0 Study Design

This study will contain 2 cohorts, those with normal serum 25(OH)D and those with low serum 25(OH)D at enrollment. The study will take place in women with ovarian, primary peritoneal, and fallopian tube cancer, subsequently referred to as ovarian cancer in this document due to the overlap in disease and treatment.

Patients who have given written consent to enroll in the study will have a serum 25(OH)D drawn in a gold-topped tube (1 to 5mL volume) at time of enrollment and prior to initiation of treatment for their cancer. Serum 25(OH)D levels will be analyzed per laboratory protocol in our University CLIA certified lab. Blood will also be drawn for analysis of serum leptin levels and VDR *FokI* SNP genotype. A purple-topped tube (7 to 10mL volume) and red-topped tube will be collected from prospective patients. The Stephenson Cancer Center Biospecimen Bank will process the red and purple-topped tube into plasma and Buffycoats, label them with a de-identified code and transfer them to Dr. Benbrook's lab. The plasma

will be used to evaluate leptin by ELISA and the Buffycoats used to evaluate the *FokI* SNP using PCR. Retrospective serum specimens will be used to measure leptin.

Patients with low serum vitamin D levels, defined as <20 ng/mL, will be provided a supply of cholecalciferol (vitamin D3), 50,000 IU weekly for 8 weeks that will be dispensed in the Stephenson Cancer Center outpatient pharmacy in order to standardize therapy. They will then be provided with a prescription for 2,000 IU of cholecalciferol (vitamin D3) daily following completion of 8 weeks of therapy based on current Endocrine Society guidelines in agreement with U.S. Preventive Services Task Force recommendations [14]. Treatment with cholecalciferol will not impact initiation of treatment for ovarian cancer. Compliance with cholecalciferol repletion will be assessed with medication reconciliation at every gynecologic oncology visit.
Vitamin D therapy will be stopped in any patient developing the above exclusion criteria of GFR <30, inability to tolerate oral medications, malabsorption syndrome, or primary hyperparathyroidism. In the unlikely event of evidence of vitamin D toxicity, treatment with vitamin D will be stopped. The Stephenson Cancer Center laboratory defines vitamin D toxicity as levels >100 ng/mL. Based on IOM literature, it would highly unlikely for individuals to experience vitamin D toxicity at the prescribed doses. Symptoms of vitamin D intoxication are caused by the resultant hypercalcemia and include anorexia, weight loss, polyuria, arrhythmias, fatigue, and soft tissue calcifications [20]. Patients experiencing these symptoms would receive testing for serum calcium and vitamin D. Vitamin D treatment would be stopped for any value indicative of toxicity.

Demographic, clinical, and disease characteristics and outcomes will be collected from all patients prospectively. The patient's treatment course information will also be collected prospectively, but will not be dictated by this study. Serum 25(OH)D and leptin levels will be collected again at the completion of primary therapy, 6 months after the completion of primary therapy, and at the time of disease recurrence. If disease recurrence occurs prior to 6 months after completion of primary therapy, this time point will be omitted. If disease recurrence does not occur prior to 1 year, serum 25(OH)D and leptin levels will be drawn at the time of the 1-year surveillance visit. If patients remain vitamin D deficient at any of these follow-up time points, they will be referred to an endocrinologist or primary care physician for further work-up and treatment of their vitamin D deficiency. Patients who are vitamin D deficient at completion of therapy but were not previously on supplement will be

referred to a primary care physician for further management. Data collection will continue for 1 year or until the time of disease recurrence. Patient's will no longer have data collected after obtaining serum 25(OH)D and leptin levels at the time of recurrence.
A retrospective cohort of women with low serum 25(OH)D that did not receive repletion of vitamin D will be used as a control group for comparison. This control group will be identified from available tumor bank serum samples including those previously identified in the above-mentioned unpublished study at the University of Oklahoma. These samples will be used to evaluate serum levels of 25(OH)D, leptin, and evaluate Buffycoats VDR SNP polymorphism for *FokI*.

Cohort	Therapy
1 (Normal 25(OH)D)	None
2 (Low 25(OH)D) (<20ng/mL)	50,000 IU cholecalciferol weekly for 8 weeks followed by 2,000 IU daily thereafter

4.0Study Population

4.1 Eligible Patients

4.1.1The study population will consist of women with newly diagnosed ovarian, fallopian tube, or primary peritoneal cancer and no previous treatment.

4.1.2A retrospective cohort of women with ovarian, fallopian tube, or primary peritoneal cancer and low serum 25(OH)D that did not receive repletion identified from available tumor bank serum samples.

4.2 Inclusion Criteria (Prospective patients)

4.2.1 Patients must have a histologic diagnosis of ovarian, fallopian tube, or primary peritoneal carcinoma per pre-treatment biopsies by laparoscopy, or interventional radiology, paracentesis, or CT guided core biopsy. Histologic documentation of the original primary tumor is required via the pathology report.

4.2.2 Patients must have adequate:

4.2.2.1 Renal function: Glomerular Filtration Rate (GFR) $\geq$ 30.

4.2.2.2 Gastrointestinal absorption: No underlying malabsorption syndrome (i.e. inflammatory bowel disease, celiac disease).

4.2.2.3 Ability to tolerate oral medication.

4.2.3 Patients taking vitamin D at the time of enrollment without a diagnosis of vitamin D deficiency.

4.2.4 Patients of childbearing potential must have a negative pregnancy test prior to the study entry and be practicing an effective form of contraception. If applicable, patients must discontinue breastfeeding prior to study entry.

4.2.5 Patients must have signed an IRB-approved informed consent and authorization permitting release of personal health information.

4.2.6 Patients must be at least 18 years old.

4.3 Ineligible Patients

4.3.1 Patients with a known pre-existing diagnosis of vitamin D deficiency.

4.3.2 Patients with renal disease and a GFR <30.

4.3.3 Patients with primary hyperparathyroidism.

4.3.4Patients with other invasive malignancies, with the exception of nonmelanoma skin cancer. Patients with concomitant endometrial cancer diagnosed at the time of their ovarian cancer are allowed to participate if the endometrial cancer is FIGO stage IB or less.

4.3.10 Patients of childbearing potential, not practicing adequate contraception, patients who are pregnant, or patients who are breastfeeding are not eligible for this trial.

4.4 Inclusion of Minorities

Potential subjects shall not be excluded from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt shall be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire ovarian, fallopian tube and peritoneal primary cancer population treated by participating institutions.

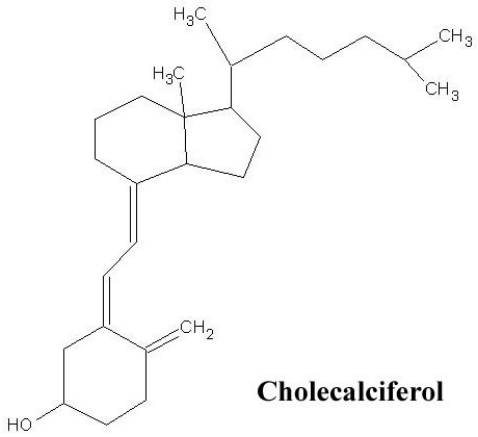
5.0Study Modalities

5.1 Cholecalciferol (vitamin D3)

Refer to the pharmacologic information for cholecalciferol. See http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6606#pro for the most complete and current information on the following:

5.1.1 Formulations

- Cholecalciferol (Vitamin D3) 50,000 IU is supplied as an oral capsule. It is a vitamin D analog. Cholecalciferol is a provitamin (25(OH)D) with an active metabolite 1,25-dihydroxyvitamin D (calcitriol). The drug is initiatlly hydroxylated hepatically and then converted into the active metabolite renally.



Cholecalciferol

5.1.2 Storage

Unopened vials of cholecalciferol are stable for the life indicated on the package stored at 15°C to 30°C (59°F to 86°F).

Adverse Effects: Consult the package inserts for the most current and complete information. No adverse reactions currently listed in manufacturer's labeling. According to the IOM, vitamin D toxicosis is highly unlikely at the prescribed doses. Symptoms of vitamin D toxicosis are caused by the resultant hypercalcemia and include: anorexia, weight loss, polyuria, arrhythmias, fatigue, and soft tissue calcifications [15].

Consult the American Hospital Formulary Service Drug Information guide,

Facts and Comparisons, or the package insert for additional information.

5.1.3 Preparation and dosing

The dosage of cholecalciferol is based on current Endocrine Society guidelines in agreement with U.S. Preventive Services Task Force recommendations [14].

5.1.4Drug ordering and distribution

Cholecalciferol will be ordered by and distributed from the outpatient pharmacy at the Stephenson Cancer Center. Study drugs will be kept in a locked space, physically separated from standard clinic or office drug supplies.

5.1.5 **Drug Accountability:**

All study drug received, dispensed and returned must be accounted for in a Drug Accountability log, including patient number and initials, date study drug dispensed, amount dispensed, amount returned (if applicable) and amount remaining in stock. The institution must maintain an accurate inventory log of all study drug received and used. Pill counts at each patient visit will be utilized to document compliance with oral medication.

6.0 Study Procedures and Treatment Plan

All necessary site-specific regulatory documents, including the PI biographical sketch, IRB approval, and IRB approved informed consent, must have been submitted to the IRB and the Stephenson Cancer Center CTO prior to beginning patient enrollment. The University of Oklahoma will submit the necessary documents to obtain national clinical trial listing

6.1 Patient Enrollment

When a suitable candidate has been obtained for protocol entry, the following steps should be taken:

6.1.1 An IRB-approved informed consent form and authorization permitting the release of personal health information must be signed by the patient or guardian. Current FDA, NCI and institutional regulations concerning informed consent will be followed.

6.1.2 All eligibility requirements indicated in Section 4.0 must be satisfied.

6.1.3 A completed, signed and dated, Patient Registration form should be filled out by the clinical study site (OU) and placed in the regulatory binder

6.1.4 Upon receipt of the signed and dated form from the clinical trials office at OU SCC, the clinical study site will enter the patient's name and study number in their Enrollment Log to verify the patient's entry into the study and additional study procedures may commence.

6.2 Treatment Plan

6.2.1 Screening visits will be conducted within 21 days prior to study drug administration.

Patients will undergo baseline evaluations prior to dosing.

6.2.2 This study will evaluate the administration of cholecaciferol to vitamin D deficient patients with ovarian cancer in relation to ability to replete 25(OH)D levels, treatment-related morbidity, and serum leptin levels.

6.3 Sequence and timing of drug administration

Vitamin D deficient patients will receive oral cholecalciferol 50,000 IU weekly starting at the time of diagnosis of vitamin D deficiency. Initiation of cholecalciferol therapy will not delay initiation of standard treatment for ovarian cancer, nor will it preclude enrollment in other clinical trials. Therapeutic dosing at 50,000 IU will continue weekly for a total of 8 weeks. Patients will then be given a prescription for maintenance dosing 2,000 IU cholecalciferol thereafter.

7.0 Dose Limiting Toxicities

As described above, vitamin D toxicosis is extremely rare at the prescribed doses. In the unlikely event of evidence of vitamin D toxicity, treatment with vitamin D will be stopped. The Stephenson Cancer Center laboratory defines vitamin D toxicity as levels >100 ng/mL.

8.0Study Parameters

8.1 Observations and Tests

The following observations and tests are to be performed and recorded on the appropriate form(s).

Observation and Tests	Screening	At each treatment visit	Completion of primary therapy	6 months after therapy completion	Time of recurrence or 1 year surveillance (if no recurrence)
History & Physical	1	X	X	X	X
Vital Signs and Weight	1				
Toxicity assessment	1	X	X	X	
Serum 25(OH)D	1		X	X	X
Serum Leptin	1		X	X	X

Serum Cr (and GFR)	1				
Red top and Purple topped blood tubes (for VDR SNP analysis)	1				
Serum pregnancy test (if potential exists)	1				

1. Must be obtained within 21 days prior to initiating protocol therapy.

All other blood draws (end of treatment, 6 months after therapy completion, Time of recurrence or 1 year surveillance) must occur within 8 weeks of expected date.

8.2 Translational Research

Requirements 8.2.1 Specimen

Requirements

A red topped and a purple topped tube of blood will be drawn from the patient at the time of screening.

The patient must give permission for her specimens to be used for this

mandatory translational research component. The participating institution is required to submit the patient's specimens as outlined below.

9.0 Evaluation Criteria

9.1.1 Response Criteria

9.1.1.1 Evaluation of Biomarkers

Clinical Response

If serum 25(OH)D is initially below the lower normal limit, it must normalize (>20ng/mL) for a patient to be considered experiencing a complete response to repletion.

9.1.2 Progression-Free Survival:

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

9.1.3 Survival:

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

10.0Duration of Study

10.1 Patients with serum 25(OH)D <20ng/mL will receive cholecalciferol 50,000 IU weekly for 8 weeks.

10.2 Following repletion, patients will receive a prescription for 2,000 IU cholecalciferol as maintenance. Per Endocrine Society guidelines, patients should continue maintenance cholecalciferol indefinitely.

11.0Study Monitoring and Safety Reporting Procedures

11.1 Adverse Event Reporting

11.1.1 Definitions (per 21 CFR 312.32(a)):

Adverse event: "*Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.*" Life-threatening adverse event or life-threatening suspected adverse reaction: "*An adverse event or suspected adverse reaction is considered "lifethreatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.*" Serious adverse event or serious suspected adverse reaction: "*An adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:*

Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse."

Suspected adverse reaction: *"Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser*

degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug."

Unexpected adverse event or unexpected suspected adverse reaction. "*An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.*"

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 CTCA version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

Furthermore, this study will fall under the purview of the Stephenson Cancer Center Data Safety Monitoring Committee (DSMC).

11.1.2 Reporting Expedited Adverse Events

In compliance with FDA regulations, as contained in 21 CFR 312.64, AEs must be reported to the Stephenson Cancer Center Data Safety Monitoring Committee by the investigator.

All serious and unexpected suspected adverse reactions must be reported directly to the Stephenson Cancer Center Data Safety Monitoring Committee either by telephone or by e-mail by the Investigator, study coordinator, clinical research associate, or other designated study personnel, within 24 hours of becoming aware of such an event. The Investigator also must report all such events promptly to the appropriate IRB/EC per their requirements.

11.1.3 Documenting Adverse Events

All AE information must be documented on the forms provided and approved by OU IRB. Additional follow-up information (e.g., test results, autopsy, and discharge summary) may be obtained to supplement AE reports. A copy of all initial and follow-up reports will be included with the patient's study files.

11.1.4 Causality Assessment of Adverse Events

The relationship between an AE and the study drug will be determined by the Investigator on the basis of his or her clinical judgment and the following definitions.

An AE will be considered associated with the use of study drug if there is a reasonable possibility that the AE may have been caused by the study drug. This definition applies to those AEs that are considered definitely, probably, and possibly related to the use of the study drug:

> **Definitely Related:** An AE that follows a temporal sequence from administration of the study drug; follows a known response pattern to the study drug; improves after stopping the study drug (positive dechallenge) and reappears after repeat exposure (positive

rechallenge); and cannot be reasonably explained by known characteristics of the patient's clinical state or by other therapies

Probably Related: An AE that follows a reasonable temporal sequence from administration of the study drug; follows a known response pattern to the study drug; improves after dechallenge; and cannot be reasonably explained by the known characteristics of the patient's clinical state or by other therapies.

Possibly Related: An AE that follows a reasonable temporal sequence from administration of the study drug and follows a known response pattern to the study drug but could have been produced by the patient's clinical state or by other therapies. An AE may be considered not associated with the use of study drug if there is not a reasonable possibility that the AE may have been caused by the study drug. This definition applies to those AEs that are considered unlikely or not related to the use of the study drug:

Unlikely to be Related: An AE assessed as unlikely to be related to study drug is defined as an AE for which sufficient information exists to indicate a high improbability that the event is related to the study drug.

Not Related: An AE assessed as not related to study drug is defined as an AE for which sufficient information exists to indicate that the etiology is unrelated to the study drug. Two or more of the following variables apply:

- The AE does not follow a reasonable temporal sequence after administration of the study drug.

- The AE is readily explained by the patient's clinical state or other therapies.

- Negative dechallenge—the AE does not abate upon dose reduction or cessation of therapy (assuming that it is reasonable to expect abatement of the AE within the observed interval).

11.1.5 Severity Assessment of Adverse Events

Severity of AEs will be graded according to the CTCAE Version 4.0.

Adverse events not included in the CTCAE, Version 4.0 must be graded as follows: Mild, Moderate, Severe, Life-threatening, and Fatal according to the following definitions:

Mild: The AE is noticeable to the patient but does not interfere with routine activity.

Moderate: The AE interferes with routine activity but responds to symptomatic therapy or rest.

Severe: The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy.

Life-threatening: The AE places the patient at risk of death at the time of the event.

Fatal: The AE results in the death of the patient.

11.2 Study Monitoring

Safety oversight will be performed by Stephenson Cancer Center's (SCC) internal Data and Safety Monitoring Committee (DSMC). The DSMC is composed of individuals with the appropriate expertise in adult and pediatric hematology and medical oncology, radiation oncology, translational and correlative science, pharmacy, nursing and biostatistics. The DSMC operates under the rules of an approved data safety monitoring plan which complies with the National Cancer

Institute (NCI) guidelines published as *Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by NCI* as of January 2005 and the "*NIH Policy for Data and Safety Monitoring*," *NIH Guide for Grants and Contracts*, http://grants.nih.gov/grants/guide/notice-files/not98-084.html.

The Data Safety Monitoring Committee is charged with oversight of participant safety, study conduct and the validity and integrity of data for clinical trials at SCC. While the focus of the DSMC is to monitor interventional investigator initiated trials (IITs) that are not subject to external monitoring, it has the authority to monitor any SCC protocol when potential concerns are identified. The DSMC also has the authority to suspend or close a study until the principal investigator addresses any issues that may cause harm or increase risks to subjects. The DSMC reports all findings to the Institutional Review Board (IRB).

Under the direction of the DSMC chair, a full board meeting is convened on a biannual basis to review the accumulated safety data, accrual information, and additional information as stated in the DSMC plan.

DSMC Auditing

In addition to monitoring, the DSMC oversees an internal auditing process to ensure subject safety and data quality. All cancer-related clinical trials active at the SCC are eligible for audit; however, priority is placed on those clinical trials that are not monitored or audited by an outside entity. If an external entity conducts an audit of a clinical trial at the SCC, then the findings of that audit are reported to the DSMC, either through the formal audit report provided by the external auditing entity, if available, or from the PI, who will report any findings communicated during the audit process.

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11.3Data Disclosure and Patient Confidentiality

Patient medical information obtained as a result of this study is considered confidential. Disclosure to third parties other than those noted below is prohibited. All reports and communications relating to patients in this study will identify each patient only by their initials and number. Medical information resulting from a patient's participation in this study may be given to the patient's personal physician or to the appropriate medical personnel responsible for the patient's welfare. Data generated as a result of this study are to be available for inspection on request by Stephenson Cancer Center Data Safety Monitoring Committee, the clinical trial office auditors and monitors, the Investigational Review Board (IRB)/Ethics Committee (EC) and the Institutional Biosafety Review Committee (or equivalent). De-identified data generated by participation in this study will be securely shared with co-investigator (Dr. Dockery) at the University of North Carolina at Chapel Hill for the purposes of data analysis and manuscript preparation.

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by a coded number to maintain patient confidentiality. All study records will be kept in a locked file cabinet or other secured area. All computer entry and networking programs will be identifiable only by coded numbers. Patient personal medical information may be reviewed by representatives of the Stephenson Cancer Center Data Safety Monitoring Committee, of the IRB, or of regulatory authorities in the course of monitoring the progress of the clinical trial. Every reasonable effort will be made to maintain such information as confidential.

12.0 Statistical Methods

Upon analysis, patients will be divided into two groups: Vitamin D Deficient Women and Vitamin D Normal Women.

Outcomes to be analyzed include differences in demographics, clinical, and tumor characteristics between groups, and differences in treatment-related morbidity or mortality between groups, including completion of treatment and treatment delays, and survival. Both 30-day postoperative surgical morbidity and chemotherapy-related morbidity will be assessed. The ability to normalize 25(OH)D levels with oral supplementation in the vitamin D deficient group will be evaluated.

Descriptive statistics will be used to summarize the demographic and clinical characteristics of patients. Chi-square and t-tests will be used to make comparisons between groups. Survival will be estimated with Kaplan-Meier curves and Cox proportional hazards regression. The anticipated enrollment is 100 patients based on estimated new diagnoses of ovarian cancer treated in the Division of Gynecologic Oncology annually at the Stephenson Cancer Center. Based on the previously mentioned unpublished data, we presume that at least 25 of the prospectively enrolled patients will be vitamin D deficient. All of the vitamin D deficient women will be repleted with oral vitamin D. We will compare outcomes between these patients and 75 vitamin D deficient ovarian cancer patients from previous years (these will include patients from the above-mentioned previous retrospective review as well as other patients with banked blood samples) using logistic regression. We will control for age, stage, and histology. With 25 prospective patients and 75 retrospective patients we will have 80% power to detect differences of 32% in chemotherapy delay between ovarian patients who were not vitamin D deficient (33%) and who were vitamin D deficient (65%).

Additionally, the association between serum leptin and 25(OH)D levels will be compared among groups, including any change in leptin levels observed in the vitamin D supplementation group. Because there is a positive linear association between BMI and serum leptin levels, BMI will be corrected for during analysis for potential relationships between serum leptin and 25(OH)D.

The proportion of patients with VDR *FokI* SNP will be assessed. We will also compare levels of vitamin D at diagnosis, differences in treatment-related morbidity or mortality including completion of treatment, treatment delays, survival and

response to vitamin D supplementation across 3 SNP allele groups (homozygous mutated, heterozygous mutated, homozygous wild type).

13.0 Data Handling and Recordkeeping

13.1 Data Collection

The Investigator will utilize an electronic CRF for each subject. Entries made in eCRF must be verifiable against source documents; any discrepancies should be explained and documented. The Investigator will be responsible for reviewing all data and CRF entries and will sign and date the designated pages in each subject's CRF, verifying that the information is true and correct. The Investigator is responsible for the review and approval of all responses.

13.2 Data Management

All CRF data will be entered into a validated database maintained by the OU Clinical Trials Office (REDCap). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources [21] All data entry, verification and validation will be performed in accordance with written standard operating procedures of the OU Clinical Trials Office. The database will be authorized for lock once all defined procedures are completed.

13.3 Data Privacy

The investigator must adhere to applicable data privacy laws and regulations. The investigator is responsible for ensuring that sensitive information is handled in

accordance with local requirements (e.g., Health Insurance Portability and Accountability Act of 1996 [HIPAA]). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained. Only the subject number and subject initials will be recorded in the CRF, and if the subject name appears on any other document (e.g., laboratory report), it must be obliterated on copies of the documents. The subjects will be informed that representatives of the Stephenson Cancer Center Data Safety Monitoring Committee, IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

13.4 Retention of Records

The Principal investigator must maintain all documentation relating to the study for a period of 2 years after marketing application approval, or if not approved, 2 years following the formal termination of clinical development of the investigational product. Whenever possible, an original recording of an observation must be retained as the source document. However, a photocopy of a record is acceptable, provided it is legible and is a verified copy of the original document. The investigator must not destroy any records associated with the study without receiving approval from the Stephenson Cancer Center Data Safety Monitoring Committee. The investigator must notify the Stephenson Cancer Center Data Safety Monitoring Committee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the Stephenson Cancer Center Data Safety Monitoring Committee must be contacted to arrange alternative record storage options.

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