Protocol Title: A Comparison Study to Assess the Value of Naturopathic Medicine Given Immediately and Continuously or Delayed Until Cycle 3 in Combination with Neo-Adjuvant Chemotherapy for Breast Cancer.

Protocol Number: MZ2014018_Neo-Adjuvant Study

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A Introduction

Study Abstract

Most health care providers are now aware of the literature citing the use of complementary and alternative medicine (CAM) treatments by patients, whether or not they divulge this use to their providers. Many times, patients are self-prescribing these treatments, and may be unaware of the potential for interactions with their conventional medications and treatments, as well as the potential for being contraindicated with their condition. Naturopathic Doctors are extensively trained in the use of integrative medicine treatments, and the management of patients utilizing both complementary and conventional treatments concomitantly. Cancer Treatment Centers of America is pioneering this model by offering patients an integrated approach to oncology care with a combination of conventional, standard of care cancer treatment, by Medical, Surgical and Radiation Oncologists, as well as evidence based complementary treatments by clinicians with doctorates in naturopathic medicine.

A variety of complementary agents are used along with conventional treatments in hopes of helping to manage and alleviate side effects of treatment. One reason for doing this is to enable patients to better tolerate treatments so that they may have optimal response to their treatment regimen. There are numerous articles, exhibiting mixed results at times, regarding improvement in quality of life of patients and modification of side effects using complementary agents along with conventional regimens. We would like to further investigate this notion by examining how patients respond to a combination of complementary agents. Additionally, we would like to determine whether or not this combination will affect measures of inflammatory, immune or possibly cancer biomarkers.

Primary Hypothesis

The addition of naturopathic medicine will improve immunologic and/or inflammatory parameters and/or quality of life in women receiving neoadjuvant chemotherapy (neo-CTx) for breast cancer.

Purpose of the Study Protocol

This protocol seeks to measure specific clinical, physiologic and quality of life parameters in 2 groups of breast cancer patients who receive neoadjuvant chemotherapy. This is a randomized, prospective, 2-arm, open label, exploratory study in which patients who give informed consent, will be randomized to receive standard neoadjuvant chemotherapy for breast cancer with naturopathic treatment given either (i) concomitant with the start of neoadjuvant chemotherapy (cohort 1); or, (ii) beginning at the start of the 3rd cycle of neoadjuvant chemotherapy (cohort 2). The goal is to conduct a battery of immunologic and quality of life (QoL) measurements longitudinally in both cohorts, prior to beginning therapy, at defined assessment points during neoadjuvant therapy, and at the end of neoadjuvant chemotherapy prior to a time when most patients will receive surgery. This protocol will determine: 1) whether the addition of Naturopathic Medicine Support (NMS) at the start of Neo-CTx for breast cancer affects immune status, inflammatory mediators and/or QoL apart from the effects produced by the neo-CTx alone; 2) whether the effects, if any, will also be produced in patients who begin NMS beginning at the 3rd cycle of neoadjuvant chemotherapy; 3) the magnitude, frequency, and kinetics of effects in both patient cohorts; and, 4) whether effects

elicited by the addition of NMS to neo-CTx are beneficial (favorable) with respect to the study parameter(s).

Prior Literature and Studies

Coenzyme Q10 (CoQ10)

Preclinical Data

Cell studies indicate that CoQ10 can help to reduce activity of matrix metalloproteinase-2 (MMP-2), thereby limiting their ability to metastasize. (Bahar et al., 2010)

Animal models of breast cancer indicate increased mitochondrial antioxidant and antitumor activity when treated concomitantly with Tamoxifen and CoQ10, riboflavin and niacin. (Perumal, Shanthi, & Sachdanandam, 2005)

Clinical Data

CoQ10 has been shown to reduce the cardio toxicity associated with Adriamycin chemotherapy treatment. (Conklin, 2005)

CoQ10 has been shown to improve cancer biomarkers (serum CEA and 15-3) in women receiving standard treatment for breast cancer. (Premkumar, Yuvaraj, Vijayasarathy, Gangadaran, & Sachdanandam, 2007)

A pilot study of patients with a variety of "end stage" cancers, including breast cancer, showed mean actuarial survival was 28.8 months versus 11.9 months for mean predicted survival with the addition of CoQ10. (and a variety of other anti-oxidants)(Hertz & Lister, 2009)

Another study shows a potential mechanism for the beneficial effects of CoQ10, demonstrating that CoQ10, as part of the CoRN protocol, administered along with Tamoxifen, can lead to decreased serum levels of IL-1B, IL-6, IL-8, TNFa and VEGF. (Premkumar et al., 2007)

CoQ10 was also shown to significantly increase DNA repair enzymes and decrease DNA methylation patterns. This has potential to lead to a reduction in tumor burden, and may suggest good prognosis and efficacy of the treatment. (Premkumar, Yuvaraj, Shanthi, & Sachdanandam, 2008)

CoQ10 is also believed to have anti-angiogenic effects as demonstrated by lowering angiogenic marker levels of bFGF, HGF, EGFR, TGF-β1, dThdPase, PGE2 and TSP levels in women undergoing treatment with Tamoxifen. (Premkumar, Yuvaraj, Sathish, Shanthi, & Sachdanandam, 2008)

CoQ10 has been shown to reduce recurrence rates, when used with standard treatment for other cancer types (melanoma). (Rusciani et al., 2007)

Yet another study demonstrates that CoQ10 with Vitamin B6 can increase IgG production, as well as increase T4 lymphocytes. (Folkers, Morita, & McRee, 1993)

Finally a review article discusses the recent clinical trials using cancer and non-cancer patients with chronic fatigue that have shown the benefit of molecular replacement plus antioxidants such as CoQ10 in reducing the damage to mitochondrial membranes, restoring mitochondrial electron transport function, and reducing fatigue. (Nicolson & Conklin, 2008)

Melatonin

Melatonin has been shown in both preclinical and clinical studies to modulate immune function and has been associated with improved outcomes and quality of life.

Preclinical Data

A study of melatonin-exposed human breast cancer cell lines published in 2011 indicated that melatonin plays a role in the regulation of cancer-related gene expression in human breast cancer cells. (Lee et al., 2011)

A study published in 2010 indicated that melatonin is associated with the inhibition of proliferation of estrogen receptor α (ERα)-positive breast cancer cell lines. (Mao et al., 2010)

A study published 2009 showed that melatonin inhibits aromatase activity and expression by regulating the gene expression of specific aromatase promoter regions. A possible mechanism for these effects would be the regulation by melatonin of intracellular cAMP levels, mediated by an inhibition of cyclooxygenase activity and expression. (Martinez-Campa et al., 2009)

In an earlier study by Garcia-Maurino, et al., the results suggested that melatonin may be involved in the regulation of human immune functions by modulating the activity of Th1 cells and monocytes via nuclear receptor-mediated transcriptional control. (Garcia-Maurino et al., 1997)

Clinical Data

One study suggests that melatonin may enhance Tamoxifen anti-tumor efficacy in other solid cancer types. (Lissoni et al., 1996)

Melatonin is associated with a significant decrease of IL-6 circulating levels, indicating that it modulates immune function in cancer patients in favor of Type 1 (cell-mediated antitumor immunity) responses. Furthermore, by activating the pluripotent cytokine system, direct growth-inhibitory properties have been observed over a wide range of tumor cell types that utilize cytokines as growth factors. Furthermore, by stimulating the cytotoxic activity of macrophages and monocytes, melatonin plays a critical role in host defense against the progression of Neoplasia. (Neri et al., 1998)

A study published in 2000 by Lissonni, et al. showed an increased response rate in patients with renal cell carcinoma treated with IL-2 combined with melatonin compared to patients treated with IL-2 alone. Moreover, patients who received concomitant IL-2/melatonin plus morphine achieved a better response than the group receiving IL-2 plus morphine without melatonin (4/14 vs. 1/16 respectively, $p<0.05$). Moreover, the 3-year survival rate for the combined IL-2/melatonin cohort was significantly higher compared to patients with IL-2 alone ($p<0.01$). Interestingly, one basis for

this study was the observation that the opioid substances (e.g. morphine) may suppress anticancer immunity and the efficacy of IL-2 itself. (Lissoni, Mandala, & Brivio, 2000)

Another study of 14 patients with several different advanced solid neoplasms that were clinically resistant to IL-2, but became responsive to IL-2 with concomitant administration of the pineal hormone melatonin (MLT). It was suggested that MLT could act by enhancing the IL-2-stimulated antitumor immune effects and/or by increasing the susceptibility of cancer cells to lysis by the IL-2-induced cytotoxic lymphocytes. In that study, a 40 mg dose of melatonin was given to patients daily. (Lissoni et al., 1994)

Melatonin has been shown to cause the release of cytokines from activated T-cell populations. A phase II study, in 1994, combined interferon treatment with melatonin given at 10 mg daily. Out of 22 patients there were seven tumor responses (33%) with three Complete Responses (CR) and 4 Partial Responses (PR) involving lung and soft tissue disease. The median duration of survival was reported as 16 months. Of the other patients studied, 9 patients achieved stable disease with 5 showing progressive disease. (Neri et al., 1994)

Reishi (*Ganoderma lucidum*)

Ganoderma licidum (*G. lucidum*) has been shown in both preclinical and clinical trials to have immune modulating effects. One clinical trial has also indicated a potential benefit on quality of life.

Preclinical Data

Preclinical data of *G. lucidum* include enhancing the proliferation and maturation of T and B lymphocytes, splenic mononuclear cells, NK cells and dendritic cells. *G. lucidum* has also been shown to effect gene expression of IL-1β, IL-6, IL-10, and tumor necrosis factor (TNF)-α. Furthermore a polysaccharide fraction was shown to enhance both innate and adaptive immunities by triggering the production of cytokines, IL-1, IL-6, IL-12, IFN-γ, TNF-α, and colony stimulating factors (CSFs) from mouse splenocytes. (Wachtel-Galor, Yuen, Buswell, & Benzie, 2011)

Clinical Data

In a 1996 Cochrane Database Systematic Review included 5 RCTs. The common primary outcomes were tumor response evaluated according to the World Health Organization (WHO) criteria, immune function parameters such as natural killer (NK)-cell activity and T-lymphocyte co-receptor subsets, and quality of life measured by the Karnofsky scale score. The results showed that those patients given *G. lucidum* given along with chemotherapy and radiation were more likely to respond positively compared to chemotherapy or radiation therapy alone. In addition immune parameters and quality of life were improved. In regards to the immune system there were increases in the percentage of CD3, CD4, and CD8. The CD4/CD8 ratio was also elevated. In this review only one study reported mild side effects of insomnia and nausea. (Jin, Ruiz Beguerie, Sze, & Chan, 2012)

In a 2003 study by Gao et al the effects of *G. lucidum* on the immune functions of advanced stage patients with cancer were evaluated. 34 patients with advanced cancer were given 1800 mg three times daily for 12 weeks. Treatment with *G. lucidum* resulted in increases in the mean plasma

concentrations of IL-2, IL-6 and interferon-gamma. The levels of IL-1 and tumor necrosis factor alpha (TNF-alpha) were decreased. There were also effects on the numbers of each lymphocyte subset. The absolute number of CD56 cells was significantly increased after 12 weeks while CD3, CD4 and CD8 were marginally increased to baseline. There was no change to the CD4:CD8 ratio. Finally there was a significant increase in NK cell activity to baseline. (Gao, Zhou, Jiang, Huang, & Dai, 2003)

In a double blind randomized study by Wicks et al of 16 healthy adults the safety and tolerability of *G. lucidum* was tested. After 10 days of oral administration of 2g twice daily no adverse events were reported. This study also showed no obvious changes in CD4, CD8 and CD19 levels however CD56 cells were increased and returned to baseline after 10 days of cessation of supplementation. Due to the small size of the study the increase in CD56 cells did not achieve statistical significance. (Wicks et al., 2007)

B Study Objectives

Primary Aim

1. Determine the impact of adding NMS to neo-CTx on hematologic and immunologic parameters relevant to general immunocompetence (e.g. White Blood Cell counts) and antitumor immunity (i.e. NK cell activity).

2. Determine the impact of adding NMS to neo-CTx on the quality of life (QoL) of patients with locally advanced breast cancer receiving neoadjuvant therapy prior to surgery as measured by the M.D. Anderson Symptom Inventory (MDASI) tool.

3. Determine whether such effects can be elicited and maintained throughout the course of neo-CTx when given continuously at the start of treatment.

4. Determine whether such effects can be elicited in patients who have received 2 of 4 planned CTx treatment cycles prior to initiating concomitant NMS therapy.

Secondary Aim

1. Determine the impact of adding NMS to neo-CTx on measures of the inflammatory response and type 1 and 2 cytokines.

2. Characterize the impact of adding NMS to neo-CTx on the concentration of circulating tumor cells.

Rationale for the Selection of Outcome Measures

As discussed in previous sections, CoQ10, Melatonin and Reishi have all been shown, individually to affect immune parameters and inflammatory cytokines. CoQ10 has been shown to improve

measures of tumor response. Additionally, previous studies have associated all 3 agents with improvement of side effects and quality of life.

The presence of circulating tumor cells has been correlated with early detection of disease progression. A novel method to detect very low concentrations of circulating tumor cells has been developed (ClearID; Cynvenio Biosystems, Inc.). In addition to the measurement of immunologic and inflammatory parameters, this study will also test blood samples from ten participants to observe the effect of neoadjuvant chemotherapy and/or naturopathic medicines on the detection of circulating tumor cells. Blood will be collected from ten participants before the start of neoadjuvant therapy cycles 1 and 3 for testing.

Dose Rationale and Risk/Benefits

Source for potential interactions was Naturaldatabase.com, a comprehensive database of herb-drug-nutrient interactions.

Melatonin:

Most clinical studies showing benefit with melatonin have used a dose of 20 mg. No known toxicity or serious side effects were reported; however, long-term human studies have not been conducted. Some uncommon side effects that have been reported in studies or case reports include drowsiness, alterations in sleep patterns, altered mental status, disorientation, tachycardia, flushing, pruritus, abdominal cramps and headache. Excessive dosages beyond those that will be given in this study may cause morning sedation or drowsiness. Melatonin should be used with caution in individuals using central nervous system depressants as concurrent use may cause additive sedation. Theoretically, melatonin may affect the disposition of the following medications: Theophylline, caffeine, clozapine, haloperidol, tacrine, fluvoxamine, and other medications associated with metabolism by cytochrome P450 1A2 (CYP1A2). It may also affect the activity of non-steroidal anti-inflammatory agents (e.g., aspirin, ibuprofen, Naproxen), phenytoin, warfarin, zafirlukast, fluvoxamine, and others affected by cytochrome P450 2C9 (CYP2C9). Melatonin may interact with calcium channel blockers. Concomitant use of melatonin and nifedipine may cause increases in blood pressure. Assessment and monitoring of any such effects is part of the standard of care at CTCA by naturopathic physicians treating patients and will continue to be the standard for patients entered on this study.

Coenzyme Q10:

CoQ10 is generally well-tolerated. In clinical studies, there have been no reports of significant adverse effects. Coenzyme Q-10 can cause gastrointestinal side effects such as nausea, vomiting, diarrhea, appetite suppression, heartburn, and epigastric discomfort in less than 1% of patients and the effects are all reversible. Some of these adverse effects can be minimized if total daily doses exceeding 100 mg are divided and administered two to three times per day. Allergic rash has also been reported but is extremely rare. Theoretically, CoQ10 may increase bleeding risk and may decrease response to warfarin. However, a small randomized controlled trial showed no effect on International Normalized Ratio (INR; a measure of blood clotting) with concurrent use of coenzyme Q10 (Engelsen, Nielsen, & Hansen, 2003). Potential adverse reactions include abdominal discomfort, headache, nausea and vomiting. There is a wide range of dosing for CoQ10 but most studies used a dose between 60 – 200 mg.

Reishi:

Side effects are uncommon however reported side effects include allergies, dryness of the mouth, throat and nasal area, itching, nausea, epistaxis. Bloody stools have been reported with use of over 3-6 months.

In regards to documented potential effects with botanicals and drugs the data is sometimes inconsistent. In patients with type-2 diabetes however, information from clinical research is inconsistent. In patients with type 2 diabetes taking G. lucidum appeared to effect HA1C but not fasting glucose. Therefore it may be possible to have additive effects with botanicals or herbs that can have hypoglycemic potential. Clinical evidence also shows that G. lucidum may reduce blood pressure in some but not all patients with hypertension therefore additive affects might be possible for patients on anti-hypertensive medications or botanicals. Finally a dose of higher than 3g daily may decrease platelet aggregation and therefore additive effects may occur with patients on medications or botanicals that have antiplatelet actions.

In regards to dosing the two clinical studies noted above in "Prior Literature and Studies" section used dosing between 4g - 5.4g daily. In the study of healthy volunteers the dose was 2g twice daily and in the study of patients with advanced cancer a dose of 1800mg three times daily was used for a total dose of 5.4g daily. [4,3]

C Study Design

Overview or Design Summary

This is a randomized, prospective, 2-arm, immediate versus delayed, open label, exploratory study in which patients who give informed consent, will be randomized to receive standard neoadjuvant chemotherapy for breast cancer with either immediate and continuous naturopathic treatment, or delayed continuous naturopathic treatment. Twenty patients will be recruited into this 2-arm design wherein 10 patients will receive immediate and continuous NMS intervention, and 10 will receive delayed NMS starting at cycle 3.

All patients will have adenocarcinoma of the breast and have been recommended to receive neoadjuvant chemotherapy. The patients can have estrogen receptor positive or negative disease, progesterone receptor positive or negative disease and HER-2 positive or negative disease. They will all receive neoadjuvant chemotherapy as per the medical oncologist and according to NCCN guidelines. Chemotherapies that may be used in combination include doxorubicin, cyclophosphamide, gemcitabine, carboplatin, docetaxel and paclitaxel. . Trastuzumab and or pertuzumab may also be used as recommended by the medical oncologist.

In one group NMS interventions will start with cycle 1 and continue through 4 cycles of neoadjuvant chemotherapy until the patient returns for blood work and evaluation following the 4th treatment of chemotherapy which is approximately 2-3 weeks after the 4th treatment is given.

The total time on NMS interventions is approximately 8 -12 weeks as the time between each cycle of chemotherapy is approximately 2- 3 weeks. The interventions will include coenzyme Q10, melatonin and reishi. The second group will start naturopathic interventions at cycle 3 and will continue through the 4th cycle of neoadjuvant chemotherapy until the patient returns for blood work and evaluation following the 4th treatment of chemotherapy which is approximately 2 - 3 weeks after the 4th treatment is given. The total time on NMS interventions is approximately 4 -6 weeks. The naturopathic interventions will be identical in each group except for the timing of the start of the intervention and the total time the patient will be taking NMS interventions.

At the start of each treatment cycle beginning with cycle 1 both groups will be given the Modified MD Anderson Symptom Inventory (MDASI). A blood sample will be collected according to standard of care with each treatment cycle to include a complete blood count, chemistry panel and tumor markers (including CA 15-3, CA 19-9, CA 27.29, Chorioembryonic Antigen [CEA] and Circulating Tumor Cells [CTC], if available). In addition, a blood sample for measurement of inflammatory markers C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) will be drawn. A tube containing preservative-free heparin (an anticoagulant) will be collected for assessment of NK cell activity isolated by a standard ficoll/hypaque gradient centrifugation. The serum will be collected and stored for potential assessment of type I and type II cytokines using a commercial multiplex cytokine assay. These assays will be conducted only if the NK assay and/or QoL results indicate the NMS therapies have measurable effects. These blood draws will be done before chemotherapy is given. The NK cell studies will be done in real time, while the collected plasma containing cytokines will be batch tested at end of study.

Assessment and monitoring of any side effects will occur at every follow-up visit as part of the standard of care at CTCA. For all patients at every visit vital signs are taken and recorded. This includes temperature, blood pressure, heart rate and respiration rate. In addition, at the patient's initial visit, height and weight will be recorded and subsequently weight will be measured for all follow-up visits.

Subject Selection and Withdrawal

C1.a Inclusion Criteria

i Participants will have signed an informed consent

Inclusion Criteria:

- Female
- 18 years or older
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Diagnosis of invasive adenocarcinoma of the breast made by core needle excisional or stereotactic biopsy.
- All patients will have adenocarcinoma of the breast and have been recommended to receive neoadjuvant chemotherapy. The patients can have estrogen receptor positive or negative disease, progesterone receptor positive or negative disease and

HER-2 positive or negative disease. They will all receive neoadjuvant chemotherapy as per the medical oncologist and according to NCCN guidelines. Chemotherapies that may be used in combination include doxorubicin, cyclophosphamide, gemcitabine, carboplatin, docetaxel and paclitaxel. Trastuzumab and or pertuzumab may also be used as recommended by the medical oncologist.

- Left Ventricular Ejection Fraction (LVEF) assessment by MUGA or Echocardiogram within 3 months of entering study
- Blood counts must meet the following criteria:
  - ANC greater than or equal to 1200 cells/mm^3
  - Platelet count greater than or equal to 100,000/mm^3
  - Hemoglobin greater than or equal to 10g/dL
  - Serum creatinine less than or equal to ULN for the laboratory range
- Adequate hepatic function by the following criteria:
  - Total bilirubin less than or equal to ULN for the laboratory range, unless the patient has an elevation greater than ULN to 1.5 times the ULN resulting from Gilbert's disease or similar syndrome due to slow conjugation of bilirubin
  - Alkaline phosphatase less than or equal to 2.5 x ULN; and
  - AST less than or equal to 1.5 x ULN for the laboratory range
- If skeletal pain present or alkaline phosphatase greater than ULN (but less than or equal to 2.5 x ULN), bone scan or PET scan must not demonstrate metastatic disease
- If AST or alkaline phosphatase greater than ULN, liver imaging (CT, MRI or PET scan) must not demonstrate metastatic disease and the requirements for hepatic function must be met
- Able to swallow oral medication
- Willing to forego naturopathic treatment for the first 2 treatment cycles in the event that randomization assigns the patient to the delayed NMS group.
- Willing to start and continue naturopathic interventions as prescribed for entire neoadjuvant treatment which includes approximately 8 - 12 weeks for one group and 4 - 6 weeks for the other group.
- Willing to forego the use of nutritional or botanical supplements during the time of the study shown to effect immune or inflammatory markers outside the use of the naturopathic agents being studied

C1.b Exclusion Criteria

i Participants are not able to understand or provide written informed consent
ii The research team deems that the participant may not be able to follow the study protocol

Exclusion Criteria:

- Stage 4 disease
- Present and continued treatment with Warfarin or any other anticoagulant therapy.
- Synchronous bilateral invasive breast cancer
- Treatment including radiation, chemotherapy, and/or targeted therapy for the currently diagnosed breast cancer prior to entering study.
- Any sex hormonal therapy e.g. birth control, ovarian hormone replacement therapy, etc. (eligible if discontinued prior to entering study)
- Continued therapy with any hormonal agent such as raloxifene, tamoxifen, or other SERM (eligible if discontinued prior to entering study)
- Prior history of breast cancer, including Ductal Carcinoma In Situ (subjects with a history of Lobular Carcinoma In Situ are eligible)
- Prior therapy with chemotherapy or targeted therapy agents for any malignancy.
- Cardiac disease that would preclude the use of the chemotherapy drugs described above. This includes but is not confined to:
    - Active cardiac disease
    - Angina pectoris requiring the use of anti-angina medication
    - Ventricular arrhythmias except for benign premature ventricular contractions controlled by medication
    - Conduction abnormality requiring a pacemaker
    - Supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication
    - Clinical significant valvular disease
    - History of cardiac disease:
    - Myocardial infarction
    - Congestive heart failure
    - Cardiomyopathy
- Uncontrolled hypertension, defined as blood pressure above 150/90 mm/Hg on antihypertensive treatment
- History of, or current symptomatic interstitial pneumonitis or pulmonary fibrosis or definitive evidence of interstitial pneumonitis or pulmonary fibrosis described on CT or chest x-ray in asymptomatic patients
- Sensory/motor neuropathy greater than or equal to grade 2, as defined by the NCI's CTCAE v4.03
- Malabsorption syndrome, ulcerative colitis, resection of the stomach or small bowel, or other disease significantly affecting gastrointestinal function
- Other non-malignant systemic disease that would preclude treatment with any of the treatment regimens or would prevent required follow up
- Conditions that would prohibit administration of corticosteroids
- Unwilling to forego the use of nutritional or botanical supplements during the time of the study shown to effect immune or inflammatory markers outside the use of the naturopathic agents being studied. Repletion of vitamins and minerals will be allowed.
- Unwilling to forego naturopathic agents being studied for first 2 cycles of chemotherapy treatment.

- Administration of an investigational agent within 30 days prior to entering study.
- Administration of therapeutic doses of the supplements being studied including Reishi, melatonin and CoQ10 in the previous 30 days.
- Administration of therapeutic doses of immune modulating botanicals in the previous 30 days.
- Pregnancy or lactation

C1.c Ethical Considerations

This study will be conducted following all local laws and regulations in the conduct of research, as well as the International Conference on Harmonization's Good Clinical Practice Guidelines. These guidelines provide a unified standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.

In addition, this study will be reviewed and approved by appropriate Institutional Review Boards prior to the initiation of any study procedures. The protocol will undergo continuing review and approval by designated IRB providing ongoing oversight of the study.

C1.d Subject Recruitment Plans and Consent Process

Subjects will be consented using a current informed consent form that has been approved by the respective study site's Institutional Review Board. Subjects will be allowed adequate time to read the informed consent, discuss the consent with study staff and others (e.g., family members, friends, or any of their health care providers), and have their questions answered prior to signing the informed consent.

C1.e Randomization Method

A random number generator will be used to produce a randomization table. Randomization of patients will occur after the patient has signed the IRB consent form.

C1.f Risks and Benefits

i Risks

Potential physical risks include:

There are minimal potential risks involved in this study. There will be additional tubes drawn for blood with each cycle; however the risk of this is minimal as patients will already be having their blood drawn.

Potential risks of side effects with naturopathic interventions are outlined in Dose Rational and Risk/Benefits.

Patients will already be scheduled to receive neoadjuvant chemotherapy treatment as per medical oncologist in order to qualify for the study so no change in conventional treatment will result as a part of this study.

Potential psychological risks include:

There are no known potential psychological risks with this study.

Potential social risks include:

There is a possible social risk of embarrassment or reputational standing while responding to questionnaires or interviews. This risk will be minimized by using trained interviewers and maintaining all study related records in locked cabinets or secure computer files.

ii Benefits

The benefits that the subject may get from being in this study are potentially improved quality of life with naturopathic interventions as coenzyme Q10 has been shown to help with fatigue. Melatonin has also been shown to improve quality of life for patients undergoing chemotherapy with reduced nausea. In addition, coenzyme Q10, reishi, and melatonin have been shown to affect inflammatory and immune modulating cytokines that may have a benefit with tumor response and quality of life with chemotherapy treatment.

C1.g Early Withdrawal of Subjects

Subjects may be withdrawn for the following reasons:

i. Inability to comply with naturopathic treatment interventions
ii. Inability to continue with conventional treatment
iii. Side effects from naturopathic treatment interventions
iv. A change in chemotherapy treatment by medical oncologist due to progression of disease or intolerable side effects
v. Subject Safety
vi. Non-compliance with study visit schedule or study regimen

C1.h When and How to Withdraw Subjects

If patients are withdrawn from study, data will be collected as to reason for the withdrawal. The PI will evaluate withdrawal and oversee withdrawal of all such subjects.

There are no risks involved with stopping naturopathic interventions at any point in the study.

C1.i Data Collection and Follow-up for Withdrawn Subjects

Data will be collected on reasons for withdrawal and included in the final analysis of the study.

Study Drug

The study regimen will consist of three common Naturopathic medicine treatments – Co-Enzyme Q10, Melatonin and Reishi.

Additionally, blood will be collected for analysis of circulating tumor cells using a new assay system called ClearID (Cynvenio Biosystems, Inc.).

C1.j Description

Melatonin, N-acetyl-5-methoxytryptamine, is synthesized by the pineal gland in response to the dark/light cycle and has been known to act as a synchronizer of the biological clock. Melatonin has a variety of therapeutic effects, such as immunomodulatory actions, anti-inflammatory effects, and antioxidant actions. Furthermore, melatonin is reported to have an anticancer function including suppression of the metabolism of tumor cells and induction of tumor suppressor genes in cancer cells, including breast cancer cells.

Coenzyme Q-10 is a fat soluble, vitamin-like compound present in virtually all cells and in especially high concentrations in the heart, liver, kidney, and pancreas. The majority of intracellular CoQ10 is found in the mitochondria. Its primary functions include activity as an antioxidant, a membrane stabilizer, and as a cofactor in many metabolic pathways, particularly in the production of adenosine triphosphate (ATP) in oxidative respiration.

Reishi is an edible mushroom that is used widely in Asia. It is used as both a food and medicinal agent. Reishi has been shown to effect the proliferation and maturation of immune cells, increase gene expression and enhance NK cell activity.

Pharmacodnamics/Kinetics

C1.k Treatment Regimen

The treatment regimen will include standard neoadjuvant conventional treatment for breast cancer. Chemotherapies that may be used in combination include doxorubicin, cyclophosphamide, gemcitabine, carboplatin, docetaxel and paclitaxel. Trastuzumab and or pertuzumab may also be used as recommended by the medical oncologist. An NMS regimen will be added to this, to include the following: Co-Enzyme Q10 at a dose of 100 mg capsule twice daily with food; Melatonin at a dose of 20 mg capsule once nightly at bedtime; Reishi at a dose of 1000 mg (in 2 capsules) three times daily for a total of 3g daily. The patients in one group will start the NMS interventions with cycle 1 and will take daily for approximately 8 - 12 weeks or through 4 treatment cycles. The patients in the second group will start the NMS interventions at the start of cycle 3 and will take daily for approximately 4 - 6 weeks or through 3 and 4 treatment cycles.

C1.l Method for Assigning Subjects to Treatment Groups

Eligible patients who sign the informed consent will be randomized by a standard randomization table method to either the immediate and continuous naturopathic treatment group, or the delayed start with naturopathic treatment.

C1.m Preparation and Administration of Study Drug

Preparation of the study drugs will be by the manufacturer, Vital Nutrients for coenzyme Q10, melatonin and Reishi. All study drugs will be prepared according to the strict quality standards set forth by Vital Nutrients and the CTCA Dietary Supplement Formulary Committee to ensure authenticity, accurate dosing and lack of contamination. Patients will self-administer the study drugs. The study drug will be provided free of charge to the patients.

C1.n Subject Compliance Monitoring

Compliance will be monitored by a Patient Supplement Study Schedule to be filled out daily by the patient and returned at each follow-up visit. Therefore compliance will be monitored by patient's self-reported diary. Patients will be given appropriate doses of supplements in unopened bottles at the start of the study and will be be given refills as needed throughout the study at return visits. Patients are not required to return unused drug or containers.

C1.o Prior and Concomitant Therapy

Concomitant therapy will be conventional neoadjuvant treatment for breast cancer.

C1.p Packaging/Labeling

Bottles of the study drugs will be packaged and labeled by the manufacturers, CNCA and JHS to include the ingredients of the study drugs and the dosing.

C1.q Blinding of Study Drug

The study drugs will not be blinded for this randomized, 2-arm, open label exploratory study.

D Study Procedures

Screening for Eligibility

We will be reviewing patient's medical records prior to consenting patients to determine study eligibility. No patient information will be recorded prior to the informed consent process.

D1.a Visit 1

The study will be explained to prospective participants on or the day prior to the Visit 1. The consent discussion and signing of the consent form will occur prior to any study related tests or procedures. The first questionnaires may be administered prior to Visit 1, as part of the standard of care for treatment at Midwestern Regional Medical Center. This baseline questionnaire will be used as part of the study and will not be re-administered after the consent forms.

On visit 1, which is day 1 of cycle 1 of neoadjuvant chemotherapy or just prior to this visit as standard of care at Midwestern Regional Medical Center, the MDASI questionnaire will be administered to both groups. Labs will be drawn for both groups including a complete blood count and chemistry panel. Tumor markers (including CA 15-3, CA 19-9, CA 27.29, CEA and CTCs) will be recorded, if available. In addition, blood for analysis of inflammatory markers (CRP and ESR), NK assay and cytokine analysis will be drawn as described above.

The NMS intervention will be started in the immediate and continuous group. No NMS treatment will be given to the NMS delayed group.

In addition blood samples will be drawn from ten participants for ClearID detection of circulating tumor cells. Blood will be collected from ten participants before the start of neoadjuvant therapy cycles 1 and 3 for testing.

D1.b Visit 2

On visit 2, which is day 1 of cycle 2 of neoadjuvant chemotherapy and is approximately 2 - 3 weeks after cycle 1 was given, the MDASI questionnaire will be administered to both groups. Blood samples for usual care and study specific laboratory analysis will be drawn for both groups as described above.

The NMS intervention will be evaluated and continued in the immediate and continuous group. No NMS treatment will be given to the NMS delay group.

D1.c Visit 3

On visit 3, which is day 1 of cycle 3 of neoadjuvant chemotherapy and is approximately 2 - 3 weeks after cycle 2 was given, the MDASI questionnaire will be administered to both groups. Blood samples for usual care and study specific analysis will be drawn for both groups as described above.

The NMS intervention will be evaluated and continued in the immediate and continuous group. The NMS delay group will begin NMS treatment.

In addition blood samples will be drawn from ten participants for ClearID detection of circulating tumor cells. Blood will be collected from the same ten participants that had samples taken prior to the start of neoadjuvant therapy cycle 1.

D1.d Visit 4

On visit 4, which is the start of cycle 4 of neoadjuvant chemotherapy and is approximately 2 - 3 weeks after cycle 3 was given, the MDASI questionnaire will be administered to both groups. Blood samples for usual care and study specific analysis will be drawn for both groups as described above.

The NMS intervention will be evaluated and continued in the immediate and continuous group. The NMS delay group will be continued on NMS treatment.

D1.e Visit 5 (End of Study Visit)

On visit 5 approximately 2 - 3 weeks after cycle 4 was given, the End of Study blood samples will be collected for usual care and study specific analysis, The MDASI questionnaire will be administered to both groups.

The patients will be scheduled for surgery or continue on to second neoadjuvant chemotherapy according to the judgment of the attending medical oncologist. Naturopathic interventions on study will be complete and analyses will be conducted.

Safety and Adverse Events

D1.f Safety and Compliance Monitoring

The lead study investigator and sub-investigators responsible for patient treatment will monitor the safety and compliance of all study subjects at MRMC utilizing the Oncore ERM study management system.

D1.g Medical Monitoring

Medical Monitoring will consist of regular monitoring by medical oncologist in addition to monitoring by naturopathic oncology providers at each treatment visit for compliance and evaluation of NMS treatment side effects. At every visit vital signs will be taken and recorded. This includes temperature, blood pressure, heart rate and respiration rate. In addition, at the patient's initial visit, height and weight will be recorded and subsequently weight will be measured for all follow-up visits.

D1.h Definitions of Adverse Events

The Common Terminology Criteria for Adverse Events (CTCAE; version 4.03) will be used to identify and quantify adverse events experienced by the patients.

D1.i Classification of Events

Possible side effects were outlined in Dose Rationale and Risks/Benefits sections. Any side effects will be described using the CTCAE handbook.

D1.j Reporting Procedures

Serious Adverse Events and adverse events that meet "severe" criteria must be directly reported within 24 hours to the designated IRB.

E Statistical Plan

Sample Size Determination and Power

This exploratory study will be limited to 20 patients with 10 patients in the neo-CTx with immediate and continuous NMS cohort and 10 in the NMS delayed until cycle 3 plus neo-CTx cohort. Because this is an exploratory study, it is not expected that adequate statistical power can be achieved to detect an effect size of 20% in favor of either NMS group for any of the parameters of interest. If a trend in favor of a difference between cohorts is observed, the study can be extended to accrue sufficient numbers to detect a 20% difference between the cohorts.

Comparison between cohorts with respect to tumor response will be judged by calculating the percentage of patients in each cohort who demonstrate a clinical and a pathologic response defined as Complete Response (CR), Partial Response (PR), or No Response (NR). Differences between the cohorts for proportion of patients who exhibit a clinical and pathologic CR, PR, or NR will be compared by logistic regression to determine multivariate odds ratios. We will examine the issue of response to be certain there is no "safety signal", but not for the issue of efficacy.

For immunologic parameters (i.e. leukocyte #s, serum cytokine levels, NK lytic function), and QoL parameters (i.e. MDASI QoL elements) descriptive statistics for each parameter at each assessment point will be calculated for both cohorts and multiple comparisons for all parameters undertaken using the non-parametric Mann Whitney test. Differences between the immediate and delayed NMS cohorts for all parameters will be considered significant at $P<0.05$.

In addition, the effects of treatment on immunologic and QoL in each cohort will be assessed by calculating the following parameters for each treatment cycle: 1) baseline level of function; 2) maximum deviation (suppression) from baseline (e.g. nadir of leukocyte counts, NK function, QoL measures); 3) maximum recovery from nadir; and, 4) time to achieve maximum recovery from nadir.

No statistical power is needed.

Interim Monitoring and Early Stopping

The addition of NMS to neo-CTx is practiced as a standard of care at CTCA. Neo-CTx alone is the standard of care for many patients with breast cancer at most other cancer treatment centers; unanticipated and/or intolerable toxicity is not expected in either cohort. Thus, except for difficulties in patient accrual, we do not anticipate a need for early study termination.

This is an open label, randomized trial with quantitative metrics chosen as the outcome measures. Data will be monitored continuously by the investigators and subjected to interim analysis by the consultant statistician at 5 patients/cohort increments throughout the duration of the study. Patients are considered off study at the time of mastectomy and/or need for a different chemotherapy treatment regimen.

F Data Handling and Record Keeping

Confidentiality and Security

Data pertaining to hematologic parameters and MDASI symptom elements will be abstracted from the electronic medical record of CTCA Midwestern by clinical data managers at Midwestern. In addition, NK function (expressed as lytic units), inflammatory markers, and cytokine levels (expressed as pg/mL serum) will be entered on the data collection forms following determination of activity in these assays at Midwestern. All Data collection forms will be stored in the protocol office within a locked cabinet in a locked research office.

Study sites will observe Health Insurance Portability and Accountability Act (HIPAA) Privacy and Security Rule standards.

Training

All research team members will show evidence of completion of the CITI (Collaborative Institutional Training Initiative) accreditation program for human subjects research.

Source Documents

Source documents for the clinical parameters are in the electronic medical record of CTCA hospitals. The laboratory results for NK function and serum cytokine levels will be obtained in the translational research laboratory of Midwestern Regional Medical Center of CTCA, and entered onto

the study data collection forms which are stored in the clinical research office of Midwestern Regional Medical Center.

Records Retention
Paper study records will be maintained for seven years from the end date of the study. At the end of this time period, study records will be shredded.

Performance Monitoring
The Principal Investigator in conjunction with the sub-investigators will be responsible for the conduct of all study procedures. The manager of MRMC's Clinical Protocol Office will be responsible for overseeing data collection and entry into the case report forms for the study, and for reporting AEs to the designated IRB. Statistical analyses and reporting of the results will be the responsibility of the investigators in conjunction with the VP Clinical Research of CTCA.

G Study Monitoring, Auditing, and Inspecting

Study Monitoring Plan
Principal Investigators at each site will monitor ongoing study performance. Auditing study performance will be conducted at least quarterly by the VPs of Integrative Medicine and Clinical Research of CTCA.

Organization and Participating Center
Principal Investigators from Midwestern CTCA hospital are listed on the title page of the protocol. They will be responsible for the conduct of the study at each site. The clinical protocol office at Midwestern CTCA hospital will support the PI and Sub-PIs in data collection, record keeping, and AE reporting to the respective IRBs.

Funding Source and Conflicts of Interest
This study is funded by Cancer Treatment Centers of America.

Committees
An executive committee consisting of the site Principal Investigators; the VP of Integrative Medicine; the VP of Clinical Research lead for integrative medicine at CTCA will be formed to oversee all aspects of the study. All issues pertaining to the study will be discussed and adjudicated by the executive committee.

Subject Stipends or Payments
Subjects who participate in the study will not receive a stipend. However, patients will be provided with the designated supplements for the duration of the period in which neoadjuvant chemotherapy is administered.

Study Timetable
The study will last for approximately 2 years.

RESEARCH SUBJECT INFORMED CONSENT AND AUTHORIZATION FORM

TITLE:	A COMPARISION STUDY TO ASSESS THE VALUE OF THE ADDITION OF NATUROPATHIC MEDICINE IMMEDIATELY AND CONTINUOUSLY OR DELAYED, IN COMBINATION WITH NEO-ADJUVANT CHEMOTHERAPY FOR BREAST CANCER.
PROTOCOL NO.:	MZ2014018_Neo-Adjuvant Study WIRB® Protocol 20141800 MZ2014018
SPONSOR:	Midwestern Regional Medical Center, Inc.
INVESTIGATOR:	Christina M. Shannon, ND, FABNO 2520 Elisha Ave Zion, IL, 60099 United States
STUDY-RELATED PHONE NUMBER(S):	Christina M. Shannon, ND, FABNO (847) 872-6364 (847) 479-5202 pager (24 Hours)

Introduction

This is a clinical trial, a type of research study. Your Naturopathic Oncology Provider will explain the clinical trial to you. Clinical trials include only people who choose to take part. This Informed Consent document describes the clinical research study that you are being asked to participate in and what the study will involve. Please take your time to make your decision about taking part in this clinical trial. Discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your Naturopathic Oncology Provider for more information.

Why is This Study Being Performed?

The purpose of this study is to observe whether treatment with naturopathic medicine supplements, while you are receiving chemotherapy for breast cancer, has an effect on your immune system and your quality of life. We will also test whether these supplements effect the gene expression by your tumor, and your response to chemotherapy. In addition if timing of your lab draw allows for you to be among the ten participants to test the effectiveness of a new process, called ClearID then samples of your blood will be used to test for circulating tumor cells.

How Many People Will Take Part in the Study?

We hope to enroll 20 participants in this research study.

What Will Happen if I Take Part in This Research Study?

PROCEDURES

After your Naturopathic Oncology Provider has answered all of your questions about the study and you have given written consent by signing this form, a physical examination will be conducted if it has not already been done by your medical oncologist as part of the normal care for treatment of your breast cancer. Laboratory tests will be done to be sure you are able to begin treatment and therefore enter the study. Some of the tests are the same as those you have had in the past to diagnose and treat your cancer. Some of these same tests will also be performed during your treatment in order to follow your progress. Additional laboratory tests will be performed as part of the study.

Your participation in this study is divided into different visits:

1. A Screening Visit (which may be the same day as your treatment visit)
2. Treatment Visits
3. A Post-Treatment Visit

Different tests are run during each of these different visits as described below.

Screening Visit

This Screening Visit is necessary to determine if you are eligible to participate in the study. The Screening Visit will take place before you receive any study related treatment.

During the Screening Visit:

- The Naturopathic Oncology Provider or nurse or Medical Oncologist will ask you about your medical history and obtain a list of all medications that you are currently taking and the previous treatments for your cancer you have received.
- A full physical examination will be performed and your height, weight and vital signs (heart rate, blood pressure, breathing rate and body temperature) will be recorded.
- Blood will be drawn for routine lab tests
- Your Naturopathic Oncology Provider will ask you to sign this consent form if you wish to participate in this study. You need to sign this form before any study specific tests are performed.

All of these tests may be completed over several clinic visits. If a recent test result is already available in your medical records, we may not need to do that test again.

Treatment Visits

Once your eligibility is confirmed after screening, you will be able to participate in the study.

Treatment visits are necessary to receive the naturopathic medicine support. The supplements you will be given are coenzyme Q10, melatonin, and reishi. Co-Enzyme Q10 at a dose of 100 mg capsule twice daily with food; Melatonin at a dose of a 20 mg capsule once nightly at bedtime; and reishi at a dose of 1000 mg 3 times daily for a total dose of 3,000 mg or 3 g. You will be assigned to either the immediate treatment group or the delayed treatment group. If you are in the immediate and continuous treatment group, you will start taking your naturopathic supplements with cycle 1 of your chemotherapy treatment and continue for approximately 8 - 12 weeks. If you are in the delayed naturopathic medicine treatment group, you will start your supplement treatment at the beginning of your 3rd cycle of chemotherapy treatment and continue for approximately 4 - 6 weeks. All participants in the study will be given the Systems Inventory Tool (MDASI) at each treatment visit. The MDASI is a questionnaire that will take approximately 10 minutes to fill out electronically or on a paper version. This questionnaire helps to measure quality of life factors.

On the day you begin each cycle of chemotherapy treatment, we will perform the tests listed below. Please note: these tests will be completed over several hours during each Treatment Visit:

- The doctor or nurse will ask you to tell them of any side effects that you may have felt since your last visit and to give them a list of all medications that you are currently taking.
- A physical exam will be performed and your body weight and vital signs (heart rate, blood pressure, breathing rate and body temperature) will be recorded.
- The naturopathic oncology provider will ask you to tell them of any side effects that you may have felt since your last visit and to give them a list of all medications that you are currently taking.
- Your doctors will review your symptoms and ask you about your ability to perform your normal activities.
- Blood will be drawn for routine lab tests.
- Blood will be drawn for study specific lab tests (approximately 16 mL). If you are among the ten participants having labs drawn for ClearID CTCs, two additional tubes of blood (about 20 mL) will be collected before you start cycle 1 and 3 of your usual chemotherapy treatment.
- Compliance will be monitored by pill count and liquid measure according to your self-reported supplement log that you will fill out between visits
- You will be asked to fill out the MDASI Survey describing your symptoms.

End of Treatment Visit

- A physical exam will be performed and your body weight and vital signs (heart rate, blood pressure, breathing rate and body temperature) will be recorded.
- A review of your symptoms and your ability to perform your normal activities will be performed.
- Blood will be drawn for routine lab tests and for study specific tests.
- The doctor or nurse and naturopathic oncology provider will ask you to tell them of any side effects that you may have felt since your last visit and to give them a list of all medications that you are currently taking.

These procedures will happen after receiving cycle 4 of your chemotherapy.

How Long Will I be in The Study?

This research study is expected to take approximately 15 weeks of active participation.

What side effects or risks can I expect from being in the study?

You may have side effects from the supplements used in this study, and they will vary from person to person. Everyone taking part in the study will be watched carefully for any side effects. However, your doctor(s) and the researchers do not know all the side effects that may happen as a result of study participation; there may be unknown side effects that could occur. Side effects with these supplements have historically been very mild if at all.

The following are side effects that have been seen with melatonin, coenzyme Q10 and reishi.

Melatonin:

- No known toxicity or serious side effects reported; however, long-term human studies have not been conducted. Some uncommon side effects that have been reported in studies or case reports include drowsiness, alterations in sleep patterns, altered mental status, disorientation, tachycardia, flushing, pruritus, abdominal cramps and headache.
- Excessive dosages may cause morning sedation or drowsiness.

Coenzyme Q10:

- Generally well tolerated. In clinical studies, there have been no reports of significant adverse effects. Coenzyme Q-10 can cause gastrointestinal side effects such as nausea, vomiting, diarrhea, appetite suppression, heartburn, and epigastric discomfort (stomach ache) in less than 1% of patients. Some of these adverse effects can be minimized if total daily doses exceeding 100 mg are divided and administered two to three times per day
- Theoretically, may increase bleeding risk and may decrease response to warfarin (a blood thinning drug). However, a small study (randomized control trial) showed no effect on blood clotting activity (INR) with concurrent use of coenzyme Q10.
- Potential adverse reactions include abdominal discomfort, headache, nausea and vomiting.

Reishi (G. lucidum)

- Side effects are uncommon however reported side effects include allergies, dryness of the mouth, throat and nasal area, itching, nausea, epistaxis. Bloody stools have been reported with use of over 3-6 months.

- In patients with type 2 diabetes taking G. lucidum appeared to affect HA1C but not fasting glucose. Therefore it may be possible to have additive effects with botanicals or herbs that can have hypoglycemic potential.
- Clinical evidence also shows that G. lucidum may reduce blood pressure in some but not all patients with hypertension therefore additive affects might be possible for patients on anti-hypertensive medications or botanicals.
- A dose of higher than 3g daily may decrease platelet aggregation and therefore additive effects may occur with patients on medications or botanicals that have antiplatelet actions.

For more information about risks and side effects, ask your Naturopathic Oncology Providers. You should talk to your Naturopathic Oncology Providers about any side effects that you have while taking part in the study. The Naturopathic Oncology Providers will take steps to treat any side effects if they appear. If the naturopathic medicine support causes side effects they will be evaluated and discussed.

As with any drug, unknown risks and side effects are also possible with supplements. You could experience a side effect that is more severe than those mentioned above or a side effect that has not been anticipated with this supplement regime. There is a chance that you could be allergic to the supplements or to one of the chemicals used in its formulation. There is also a chance that other medications you may be taking could interact with this treatment regime. For your safety, you must tell the Naturopathic Oncology Provider or nurse about all medications you are taking before you start the study. Also, please tell the Naturopathic Oncology Provider or nurse before starting any non-study medications while you are on the study, including any over the counter medicines such as cough and cold remedies.

The risks of having blood drawn include pain, bruising, and rarely, infection. Blood will be drawn by experienced technicians and whenever possible it will be obtained at a time when blood is being obtained for other tests your Medical Oncologist has ordered.

There is not enough medical information to know what the risks might be to you if you become pregnant, your breast fed infant or your unborn child. You cannot take part in this study if you are pregnant or lactating (breast feeding). Therefore, all women who are sexually active and can become pregnant must use birth control measures while in this study. Breast feeding mothers must stop breast feeding to take part in this study.

The following birth control measures are acceptable: condoms or a diaphragm. Women who could possibly become pregnant must have a pregnancy test before taking part in this study. For the pregnancy test, a blood sample will be taken within 7 days before you receive your first dose of chemotherapy. You will be told the results of the pregnancy test. If the pregnancy test is positive, you will not be able to take part in the study.

Are there benefits to taking part in this research study?

If you agree to take part in this study, there may or may not be direct medical benefit to you. Your cancer may respond well to treatment or it may get worse. The information obtained from this study

may help doctors better understand cancers and this may eventually be helpful to future cancer patients.

What other choices do I have if I don't take part in this research study?

You do not have to be in this study to receive treatment for your condition. You can continue with conventional treatment with your Medical Oncologist and choose to not receive any naturopathic support, or to receive it without being part of the study. You should talk to the Naturopathic Oncology Provider and your Medical Oncologist about each of your choices before you decide if you will take part in this study.

Can I stop being in the study?

Study participation is voluntary. You can decide not to be in the study or you can decide to stop at any time. Tell the Naturopathic Oncology Provider if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the Naturopathic Oncology Provider if you are thinking about stopping so any risks from stopping the naturopathic support can be evaluated. Another reason to tell your Naturopathic Oncology Provider that you are thinking about stopping is to discuss what follow up care and testing could be most helpful for you.

Leaving the study will not affect your medical care. You can still get your medical care from our institution.

Why Might I Be Taken Out of the Study Early?

The Naturopathic Oncology Provider and/or study sponsor may decide to take you off this study without your consent if:

- You fail to follow the Naturopathic Oncology Provider's instructions.
- You experience a serious adverse event (harmful side effect) that may require evaluation.
- Your disease does not respond to your prescribed chemotherapy and your treatment needs to be changed by your Medical Oncologist.
- You experience side effects that are considered to outweigh benefits of your participation.
- You become pregnant.
- The research physician feels it is in the best interest of your health and welfare.

You may stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the Naturopathic Oncology Provider and your Medical Oncologist first.

In the event that you withdraw from the study, we will ask you to continue to be followed and clinical data will continue to be collected from your medical records.

Will I need to pay for the tests and procedures?

Because all of the drugs used in this study are part of regular treatment for your cancer at Midwestern Regional Medical Center, Inc., you or your insurance company/third party payer will be billed for all routine procedures and drugs associated with this study including the cost of treating injuries resulting from such routine procedures. Routine procedures and drugs are those that you would likely receive whether or not you are in this study. You will be responsible for any deductibles or co-payments that are associated with your insurance coverage. Examples of procedures and drugs that may be billed to you/your insurance company include routine blood tests to be certain you can receive your chemotherapy, and the drugs used to treat your cancer. However, Midwestern Regional Medical Center, Inc. will pay for any procedures or tests being done as part of this study that are not part of your routine care. All study supplements will be covered by Midwestern Regional Medical Center.

Will I be paid for taking part in this study?

No, you will not be paid for participation in this study.

What happens if I am injured because I took part in this research study?

If you get injured or sick as a direct result of being in this study, call the study doctor immediately. If you require immediate medical care to treat an illness or injury that is determined by the Investigator to be caused directly by participation in this study, and you were following the directions given to you as a study participant, then Midwestern Regional Medical Center agrees to pay the cost to cover this immediate medical care. You understand that Midwestern Regional Medical Center has no plans to cover the costs of further treatment beyond immediate and necessary care, nor do they have plans to give you money as compensation for such injury. There are no plans to pay for the cost of long-term care for illness or injury. If you are injured, the study doctor will discuss the available treatment options with you.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study in a timely manner.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES
What information may be used and given to others?

If you choose to be in this study, the study doctor will get personal information about you. This may include information that might identify you. Your personal health information (PHI) from your original and current medical records and all data resulting from your participation in this research will be

collected during the course of this study. This may include (but not be limited to): results of tests or examinations, medical procedures, tissue or blood sampling and medication records.

Your PHI will be used for regulatory purposes, to conduct the study, and to analyze the results of this research study. It may also be used in scientific presentations and publications, but in a way that will not identify you by name. Your PHI will be kept confidential, and unless required by law, will not be made publically available.

The study doctor will get your personal and medical information. For example:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits.

Who may use and give out information about you?

The following parties are authorized to use and/or disclose your PHI in connection with this study:

- The Principal Investigator, Christina M. Shannon, ND, FABNO
- Midwestern Regional Medical Center research personnel
- Western Institutional Review Board body that ensures the protection of human subjects enrolled in research studies at Midwestern Regional Medical Center

Who might get this information?

The parties listed in the preceding paragraph may share this information with:

- The Office for Human Research Protection in the U.S. Department of Health and Human Services (OHRP)
- The Food and Drug Administration (FDA)
- Sponsor representatives
- Western Institutional Review Board
- Midwestern Regional Medical Center internal monitoring representative(s)

These recipients may disclose your PHI to other parties, and are not required by law to protect your privacy.

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?

If you decide not to give permission to use and give out my health information, you will not be able to participate in this research study (or receive any research-related treatment). Signing this form is not a condition for receiving any medical care outside of the study.

May I review or copy my information?

To maintain the integrity of this research study, you may not have access to any health information collected and developed as part of this study until the study is completed. At that time, you would have

access to such health information if it was used to make a medical decision about you (e.g., if included in your medical record).

May I withdraw or revoke (cancel) my permission?

You are free to withdraw your authorization of use and disclosure of PHI (and to discontinue participation in this study) at any time. If you withdraw your permission, your PHI will no longer be used or disclosed in the study, except to the extent allowed by law (e.g., necessary to maintain the integrity of the research). If you wish to withdraw authorization for the research use and disclosure of PHI in this study, you must write to:

Christina M. Shannon, ND, FABNO
2520 Elisha Ave.
Zion, IL 60099

When will this authorization end?
This authorization does not expire.

Is my health information protected after it has been given to others?

There is a risk that your information will be given to others without your permission.

What do I do if I have questions about the study?

If you have any questions concerning your participation in this study, or if you experience a research related injury or become ill as a result of being in this study, contact the Naturopathic Oncology Provider Christina M Shannon, ND, FABNO at: (847) 872-6364 M-F 8:00am-5:30pm CST.

If you have questions about your rights as a research subject, or if you have questions, concerns, input or complaints about the research, you may contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com

WIRB is a group of people who perform independent review of research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff. Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions. You will be given a copy of this signed and dated informed consent to keep.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Consent

I have read this consent form (or it has been read to me) and understand it. All my questions about the study and my part in it have been answered to my satisfaction. I freely consent to be in this research study.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

By signing this consent form, I have not given up any of my legal rights.

I will receive a copy of this fully signed and dated consent form for my files.

Printed Name of Patient

Signature of Patient Date

I, the undersigned, have fully explained this informed consent to the patient named above.

Printed Name of Person Conducting Informed Consent Discussion

Signature of Person Conducting Informed Consent Discussion Date