Meriva for Treatment-induced Inflammation and Fatigue in Women with Breast Cancer

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Meriva for Treatment-induced Inflammation and Fatigue in Women with Breast Cancer

PI: Andrew H. Miller, M.D.
Department of Psychiatry and Behavioral Sciences
Emory Winship Cancer Institute
Emory University School of Medicine

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(i) Background and objectives

As many as 60% of breast cancer (BrCA) patients receiving radiation are known to develop fatigue with about 30% suffering persistent fatigue several months to years after treatment completion (12-23). The physical, psychological, and molecular mechanisms by which patients develop fatigue are poorly understood and most likely multi-factorial. One pathway that has received considerable attention is nuclear factor-kappa B (NF-kB)(24). The NF-kB pathway has emerged as having an important role not only in cancer treatment resistance but in the development of fatigue. NF-kB activation leads to over expression of interleukin (IL)-1beta, IL-6, and tumor necrosis factor (TNF)-alpha, all factors related to inflammation and factors that have been found to be upregulated in patients receiving radiation as well as BrCA survivors with fatigue (25-29). A recently published study looking at TNF-alpha, fatigue and cachexia in cancer patients receiving docetaxel showed that NF-kB is upregulated in fatigued patients and that agents which inhibit TNF-alpha lead to better tolerance of chemotherapy dose escalation (30). Work by our group and others has shown that ionizing radiation increases NF-kB pathway activity in circulating immune cells (as well as within breast cancer cells) and that this effect is most pronounced in women previously treated with chemotherapy (31, 32). Our work has shown that the NF-kB pathway activity in circulating immune cells is also related to fatigue development in BrCA patients treated with radiation and that patients most at risk for persistent fatigue and NF-kB pathway activity are those who have received chemotherapy for their breast cancer (31).

Curcumin, a known inhibitor of NF-kB, has been shown to decrease NF-kB activation in human participants. In a recent study, 8 grams of curcumin by mouth daily for 8 weeks was well tolerated in patients with pancreatic cancer and other pre-malignant conditions with no associated toxicities (6, 8). Although there is concern over the body's absorption of curcumin, the bioavailability of curcumin in the study of pancreatic cancer patients was shown, with peak drug levels at 22 to 41ng/mL that remained relatively constant over the first 4 weeks of treatment with 8 grams of curcumin daily (8). Clinical trials with daily dosages of 1,125 to 2,500mg have also confirmed the safety of curcumin and also shown its ability to decrease inflammation in patients with rheumatoid arthritis and in post-operative patients (6, 33, 34). In vivo murine models of chronic fatigue syndrome have also shown that curcumin may also alleviate symptoms of fatigue (35). While these studies are promising, very little is known about the capacity of Meriva to inhibit NF-kB in women treated for BrCA. We hypothesize that oral Meriva, a known inhibitor of NF-kB, may be used to decrease levels of NF-kB activity in BrCA patients previously treated with chemotherapy who go on to receive radiotherapy (XRT), a carefully chosen group of patients at particular risk for high levels of NF-kB DNA binding (a direct measure of NF-kB pathway activity).

We have chosen to administer oral Meriva, 500mg BID, in our patient population based on the above data. Meriva-500 is a curcumin formulation that also contains phosphatidylcholine, derived from soy that has been shown to aid in absorption of curcumin (9), permitting a lower overall dose of curcumin. Of note, 1000 mg Meriva contains 200 mg curcuminoids (>90% curcumin).

By decreasing activity of NF-kB, fatigue may improve in BrCA patients taking Meriva. Results from this study will contribute to the limited research available on the capacity of curcumin treatment, including Meriva, to inhibit NF-kB and its downstream mediators in vivo as well as symptoms of fatigue associated with excessive NF-kB pathway activity in BRCA patients.

The primary objective of this protocol is to determine if Meriva reduces NF-kB DNA-binding and its downstream mediators in patients receiving XRT for their breast cancer after having completed chemotherapy. Patients who have received prior chemotherapy will be eligible, because we have found that this enriched population is at particular risk for exhibiting increased NF-kB DNA binding following XRT. NF-kB DNA-binding is a direct measure of NF-kB pathway activity, while plasma concentrations of TNF-alpha and its soluble receptor sTNFR2, interleukin (IL)-1 receptor antagonist (IL-1ra), and C-reactive protein (CRP) are downstream indicators of NF-kB activity.

Secondary objectives will be to 1) determine if Meriva decreases levels of fatigue as measured by the Multidimensional Fatigue Inventory (MFI) in BRCA patients, and 2) determine longitudinal variances in skin changes measured by ultrasound in breast cancer patients undergoing XRT. Results from this study will contribute to the limited research available on the capacity of Meriva and curcumin to inhibit NF-kB and its downstream mediators in vivo.

(ii) Study location, personnel, and Institutional Review Board

Study location

Studies proposed in the current application will take place either at the Emory Winship Cancer Institute, 1365-C Clifton Rd NE, Atlanta, GA 30322, or the Emory University Hospital Midtown, 550 Peachtree St NE, Atlanta, GA 30308.

Personnel

Sponsor Investigator: Andrew H. Miller, MD; 1365-B Clifton Rd NE, Suite 5100, Atlanta, GA 30322; Dr. Miller is the Director of Psychiatric Oncology at the Emory Winship Cancer Institute, has many years of experience studying the psychiatric changes in cancer patients as well as novel therapies to reverse these features. Please also see attached CV.

Co-Investigator: Mylin Torres, MD; 1365-B Clifton Rd NE, Suite 5100, Atlanta, GA 30322; Dr. Torres is a radiation oncologist with multiple years of experience with breast cancer patients and study of fatigue symptoms experienced by women with BrCA. Please also see attached CV.

Co-Investigator: Karen Godette, MD; 1365-B Clifton Rd NE, Suite 5100, Atlanta, GA 30322. Dr. Godette specializing in breast cancer. Please also see attached CV.

Co-Investigator: Thaddeus Pace, PhD; Dr. Pace has multiple years of experience measuring inflammatory activation across a number of disorders including major depression and anxiety. He has worked with Drs. Miller and Torres for the last several years to measure NF-kB pathway

activation and other inflammatory biomarkers in women after treatment for BrCA with increased fatigue symptoms. Please also see attached CV.

Co-Investigator: Tian Liu, PhD; 1365-A Clifton Rd NE, Suite 1313, Atlanta, GA 30322; Dr. Liu is a board certified in Therapeutic Radiologic Physics with expertise in quantitative assessment of radiation tissue toxicity using ultrasound imaging. Please also see attached CV.

Institutional Review Board

All procedures described in this protocol will take place under the supervision of the Emory University Institutional Review Board, 1599 Clifton Road, 5th Floor East, Atlanta, GA 30322, Telephone: (404) 712-0720, Fax: (404) 727-1358.

(iii) Patients inclusion and exclusion criteria

Female breast cancer patients over the age of 18 who were previously treated with standard anthracycline- and/or taxane-based chemotherapy will be recruited for this study. Patients enrolled in the study will meet standard criteria for whole breast XRT or chest wall XRT for patients who have had mastectomies. Patients will be included if they have a National Comprehensive Cancer Network score for fatigue over 3 (NCCN>3) as determined by the standard fatigue scale of 0-10 unless otherwise approved by the principle investigator or PI's designee. Participants will be excluded for medical conditions that are contraindications to XRT and/or might confound the relationship among fatigue and inflammation, including pregnancy, unstable major psychiatric disorders, autoimmune (active within the past 6 months) or inflammatory disorders, chronic infectious diseases (e.g. HIV, hepatitis B or C), neurologic disorders and uncontrolled cardiovascular, metabolic, pulmonary or renal disease (as determined by medical history, physical examination or laboratory testing) unless otherwise approved by the PI or PI's designee. Participants with an unstable major psychiatric disorder, as assessed by study clinician, or a diagnosis of Alcohol Abuse (more than 5 drinks in a 24 hour period) or Substance Dependence within the past 1 year (as determined by a standard psychiatric interview) will be excluded unless otherwise approved by the PI or PI's designee. Participants with an IDS score > 32 or IDS #18 score 2≥ will be referred to Dr. Andrew Miller. Participants with uncontrolled or chronic pain, a score greater than 4 on the standard pain scale, will be excluded unless otherwise approved by the principle investigator or PI's designee. Participants taking drugs known to affect the immune system (e.g. glucocorticoids, methotrexate, sulfasalazine and nonsteroidal anti-inflammatory agents) will also be excluded unless otherwise approved by the principle investigator or PI's designee. To protect against possible side effects of the study drug, women who are pregnant or nursing a child may not take part in this study. Subjects of childbearing ability must agree, with the study doctor, on a method of birth control to use throughout the study. Subjects who think they have gotten pregnant during the study must notify the study doctor immediately. Pregnant women will be taken out of the study. Patients using over the counter supplements or other natural products within one week of treatment, excluding vitamins and calcium supplementation, or at the discretion of the enrolling physician, will be excluded. Patients who have evidence of infection as determined by history, physical exam or laboratory testing (complete blood count and urinalysis) at baseline will be excluded unless otherwise approved by the PI or PI's designee.

Patients with anemia (HEM < 10g/dl) at baseline will be excluded unless otherwise approved by the PI or PI's designee. In addition, patients who develop evidence of infection (as determined by history, physical exam or laboratory testing) during the study will be discontinued from the study unless otherwise approved by the PI or PI's designee. Patients will be asked to refrain from having more than one alcoholic beverage per day.

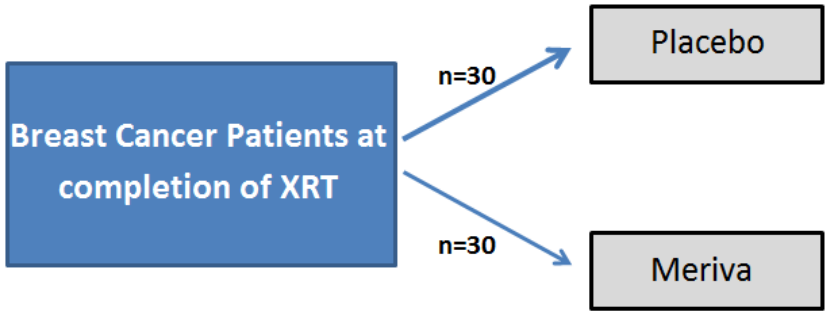
This protocol proposes to enroll 60 total patients, with 30 randomized to the Meriva arm and 30 randomized to the placebo arm of the study.

(iv) Design

This double-blind, placebo controlled, randomized clinical trial will enroll BrCA patients seen at the Emory Breast Centers (Winship Cancer Institute of Emory University and Emory University Hospital Midtown) or in the community for XRT who were previously treated with chemotherapy. These patients will be approached for enrollment on this therapeutic study during the first three weeks of receiving radiation therapy or one to three months post XRT.

In patients previously treated with chemotherapy, we will administer placebo or Meriva daily for approximately 6 weeks, beginning immediately after the completion of XRT or up to 3 months post-XRT. Patients will be randomized to placebo or Meriva-500 (500 mg PO BID) using a computerized system under the control of Emory Pharmacy. Randomization will occur in blocks of 10. Meriva-500 will be obtained from Thorne Research. Blood will be drawn at baseline and at the first follow-up appointment to determine NF-kB DNA-binding in peripheral blood mononuclear cells, expression of NF-kB regulated genes, and plasma cytokine concentrations. The final study visit will occur during the 6 week treatment period. Study Coordinator will make an effort to coincide the follow up visit and six week post-radiation follow up visit. Because placebo or Meriva is being given after XRT is complete, it is unlikely to alter the efficacy of the XRT or enhance side effects of XRT.

Patients will receive daily Meriva treatment for approximately 6 weeks beginning immediately after radiation therapy (XRT) or up to 3 months post-XRT. Peripheral blood will be drawn during the last week of XRT and again after 6 weeks of Meriva (or Placebo) for assessment of NF-kB pathway activation.



Thirty patients will be enrolled per arm. NF-kB DNA-binding, downstream mediators of NF-kB activity and microarray analysis of NF-kB regulated genes will be used to determine NF-kB pathway activation. If any of these measures of NF-kB DNA binding activity (the primary outcome variables) decrease to the mean level of non-chemotherapy treated women who receive XRT, the 500 mg BID dose level will be considered successful.

(v) Dosing

The 500 mg BID dose of Meriva that will be used in this protocol was selected after consulting with Stefano Togni, DVM, Head of Business Development at Indena S.p.A (Milan, Italy) and Giovanni Appendino, Chief Scientific Advisor, Indena S.p.A (Milan, Italy). The dose proposed for use here is similar to doses used in other studies investigating Meriva (1-4). For example, the single dose selection is also supported by a recent study by Cuomo and colleagues showing that 200-300 mg of curcumin as Meriva (i.e. a single Meriva dose of 1000-1500 mg) resulted in 29-fold higher for Meriva than for its corresponding unformulated (non phosphatidylcholine) curcuminoid mixture. In terms of the length of Meriva treatment, 6 weeks was chosen because it is the period of time over which we have observed a significant increase in NF-kB pathway activity related to fatigue symptoms (31).

We propose to increase the dose of Meriva 500 administered to patients randomized to the active arm of the study from 1 to 2g total per day (500mg to 1g BID, respectively). This dose increase will be implemented 1) after 10 patients have completed the protocol (5 active and 5 placebo), 2) if no statistically significant differences are noted at the primary study endpoint (peripheral blood mononuclear cell NF-kB DNA-binding) between patients randomized to the active arm and patients randomized to the placebo arm, and 3) no dose-limiting side effects have been encountered. Dose-limiting side effects are considered to be a Grade 3 (Based on NCI Common Terminology Criteria for Adverse Events) or higher adverse event that is deemed to be probably related to the drug.

The change to 2g/d dose is supported by Mantovani and colleagues who reported beneficial effects of 2g/d Meriva on inflammatory biomarkers in cancer patients taking Meriva for 1 month (50). Also supporting this modification is a trial comparing the analgesic effects of 1.5g vs. 2g Meriva in a mixed patient group with different sources of pain (e.g. arthritis, neuropathy, recurrent headaches) (51). In general the results of this study suggest that Meriva at 2g/d may be more efficacious than Meriva at 1 g/d. Finally, a recent paper by Drobnic and colleagues found that 2g/d decreased inflammatory markers and muscular damage in healthy men undergoing intense physical exercise (52). No tolerability issues were noted in either of these studies except for mild nausea and heartburn in the report by Di Pierro et al. (51), which was attributed to the bulk of capsules consumed and not the content of the capsules.

Of note, because of difficulty obtaining enough cells from the blood of the first 10 subjects who completed the study, we were unable to measure peripheral blood NF-kB DNA binding. Therefore, because we could not statistically compare NF-kB DNA binding between groups, the Meriva dose of 1 g per day was maintained without an increase (as per protocol). In addition, statistical consultation based on IL-6 values in the first 10 completed subjects suggested that continuing enrollment at the Meriva 1 mg dose would give sufficient power (>0.80) to detect a difference in this NF-kB-related inflammatory endpoint at study completion or after enrollment of at least 40 subjects. Similar findings were observed with fatigue. For these reasons, the Meriva dose will be continued at 1mg per day for the entirety of the study for all subjects.

Although a maximum tolerated dose (MTD) for Meriva has not yet been identified in any population, most published studies have tested doses of either 1 or 2 g/d Meriva (containing 200-400 mg curcuminoids)(53)**.** By extrapolation of pharmacokinetic data (54,55), 2 g/d Meriva (containing 400 mg curcuminoids) dose may be bioequivalent to either 4 or 12 g/d non-complexed curcuminoids, corresponding to the middle range of curcuminoid doses previously tested in humans. Of note, the highest oral dose of Meriva being tested in humans is 4 g/d Meriva (containing 800 mg curcuminoids) (NCT01859858). However this study is ongoing, and information related to effectiveness and adverse events (AEs) is not available. All reported AEs for Meriva up to 2 g/d have been limited to grade 1 or 2 gastrointestinal symptoms and chronic toxicity studies in rats suggest that a human equivalent dose of 24 g/d Meriva is safe in humans (56).

(vi) Observations and measurements

Based on work performed in prior studies, we do not anticipate biomarker responses that would suggest adverse reactions to Meriva (1-4). We will therefore not collect blood samples during the 6 week treatment with Meriva to monitor adverse biomarker responses. Research blood will be collected at baseline during the last week of XRT or up to three months post XRT and at the conclusion of the 6 weeks treatment with Meriva. Patients will be interviewed weekly by phone to ensure they are not experiencing side effects previously described for curcumin, including nausea and diarrhea. If they do report worsening of these symptoms compared to before they started Meriva, they will be asked to immediately discontinue taking Meriva and come to the clinic for full physical evaluation. In the case that a patient experiences adverse side effects and stops taking Meriva, self-report information and blood samples will still be collected at the early termination visit.

Curcumin Visit I: Screening

- Information regarding disease characteristics (including stage, tumor size, grade)
- Patient demographics (including age, race, co-morbidities, social history)
- Systemic treatment (including hormone therapy, systemic therapy), surgical treatment, and radiation treatment will be collected and recorded.
- Informed consent process
- Physician or NP evaluation or modified physical
- CBC with diff
- Serum quantitative pregnancy test
- Urinalysis with microscopy
- Self-report of fatigue level and pain on a scale of 0-10, 0 being none and 10 being extreme. The patient's self-report of fatigue at these visits will be used to assess the grade of their fatigue.
- Inventory of Depressive Symptomatology – Self Reported (IDS-SR)[41]- Participants with an IDS score > 32 or a score of 2 or higher on IDS item #18 will be referred to Dr. Andrew Miller
- PROMIS Fatigue Short form [49]
- Patient reimbursement
- Review labs for infection and anemia

Curcumin Visit II: Baseline (XRT end – last week of XRT or within 3 months after)

- Inclusion criteria completed

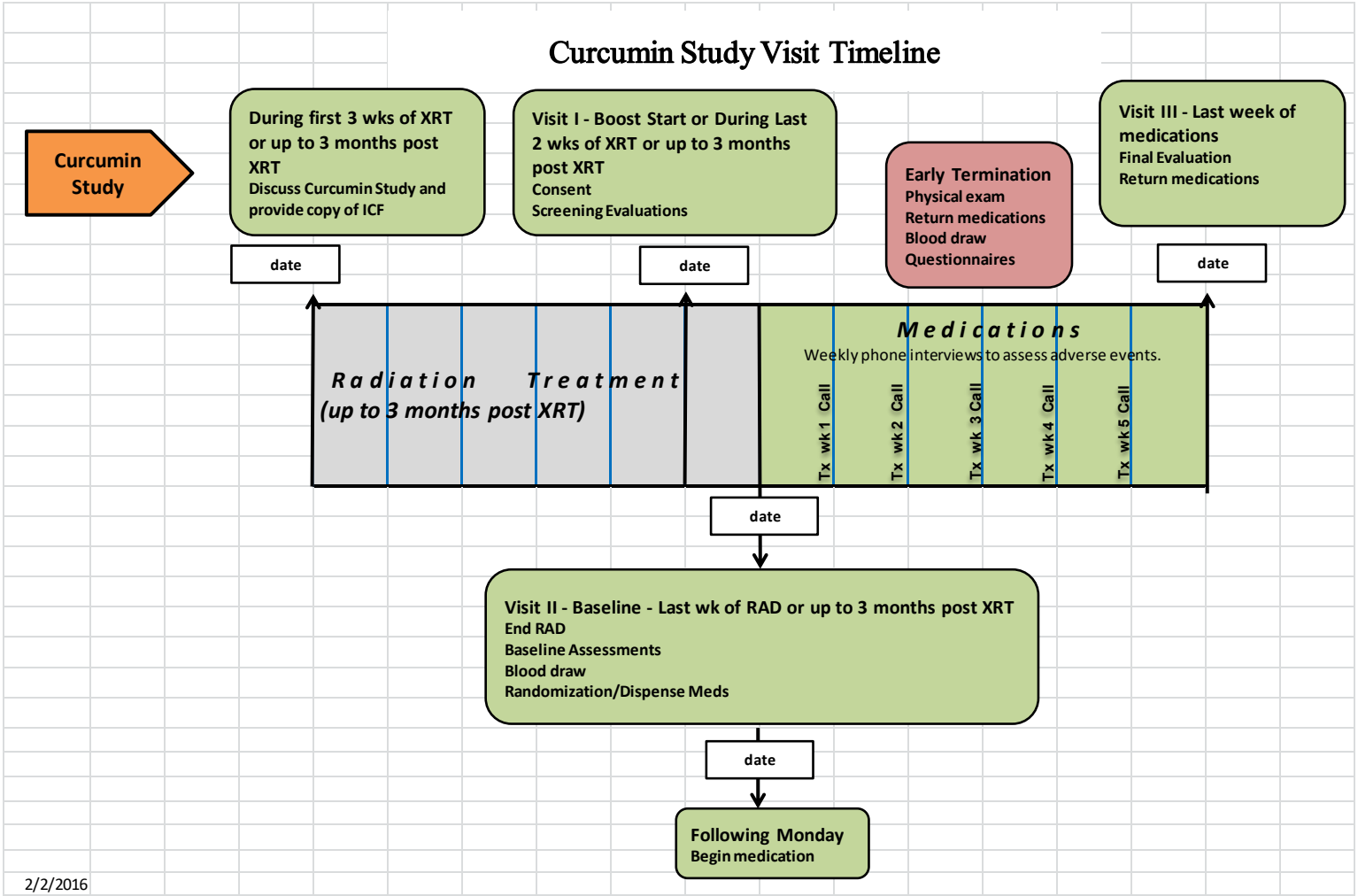
- Mediterranean diet survey, Inventory of Depressive Symptomatology – Self Reported(IDS-SR)[41], Pittsburgh Sleep Quality Index (PSQI) [42-45], Perceived Stress Scale (PSS)[46], Godin Leisure-Time Exercise Questionnaire (GLTEQ)[48], Multidimensional Fatigue Index (MFI) (36) and PROMIS Fatigue Short form [49]
- Self-report of fatigue level and pain on a scale of 0-10, 0 being none and 10 being extreme.
- Fasting blood draw for research (two 4 ml purple tops, two 6 ml purple tops, and 1 tempus tube)
- Ultrasound scan and photographs at PI's discretion
- Randomization
- Dispense medications and medication diary
- Patient reimbursement

Compliance:

Patients will be asked to fill out a medication diary daily and report any missed doses during weekly telephone interviews. Patients who report taking less than 75% of their medication between interviews may be excluded from study participation at PI's discretion.

Curcumin Visit III: final evaluation of the last week of Meriva or placebo treatment

- Physician or NP evaluation or modified physical



- CBC with diff– review for infection and anemia
- Fasting blood draw for research (two 4 ml purple tops, two 6 ml purple tops, and 1 tempus tube)
- Ultrasound scan and photographs at PI's discretion
- Self-report of fatigue level and pain on a scale of 0-10, 0 being none and 10 being extreme.
- Inventory of Depressive Symptomatology – Self Reported (IDS- SR)[41], Pittsburgh Sleep Quality Index (PSQI)[42-45], Perceived Stress Scale (PSS)[46], Godin Leisure-Time Exercise Questionnaire (GLTEQ)[48], Multidimensional Fatigue Index (MFI) (36) and PROMIS Fatigue Short form [49]
- Collect unused medications and medication diary
- Patient reimbursement

During the screening visit Curcumin Visit 1, a urinalysis, CBC with differential, serum quantitative pregnancy test, and physician evaluation or modified physical by the study NP will be performed. A subset of patients may have an ultrasound scan and photographs done by Radiation-Oncology research team. The lab tests will be processed in the Emory Medical Laboratory (EML) system. The results of the evaluation or modified physical and urinalysis as well as the CBC with differential will be reviewed to rule out infection or anemia to verify eligibility. If infection or anemia or pregnancy is detected, the patient will be withdrawn from the study.

An ultrasound of the treated breast or chest wall and untreated breast and axilla may be performed at the baseline and final evaluation visits to assess cutaneous toxicity. These scans will be conducted based on the availability of research staff and space to conduct the scan. Each scan will take between 5 and 10 minutes to perform. Photographs of the treated breast (or chest wall) as well as the contralateral breast will also be taken. Ultrasound data and photographs will be stored in a computer for later review.

The patient will be randomized to Meriva or placebo at Curcumin Visit II. Medications will be dispensed, to be started the following Monday. A physician evaluation or modified physical will also be performed at the final evaluation, Curcumin Visit III. A physical exam will be performed at the time of early termination as well as a CBC with differential, research bloods, and self-report forms.

For safety precaution, patient will be asked to repeat Curcumin Visit I if a lapse of 30 days or greater occurs between Curcumin Visit I and Curcumin Visit II.

See checklist below for details on Curcumin Study Visits. **Laboratory Measures**

Sample Collection & Handling

Blood will be collected using purple top vacutainers (containing EDTA additive) and a tempus tube. The blood volume per tube will be 3 – 3.5 ml for the 4 ml tubes, and 5 – 5.5 ml for the 6 ml tubes. Four purple top tubes and a tempus tube will be collected at baseline and at the final evaluation under fasting conditions. Prior to collection, study numbers will be determined and barcoded labels will be placed on collection aliquots.

Curcumin Study Checklist										
	CLINIC VISIT	CLINIC VISIT	CLINIC VISIT						CLINIC VISIT	CLINIC VISIT
Procedure	Initial Meeting	Visit I Screening	Visit II Baseline	Tx wk 1 Call	Tx wk 2 Call	Tx wk 3 Call	Tx wk 4 Call	Tx wk 5 Call	Visit III	Early Termination
Curcumin ICF for review	x									
Curcumin Consent		x								
Inclusion Criteria		x								
Demo Sheet		x								
Physician/NP Evlauation		x							x	
Physical Examination										x
Urinalysis		x								
Serum quantitative pregnancy		x								
CBC w/diff		x							x	x
Review labs for infection and anemia		x							x	x
Blood draw for research: 4 purple tops and 1 tempus			**						**	**
Randomize/dispense meds			***							
Patient reimbursement		x	x						x	x
Phone Interview				*	*	*	*	*		
Meds returned/counted									x	x
Meds diary returned									x	x
Concomitant Medications reviewed		x	x	x	x	x	x	x	x	x
Adverse Events Reviewed				x	x	x	x	x	x	x
Ultrasound scan and photographs			x						x	
Fatigue Level		x	x						x	x
Pain Level		x	x						x	x
Mediterranean Diet Survey			x							
GLTEQ			x						x	x
MFI 20			x						x	x
PSS			x						x	x
IDS-SR		x	x						x	x
PSQI			x						x	x
PROMIS		x	x						x	x
** Weekly phone interviews for Adverse Event Assessment/ Medication Compliance. If indicated, stop medications and come in for physical exam.*										
*** Plasma analysis of inflammatory markers, PBMC analysis of NF-kB DNA binding, and gene expression.*										
**** Medication dispensed during treatment check by physician or nurse practitioner. Medication to begin the following Monday after medications are dispensed.* *v. 12/19/2017*										

Blood samples will be drawn at the same time of day between 9:00-11:00 am (to reduce potential circadian effects) under sterile conditions at each of these visits. Whole blood for plasma, buffy coat, and peripheral blood mononuclear cells (PBMCs) will be collected into EDTA vacutainer tubes. Two tubes will stored at 4°C for less than 45 minutes, after which plasma and buffy coat will be separated by centrifugation at 1000 x g for 10 minutes at 4ºC, aliquoted into siliconized polypropylene tubes and stored at -80ºC until assayed. Two tubes will be kept at room temperature for less than 45 minutes, after which plasma will be replaced

by saline for the isolation of PBMCs using density gradient centrifugation. PBMCs will be stored in freezing serum (90% fetal bovine serum, 10% DMSO) at -80ºC until nuclear extraction or mRNA isolation.

Plasma Analysis of Inflammatory Markers

Plasma concentrations of TNF alpha, sTNFR2, IL-ra, and IL-6 will be determined using sandwich ELISA according to manufacturer's protocol (R & D Systems, Minneapolis, MN). Each determination (excluding the soluble cytokine receptors which require less sample) requires 100-150µl of sample, and all samples will be assayed in duplicate. ELISA assays will be performed in Dr. Pace's laboratory. Quality control plasma of both low and high cytokine concentrations will be included with every assay. The mean inter- and intra-assay coefficients of variation for control samples are reliably 10% or less. High sensitivity CRP will be measured in the CLIA certified laboratory of the Emory University Hospital using a standard turbidimetric assay.

NF-kB DNA Binding

Peripheral blood mononuclear cells (PBMC) will be isolated on ficoll-hypaque gradients before nuclear protein extraction and DNA-binding analysis. DNA-binding of NF-κB will be determined by an ELISA kit as previously described by our group (Active Motif [Carlsbad, CA])(37, 38). Like electrophoretic shift assays (EMSA), the enzyme-linked immunosorbent assay (ELISA)-based method measures transcription factor binding to their consensus DNA sequences. The ELISA-based approach detects DNA-protein interaction by observing transcription factor consensus sequence binding in a 96-well plate. The consensus sequence is fixed to the bottom of the well and specificity is demonstrated by adding a soluble consensus sequence to control wells. We have demonstrated that the ELISA-based approach has high sensitivity and specificity for detecting activated transcription factors by running nuclear extracts in both EMSA and DNA-binding ELISA with the same effects observed (39).

Gene Expression

RNA will be isolated from PBMCs collected as described above using an RNeasy Mini Kit (Qiagen, Hilden, Germany). The A260/A280 ratio will be used to assess RNA purity. Samples will be analyzed in the Biomarker Profiling Core at The Emory Winship Cancer Institute for gene expression analysis using an Illumina platform. Initial data analysis will be conducted using the BeadStudio software from Illumina, and the data will then be exported to the TELiS system available online (40). The TELiS database in conjunction with the PromoterStats statistical tool will be used to identify transcription factors (i.e. NF-kB) driving gene expression detected in the microarray. Of note, previous studies using the TELiS database have identified profiles of gene expression that reflect NF-kB signaling activity (40).

Microarray Analysis

Specimens collected in Tempus tubes will be used for microarray analysis. 2-8µg of high quality RNA may be extracted per 1mL of blood. Tempus tubes contain up to 4mL of blood,

and therefore at least 8µg of RNA will be extracted for analysis and validation. RNA will be molecularly characterized using an Illumina BeadStation and will be run on the HumanHT-12 Beadchips or a comparable chip. Specimens will have RNA extracted for expression profiling in a batched manner to allow for minimal variation in extraction, in vitro transcription (IVT) labeling, and hybridization to the Beadchips. The primary endpoint of the microarray data analysis will be to determine if genes regulated by NF-kB exhibit decreased expression when patients are treated with Meriva vs. placebo.

Outcome Measures

The primary outcome to be measured will be the change in NF-kB DNA binding and its downstream mediators (plasma concentrations of TNF-alpha, sTNFR2, IL-1ra, IL-6 and CRP)after six weeks of treatment with daily placebo or Meriva. The secondary endpoint will be the change in fatigue from baseline to six weeks after treatment with Meriva or placebo. . Microarray analysis will also be performed before and after treatment to look at the expression of NF-kB response genes: **Primary Hypothesis: Patients responsive to Meriva will have decreased NF-kB DNA binding, decreased activation of NF-kB responsive genes and decreased downstream mediators of NF-kB pathway activation.**

Analytical Plan

Power analysis: Based on a preliminary data, the mean change of NF-kB DNA binding from baseline among patients who underwent six weeks XRT was 8.2 ng NF-kB per assay well (SD = 9.0). We hypothesize that in this study the patients in the placebo group will have the similar response as in the preliminary data, and patients who receive Meriva, the mean change of NF-kB DNA-binding level from baseline to 6 weeks post XRT is 0.0 with a reduced SD of 4.5. Based on alpha of 0.05 and a n = 11 per group, we will have 82% power to detect the above hypothesized difference by one-sided two-sample t test. We believe such a difference is clinically meaningful and is well within the range of differences observed in chemotherapy vs. no chemotherapy patients and fatigued vs. non-fatigued patients.

Statistical analysis plan: Primary objectives: the mean changes of NF-kB DNA binding from baseline to Week 6 will be compared between two groups using two-sample t test. The change of plasma concentration of NF-kB downstream mediators from baseline will be compared between two groups using two-sample t-test/Wilcox sum rank test for continuous measures and using Chi-square test/Fisher's exact test for categorical measures. Secondary objectives: The change of MFI over time in two groups will be compared by the GEE model.

(vii) Chemistry, manufacturing, and control information

a. Drug substance

Curcumin, (1*E*,6*E*)-1,7-bis (4-hydroxy-3-methoxyphenyl) -1,6-heptadiene-3,5-dione, is the major active ingredient in Meriva-500. Meriva also contains lesser amount of the other two curcuminoids, desmethoxycurcumin and bis-desmethoxycurcumin. Curcumin is the orange pigment in turmeric spice (the primary ingredient in many food curries). Meriva-500 also contains "phytosomes", or phosphatidylcholine (PC), that is extracted from soy. PCs are a major

component of animal cell membranes. The combination of PC with curcuminoids improves the absorption of curcumin. A recent article by Cuomo and colleagues indicates that absorption of curcuminoids was about 29-fold higher for Meriva than for its corresponding unformulated curcuminoid mixture (9). Information about preparation, acceptable limits and analytical methods used to insure identity, strength, quality, and purity of Meriva is provided in the Manufacturing Protocol provided by Thorne Research (see Appendix 3). We attest that research activities proposed under this IND will only administer batches of Meriva-500 that contain less than 10 µg/day of lead and not more than 1.5 µg/day of arsenic.

b. Drug product

Details regarding components, the name and address of the drug product manufacturer, description of manufacturing and packaging procedures, acceptable limits and analytical methods used to assure identity, strength, quality, and purity of the drug product, and information about Meriva's stability are all provided in the Manufacturing Protocol provided by Thorne Research (see Appendix 3). Component Certificates of Analysis, Meriva and placebo Letters of Formulation, and Manufacturing Flow Chart are presented in Appendix 4.

c. Placebo

Details about the placebo are provided in the Manufacturing Protocol provided by Thorne Research (see Appendix 3). Component Certificates of Analysis, Meriva and placebo Letters of Formulation, and Manufacturing Flow Chart are presented in Appendix 4.

d. Labeling details

Details about Meriva and placebo labeling are provided in the Manufacturing Protocol provided by Thorne Research (see Appendix 3).

e. Environmental analysis requirements

I claim categorical exclusion under 21 CFR 25.31(e) for the study under this IND. To my knowledge, no extraordinary circumstances exist.

(viii) Pharmacology and toxicology

a. Pharmacology and drug disposition

Bioavailability of Meriva has been documented in both animal and human studies. A published report on Meriva bioavailability in rats is presented in Appendix 5. An original report on absorption of Meriva in humans compared to a curcumin preparation without phosphatidylcholine is presented in Appendix 6. On the whole bioavailability of curcuminoids after treatment with Meriva is good in both rats and humans.

b. Toxicology

Acute toxicity of Meriva has been examined in rats following a single oral administration (2000 mg/kg body weight, see Appendix 1). After 3 days, there were no changes in body weight.

Necropsy revealed no internal or external abnormalities. This study concluded that there is very slight toxicity in rats after 2000 mg/kg Meriva. The LD50 was stated to be significantly greater than 2000 mg/kg

c. 21 CFR Part 58 compliance

The toxicology study was conducted in compliance with the good laboratory practice regulations in Part 58.

(ix) Previous human experience

While there are numerous studies in humans that have examined curcumin in various formulations, fewer exist that use the Meriva formulation (i.e. curcumin with phosphatidylcholine) specifically. Meriva has shown considerable disease-modifying promise in several disorders, including in type-2 diabetes (1), osteoarthritis (2, 3)(Appendix 2), and chronic anterior uveitis (4)(Appendix 2). In each of these studies toxicity and tolerability problems were not reported.

With respect to cancer, 8 grams of curcumin (non phosphatidylcholine formulation) by mouth daily for 8 weeks was well tolerated in patients with pancreatic cancer and other pre-malignant conditions with no associated toxicities (6, 8). In one of these studies a subgroup of patients exhibited a decrease in tumor mass that corresponded to inflammatory biomarkers, including plasma interleukin-6. Clinical trials with daily dosages of 1,125 to 2,500mg have also confirmed the safety of curcumin and also shown its ability to decrease inflammation in patients with rheumatoid arthritis and in post-operative patients (6, 33, 34). While these studies are promising, very little is known about the capacity of curcumin to inhibit NF-kB in women treated for BrCA.

(x) Additional information

Drug abuse potential

A review of the literature reveals no potential risk of drug abuse for curcumin generally, and Meriva specifically.

(xi) Potential risks and benefits to subjects:

Potential risks: The risk to patients is minimal. Blood draws will be performed at two different time points during the course of this study.

All patients will be assigned a study number, and this number will be used in place of patient's names or identification numbers so there should be minimal risk of loss of patient confidentiality. The master sheet containing the patient number and study ID will be kept in a password protected database.

Curcumin doses up to 8 grams per day have been shown to be well tolerated with minimal side effects. It is not expected that curcumin doses proposed in this study will cause untoward adverse effects.

A recent literature review identified a study which suggested that curcumin may aggravate iron deficiency. However, patients will be screened for evidence of iron deficiency as evidenced by their hemoglobin and hematocrit. No patient with evidence of iron deficiency will be admitted to the study. All patients will be evaluated for evidence of iron deficiency upon completion of the study as per protocol.

Potential benefits: Patients undergoing this study may have improvement in their fatigue levels.

(xii) Data and Safety Monitoring Plan:

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will oversee the conduct of this study. This committee will review all pertinent aspects of study conduct including patient safety, compliance with protocol, data collection and efficacy. The committee will review the charts of 10% of patients enrolled to the study and two of the first 5 patients entered to the study. Reviews will occur annually if categorized by the committee as a low to moderate risk study or biannually if considered a high-risk protocol. The committee will conduct additional audits if necessary at any time-point. The Principal Investigator will notify the DSMC about the accrual of patients when the first 5 have been entered to the study. The PI will also notify the DSMC of the study status within 2 months before the next annual review is due.

(xiii) Adverse Event Reporting

Enrolled participants will be monitored closely by study clinicians for any adverse events. All adverse events will be collected using the NCI Common Terminology Criteria for Adverse Events version 4.0. If any overt study-related adverse events occur, a decision will be made about study continuation. Additionally, a record of adverse events for study participants will be reported to the DSMC on a regular basis. Subjects will be closely monitored during the course of the study for development of any serious or unexpected adverse reactions. Those events meeting Emory IRB criteria for a reportable event will be reported to the IRB or the Winship Cancer Institute DSMC according to standard regulations and procedures. The Emory IRB Reportable Events Guidelines are included in an attachment.

(xiv) Data Quality Monitoring Plan:

Periodic chart monitoring will be conducted by study personnel to validate integrity of the data. Chart reviews will take place after each block of five subjects and may include, but not be limited to, the presence of a signed informed consent document, documentation that the informed consent was obtained prior to performance of any study-related evaluations, documentation related to billing compliance, treatment calendars, enrollment reported to OCR, enrollment recorded in Oncore ®, treatment order and/or prescription form copies, and source documentation as defined in the Winship Clinical Trials Office's Standard Operating Procedure.

The project will be subject to random chart audits conducted by the Winship Clinical Trials Office in accordance with Standard Operating Procedures. A minimum of 5 subject charts may be randomly audited as requested by the PI, the Associate

Director for Clinical Research, the Director of the CTO, the IRB, the ORC, or other Emory research compliance personnel, or the assistant director on an as needed basis.

1. Any of the above persons may request a random audit of clinical trials records for the subjects enrolled on any study managed by this office.

2. When records are requested they will be made available to the person listed above within 2 hours.

3. Chart review may include, but not be limited to, the presence of a signed informed consent document, documentation that the informed consent was obtained prior to performance of any study-related evaluations, documentation related to billing compliance, treatment calendars, enrollment reported to OCR, enrollment recorded in Oncore ®, treatment order and/or prescription form copies, and source documentation.

4. Audit will be performed by the persons listed above in "Procedure" or the internal monitors.

5. Audit results may be reviewed by the Winship CTO Director, the Assistant Director of Regulatory/Compliance, the Assistant Director for Clinical Research and the Office of Research Compliance. Significant findings will be discussed with the nurse, coordinator, principal investigator, and Director.

6. Deficiencies will be corrected within five working days and presented to the Assistant Director for review at that time. A corrective and preventive action plan will be developed as indicated by the audit results.

   Quality Improvement

   Charts with significant deviations from Winship CTO policy will indicate the need for further audit of records belonging to the involved nurse or coordinator. Limited findings of noncompliance will signal a need for increased education and/or quality monitoring. Significant noncompliance can lead to disciplinary action.

   Failure to comply with this policy may be grounds for discipline by the University. Any disciplinary action taken by the University will follow the rules governing the individual's employment category.

(xv) Payment to subjects: (Maximum compensation per participant=$250.00 or $300)

Participants will be paid $50.00 at Visits I, II, and III. Participants will be compensated an additional study visit's compensation of $50 per repeated study visit or, if indicated by the PI, repeated study visit procedures. They will also be paid $20.00 per weekly phone interviews completed, which they will receive at Visit III. If participant is asked to discontinue placebo or curcumin, he or she will be paid $50 for coming into the clinic for a full physical exam. Participants will be given a parking voucher for all study visits. Further compensation (up to an additional $25 per screening visit) will be provided to cover travel expenses for you if you live equal to or greater than 50 miles outside of the Atlanta city limits.

(xvi) Informed consent:

A study investigator will obtain informed consent from every patient agreeing to participate in this study.

(xvii) Confidentiality:

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. Any patient identifiers (patient name, medical record number, date of birth) will be removed from the database prior to analyzing the data, producing an anonymous analytical data set. These same patient identifiers (name, medical record number, date of birth) will be removed from collected specimens before storing the samples in preparation for analysis. A unique number will be used to link collected specimens with questionnaires collected for each patient but this number will not be traceable to the specific patient. All data will be secured on password-protected computers accessible only to the investigators or support staff involved in the investigations (data manager and/or students), and will not be shared publicly. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

(xviii) Recruiting Methods:

Breast cancer patients previously treated with chemotherapy who are candidates for definitive radiation administered in one of the Emory Breast Centers or in the community will be approached for participation in this study. Social media marketing campaigns may be conducted for recruitment purposes. An overview of the study will then be provided in person or over the phone by study clinicians or trained study staff to prospective candidates. A telephone prescreening interview may be conducted on candidates providing verbal consent. If a subject shows interest in the study, research staff members will describe the general procedures involved and will answer relevant questions. If a subject remains interested in participation, the detailed nature, purpose, procedures, benefits, risks of, and alternatives to this research study will be explained to each subject, and written informed consent will be obtained by the study clinician who provides this information. Informed consent will be documented on the Institutional Review Board-approved form. A copy of the signed consent form will be given to the participant and the original document filed in a central study consent binder. The consent binder(s) and subject casebooks containing information gathered as part of the study will be kept in a locked office and/or cabinet.

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Emory IRB Reportable Events Guidelines

1. The investigator must report the following events promptly to the IRB (report within 10 days of becoming aware of the event):
    a) **Deaths** at Emory-affiliated sites that are possibly, probably, or definitely related to the study procedure, drug, or device
    b) **Unanticipated problems involving risks to participants or others** (UPs), at both Emory affiliated and non-Emory-affiliated sites. Note: UPs are always possibly, probably, or definitely related to the research (otherwise it's not a UP)
    c) **Anticipated events** at Emory-affiliated sites that occur with a greater frequency, duration, or severity than what is documented in the protocol, informed consent, and investigator's brochure (these events become UPs because even though they are anticipated, it is **unanticipated** that the expected events are happening at a greater frequency, duration, or severity)
    d) Other **unanticipated information**, at both Emory-affiliated and non-Emory-affiliated sites, that changes the risk benefit ratio or that indicates participants or others might be at greater risk of harm than was previously known (e.g. any change to the protocol taken without prior IRB approval in order to eliminate apparent immediate hazards to participants and any publication in the literature, DSMB report, or interim result that indicated an unexpected change to the potential risks of the study)
    e) **Protocol deviations** at Emory-affiliated sites in which there have been a substantive deviation from the IRB-approved protocol AND the deviation adversely affected 1) the rights, welfare or safety of subjects; 2) the integrity of the research data; or 3) the subjects' willingness to continue participation.
    f) **Non-compliance** or cases of alleged non-compliance for Emory-affiliated sites

2. The investigator must report the following events to the IRB periodically (usually at continuing review):
    a) **Deaths** at Emory-affiliated sites that are not related to the study procedure, drug, or device (for example, a death from cancer that is related to disease progression and NOT the intervention) need to be reported as a summary. The sponsor and PI should follow their data and safety monitoring plan to track trends using all available data. If in an aggregate analysis, the investigator and sponsor find some association of the deaths to the study, they must report these promptly to the IRB.
    b) **A summary of UPs** for both Emory-affiliated and non-Emory-affiliated sites

c) **A summary of serious adverse events that are related to the research** for Emory-affiliated sites

3. The following events are **NOT** reportable to the IRB
   a) Anticipated or unanticipated events, whether serious or not, that are not related to the study procedure, drug, or device.
   b) Serious adverse events that are not related to the research

Emory IRB
9/9/2009