Phase II Study of Pharmacologic Manipulation of AGE (Advanced Glycation Endproducts) Levels in Prostate Cancer Patients Receiving Androgen Deprivation Therapy

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DEFINITION OF TERMS USED

ADT	androgen deprivation therapy
AE	adverse event
AGE	advanced glycation endproducts
AGER	receptor for AGE
ALT	alanine transaminase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BID	two times per day
BMI	body mass index
BUN	blood urea nitrogen
CBCD	complete blood count with differential
CDC	Center for Disease Control and Prevention
CML	carboxymethyllysine
CMP	comprehensive metabolic panel
CRP	c-reactive protein
CTCAE	Common Toxicity Criteria for Adverse Events
DSMC	Data Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GRAS	generally recognized as safe
GSE	grape seed extract
HCC	Hollings Cancer Center
Hgb	hemoglobin
HMS	hypogonadal metabolic syndrome
ICH	International Code of Harmonization
ID	identifier
IDS	Investigational Drug Services
IIT	Investigator Initiated Trial
IRB	Institutional Review Board
LDL	low density lipoprotein
MG	methylglyoxyl
MTD	maximum tolerated dose
MUSC	Medical University of South Carolina
NADHP oxidase	nicotinamide adenine dinucleotide phosphase-oxidase
NYHA	New York Heart Association
OPC	Oligomeric Procyanidin Complex
OTC	over the counter
PCa	prostate cancer
PI	Principal Investigator
PO	by mouth
PSA	prostate specific antigen
RAGE	receptor for AGE
ROS	reactive oxygen species
SAE	serious adverse event
SIS	Sponsor-Investigator Support Unit
sRAGE	soluble form of RAGE
USP	United States Pharmacopeia
VAMC	Ralph H. Johnson VA Medical Center
VCAM-1	vascular cell adhesion molecule-1
VLDL	very low density lipoprotein

1 BACKGROUND

1.1 AGEs are Lifestyle-Associated Mediators of Degenerative Diseases.

Despite great progress in the treatment of many cancers, specific populations across the world still suffer disproportionately high levels of cancer incidence and mortality. Cancer disparity is most evident in our African American populations who bear the highest cancer burden for many tumor types. Poor diet, low income, obesity, and a lack of exercise are established lifestyle factors that are known to increase cancer burden and are often more prevalent in African American communities (1-3). As our understanding of tumor biology advances, it is becoming increasingly clear that these interrelated lifestyle factors have distinct molecular consequences on the biologic make up of tumors, altering cell signaling events and gene expression profiles to contribute to cancer disparity outcomes such as its earlier development or its progression to more aggressive disease. Sparse information exists about the genetic and biologic factors that contribute to differential cancer survival and mortality rates observed in minority populations. A greater understanding of the interplay between risk factors and the molecular mechanisms associated with cancer disparity will significantly affect minority health.

We recently reported a potential mechanistic link between sugar-derived metabolites (collectively AGEs or advanced glycation endproducts) and cancer, which may provide a molecular mechanism to account for the consequence of our lifestyle choices that can directly affect tumor biology and contribute to cancer (and generalized health) disparity (4).

1.2 AGE Accumulation Is Inherently Linked to Lifestyle

Systematic reviews and meta-analysis studies support the view that eating unhealthily, being overweight or obese and/or sustaining a sedentary lifestyle can increase risk of cancer, risk of cancer recurrence, and decrease overall survival rates (5,6). A recent statement from Cancer Research UK estimated that lifestyle accounts for around 40% of cancer cases, second only to smoking. This is racially significant as the highest rates of being overweight and obese (defined as a BMI >25) and the lowest adherence to CDC-recommended physical activity guidelines (defined as a minimum of 150 minutes per week) occur among the African American populations at highest risk of developing and dying of cancer (7). A family tradition of high-calorie “soul foods” with a heavy use of fat and sugar exists for many African American families. In addition, low income promotes the use of cheap, unhealthy, and highly processed foods, which can lead to weight gain, obesity, and increased cancer risk. Poverty rates within African Americans communities are among the highest in the country and they are also more likely to live in designated “food deserts” where people have limited access to healthy affordable food (8). All of these lifestyle factors not only contribute to health disparity and increase cancer risk but significantly contribute to the exogenous AGE accumulation pool in our bodies:

The typical Western diet comprising red meat, refined grains, and high fat/high sugar foods are associated with systemic disease and are particularly AGE-laden, contributing as much as 30% of the AGEs accumulated within our bodies (9). The consumption of AGE-rich diets by mice increases circulating and tissue AGE content to promote conditions such as atherosclerosis, diabetes, and kidney disease, all of which are inhibited by dietary AGE restriction (9). Although human studies are limited, associations between elevated AGE and serum biomarkers of oxidative stress, endothelial dysfunction, inflammation, hyperlipidemia, and hyperglycemia have been identified in patients with impaired renal function and diabetes (9). Evidence supports dietary AGE restriction for the reduction of 8-isoprostanes and TNFα in healthy adults and reduced glucose and insulin resistance and AGE-modified low-density lipoprotein in type II diabetes patients (10).

AGE content in foods is not only dependent on nutritional content but also on how the food is prepared. Cooking methods involving dry heat such as grilling, broiling, and searing, used to improve food flavor, aroma and appearance, accelerate the glycation reaction between sugars

and proteins to significantly increase overall AGE content (9). Frying meats, for example, can increase AGE content by as much as 10 fold. Thermal processing and/or irradiation by food manufacturers, used to improve food safety, preservation, and taste also rapidly accelerates the AGE-forming reaction (9). Due to beneficial effects on flavor, synthetic AGEs are now directly added into the manufacturing process for several food items. Processed foods are now one of the most common food items in groceries baskets across the country and due to their relatively low cost are often most heavily used by low-income families.

Recent data from the European Prospective Investigation into Cancer and Nutrition Study conclude that a sedentary lifestyle poses twice the risk of premature death as being overweight or obese (11). Studies of the effects of physical activity on AGE levels are limited and are mainly carried out using animal models but indicate that regular physical activity can help maintain or even reduce AGE levels in our bodies. In obese rats, regular moderate exercise reduced advanced glycation early diabetic nephropathy, lowered plasma AGE-associated fluorescence as well as overall renal AGE content (12). Similarly, increased physical activity in middle-aged senescent rats reduced both cardiac fibrosis and circulating AGE levels (13). In nondiabetic middle-aged women, a 12-week lifestyle modification consisting of an initial educational session followed by encouragement showed that the number of daily walking steps significantly correlated with AGE levels. Decreases in AGEs correlated with reduced body weight and body fat content (14).

In summary, AGEs are inherently linked with poor lifestyle and play a pathogenic role in multiple diseases associated with growing older. Approaches to define the molecular consequences of AGE accumulation may define novel therapeutic targets and potential biomarkers with which to reduce cancer incidence and mortality, particularly in minority populations.

1.3 AGE Accumulation, RAGE, and Stress Response

Persistent, unchecked inflammation and a related increase in oxidative stress are major biologic consequences of poor lifestyle and an underlying factor behind most, if not all, systemic diseases. A healthy diet and regular exercise has been shown to reduce chronic inflammation associated with diabetes and cardiovascular disease in the absence of weight loss, and studies indicate that increased physical activity is associated with lower inflammatory marker levels (19, 20).

A major pathogenic consequence of AGE accumulation is the perpetual activation of immune-mediated chronic inflammation and the generation of ROS, which results in a perpetual inflammatory microenvironment susceptible to disease development. CRP is a marker of inflammation that is linked with increased risk of heart disease, diabetes, and some cancers. In diabetes, serum AGE levels are an independent determinant of CRP levels due to a chronic inflammatory response (15). African Americans have an increased burden of chronic inflammation, which is independent of BMI and other potential confounding factors (16). African Americans have higher CRP levels than Caucasian American, which correlates with obesity and other metabolic and disease risk factors (24). Clinical and epidemiologic evidence also identifies African American race as an independent risk factor for elevated oxidative stress (17) and the increased expression and/or activity of critical oxidative stress markers (18) .

AGEs contribute to immune-mediated chronic inflammation by functioning as ligand for the transmembrane receptor for AGE known as RAGE (or AGER; Fig 1). Mechanistically, AGE-mediated activation of RAGE results in the increased activation of proinflammatory transcriptional regulators, including nuclear factor-kappa B (NF-κB), STAT3, and hypoxia inducible factor 1 (HIF1). In diabetes, RAGE activation perpetuates NF-κB activation in a feedback loop involving *de novo* synthesis of NFκB-p65, which functions to maintain a persistent pool of this key proinflammatory regulator. Increased activation of these critical transcription factors increases the secretion of cytokines/chemokines such as IL1β, IL6, and TNFα, leading to the increased recruitment of lymphoid and myeloid immune cells into tissues, elevated ROS production, and an

inflammatory response (19). To perpetuate the cycle and add further fuel to the fire, reactive intermediates generated during AGE formation (i.e., Schiff's Bases and Amadori products) can directly increase ROS production and increased ROS presence can in turn further promote the formation of AGE precursors such as methylglyoxal to create a cyclic and persistent inflammatory response (20) . Significantly, antioxidants can inhibit AGE-induced changes in glucose consumption and lower ROS levels. AGE activation of RAGE increases heme oxygenase-1, nuclear translocation of NF-κB, and increased endothelial expression of vascular cell adhesion molecule-1 (VCAM-1), all of which function to increase oxidative stress and elevated levels of ROS (21). RAGE loss of function inhibits all of these AGE-mediated effects.

1.4 AGEs and Cancer

It is now generally accepted that chronic inflammation, oxidative stress, and cancer are intrinsically linked, and an inflammatory microenvironment is an essential element for both the onset and growth of tumors. In precancerous lesions, a constant state of inflammatory response and increased ROS production can cause both genetic and epigenetic alterations to alter gene expression and increase cancer risk (22). In established tumors, inflammation is thought to mediate cross-talk between cancers cells and the stroma, resulting in the active recruitment of immune cells to the tumor microenvironment and increased oxidative stress (22). The inflammatory milieu created contributes to tumor onset and progression by promoting genetic instability, cell survival, growth, and metastatic potential.

Although the mechanistic links between AGEs and lifestyle have been identified in diseases such as diabetes and cardiovascular disease(9), a potential contribution to the development and progression of cancer is relatively understudied. AGE presence in human tumors was first demonstrated in larynx, breast, and colon tumors by immune-histochemical staining. Exogenous AGE treatment of breast (23) and prostate (24) immortalized cancer cell lines promotes cell growth, migration, and invasion. In prostate cancer, AGE-modified basement membrane promotes the invasive properties of prostate epithelial cells and correlates with decreased survival (24). A recent article found that the dietary-derived AGE carboxymethyl-lysine was associated with modestly increased risk of pancreatic cancer and may partially explain the positive association between red meat and pancreatic cancer (25). Increases in the exogenous AGE pool mediated by poor diet and a sedentary lifestyle may contribute to tumor development and growth through the perpetual activation of immune response. This would be particularly significant in population groups with the highest prevalence of poor lifestyle and cancer risk, such as our African American communities, which evidence suggests may have higher AGE accumulation levels (4).

The receptor for AGEs, RAGE, is also overexpressed in a number of tumors and evidence suggests a direct link between RAGE activation with the proliferation, survival, migration, and invasion of tumor cells. Loss of RAGE in inflammatory mouse models confers resistance to skin carcinogenesis and suppresses tumor growth (19). In prostate cancer, RAGE preferentially interacts with AGE over other potential RAGE ligands and AGE treatment of prostate cancer cells induces both cell growth and invasion (26).

Our group examined circulating and tumor AGE levels in clinical specimens of prostate cancer and identified a race specific, tumor-dependent pattern of accumulation (4) . AGE levels were significantly elevated in both serum and tumor, with highest accumulation occurring in more aggressive tumors. When examined in a matched cohort of patients, high AGE levels in the serum correlated with high AGE accumulation in cancer tissue (4). Significantly, when the data were stratified by race, AGE metabolite levels were significantly higher in serum from African American cancer patients compared with Caucasian. These initial data indicate that AGEs may represent a potential mechanistic link between cell metabolism and cancer, which may also provide a biologic consequence of the lifestyle risk factors that drive cancer health disparity.

Based on associations between active metabolism, lifestyle, and immune response, increases in exogenous AGE accumulation may represent a biologic mechanism contributing to cancer disparity and may represent a novel paradigm to explaining the increased cancer incidence and mortality figures observed within minority populations. A series of recent articles has highlighted the tumor-associated immune response as a critical pathway contributing to cancer disparity in African Americans. An examination of expression differences based upon tumor composition shows that cytokine signaling associated with an increased immune response was found to be a predominant pathway increased in African American prostate cancer patients (2). Upon closer analysis, the majority of race-specific differential gene expression was found in the stromal compartment of the tumor (2). A similar race-specific increase in immune response gene copy number and gene expression was seen in matched radical prostatectomy tissues (27) and in Gleason 6 prostate tumors (1).

An analysis of more than 500 genes previously associated with prostate cancer shows that African American prostate tumors have significant upregulation of NF-κB and inflammatory cytokine factors (IL6, IL8, IL1B, C-X-C chemokine receptor type 4, and fatty acid synthase) compared with European Americans (28). In breast cancer, race is an independent predictor of elevated IL6 levels (29). Clinical and epidemiologic evidence also identifies African American race as an independent risk factor for elevated oxidative stress and ROS levels. For example, NADPH oxidase catalyzes the reduction of superoxide ($O_2\cdot$) radicals to ROS. Significantly, HUVEC cells from African Americans show higher levels of nitric oxide, lower superoxide dismutase activity, and increased expression of the NADPH oxidase subunit p47phox protein than their Caucasian counterparts (18). These combined data further indicate that the immune-mediated inflammatory response may be elevated in African American cancer patients and therefore may be more susceptible to the pathogenic effects of AGE accumulation. Such a heightened inflammatory response may be a major contributor to the development and progression of cancer and contribute to the dire cancer incidence and survival rates observed in this population.

The existence of AGE metabolites, their connections with diet and lifestyle, and their contribution to systemic disease are relatively unfamiliar to the general public as well as the cancer research community. Although emerging research has identified increased levels of AGEs in the circulation and tumor of cancer patients and has identified a significant role in carcinogenesis for their cognate receptor RAGE, it is not known if the same AGE–RAGE–mediated biologic pathways established in other systemic diseases are at play in the tumor microenvironment and to what extent AGEs derived from poor diet and a sedentary lifestyle contribute. Overall, supporting evidence for dietary restriction and/or physical activity interventions to reduce AGE levels in humans is hampered by the need for long-term high-quality randomized control trials with larger cohorts and defined disease outcomes. The difficulties of effecting these changes over long periods of time in a wide spectrum of patients are well known. The development of pharmacologic methods to manipulate AGE levels could be a significant aid to defining the role of AGEs in cancer development and progression.

1.5 Prostate Cancer and the Hypogonadal Metabolic Syndrome: Possible Role for AGEs.

The primary treatment for advanced prostate cancer is ADT. While highly effective at producing regression of prostate cancer, ADT is not curative. Furthermore it has significant side effects due to the lack of testosterone. Adverse effects of ADT include decreases in bone mineral density; metabolic changes such as weight gain, decreased muscle mass, and increased insulin resistance; decreased libido and sexual dysfunction; hot flashes; gynecomastia; reduced testicle size; anemia; and fatigue (30). Several observational studies suggest an increased risk of diabetes (31,32) and cardiovascular events (33), although most published studies report that ADT is not linked to greater cardiovascular mortality. Randomized trials have found value in treatments for some adverse effects including bone loss (bisphosphonates, denosumab, selective estrogen receptor modulators), markers of metabolic syndrome (exercise, diet, metformin), gynecomastia

(tamoxifen, prophylactic radiation), muscle loss (resistance and aerobic exercise), and hot flashes (venlafaxine, medroxyprogesterone, cyproterone acetate, gabapentin).

A subset of ADT toxicities is referred to as the HMS because of its resemblance to the metabolic syndrome in the diabetes and cardiovascular literature. The HMS consists of increased body fat (particularly subcutaneous fat), obesity, insulin resistance, sarcopenia, elevated triglycerides and VLDLs, and increased adiponectin. Additional significant metabolic toxicities include loss of bone mass, and increased risk of an acute cardiac event. The HMS differs from the standard metabolic syndrome by the absence of hypertension (present in standard metabolic syndrome), and the elevated levels of adiponectin (reduced in standard metabolic syndrome; (34)).

Components of the metabolic syndrome (whether pre-existing or associated with ADT) are associated with poor outcomes from prostate cancer treatment (35). Obesity is associated with shortened progression-free survival after active surveillance (36), prostatectomy (37) and radiation (38,39), and with shortened time to castration-resistant disease in subjects receiving androgen deprivation therapy (40). Poor glycemic control is associated with biochemical recurrence after radical prostatectomy (44) and in more advanced patients (41), and with impaired overall survival (42)

Since AGEs are implicated in the metabolic syndrome described from diabetic and cardiac subjects, it is likely that they will play a role in the metabolic syndrome associated with prostate cancer and androgen deprivation. Thus, development of methods to modulate AGE levels may provide additional tools to improve cancer-specific outcomes in prostate cancer patients.

1.6 Pharmacologic Manipulation of AGE levels

AGEs accumulate in our tissues and organs over time and contribute to the development and complications associated with diseases of advancing age, including diabetes, cardiovascular disease, renal failure, arthritis, and neurodegenerative disorders (43). The rate of AGE accumulation in our bodies results from a balance between (i) their endogenous accumulation during the breakdown of sugar via the non-enzymatic, spontaneous glycosylation of proteins, lipids, and DNA; (ii) their exogenous intake through the foods we consume and other lifestyle factors such as drinking alcohol, smoking, and a sedentary lifestyle; and (iii) their inefficient removal via renal and/or enzymatic clearance, around 10% to 30% of exogenous AGEs are absorbed intestinally but only a third of those are excreted in urine and feces (9). AGEs bind to several receptors proteins, most clearly the RAGE. Receptor engagement then activates a variety of signaling pathways, including NF□B. These documented features of AGE production, accumulation, elimination, and signaling provide guidance for the development of pharmacologic approaches to AGE modification. Agents with at least some activity in diabetic or chronic kidney disease populations (animal models or patients) include glucose regulators, antioxidants, RAGE regulators, and oral AGE-binding resins.

1.6.1. Glucose regulators. Metformin has been widely studied as an agent to modulate AGE levels in diabetic populations and intact animal models(44,45). Most studies demonstrate that metformin reduces the plasma levels of some AGE species, usually methyglyoxal metabolites. In contrast metformin effects on the more abundant carboxymethyllysine species are less consistent. Metformin has been used in prostate cancer patients to improve insulin sensitivity but direct effects on AGE levels in that population have not been assayed (45).

1.6.2. Antioxidants. An extensive literature documents the effects of antioxidant grape seed extracts on AGE production and levels in animal models (46-52). The polyphenol-rich fractions from grape seeds and skins consist predominately of multimers of catechins and epicatechins, their gallic acid esters, and (at times) other polyphenols such as resveratrol. Administration of these materials (either as purified compounds or complex mixtures) reproducibly reduces AGE levels and AGE effects on end organs in animal models of diabetes, obesity, and cardiovascular

disease. In patients (usually obese, diabetic, or chronic kidney disease subjects) AGE levels decrease and sRAGE increase. End-organ damage may also improve (53,54).

1.6.3. RAGE regulators. Down-regulation of RAGE or increased secretion of sRAGE can reduce signaling through the AGE-RAGE axis. Multiple agents have been described as down-regulating RAGE levels in cultured cells, or increasing sRAGE in the plasma of treated animals. Pioglitazone, statins, ACE inhibitors, and AT-1 receptor antagonists have all been shown to have activity through these mechanisms (55,56).

1.6.4. AGE-binding resins. The phosphate-binding resin sevelamer has been shown to bind AGEs in vitro, and to lower age levels in the plasma of patients with chronic kidney disease(57).

2 STUDY OBJECTIVES

2.1 Study Overview

The overall goal of this Phase II study is to identify safe pharmaceutical agents that can reduce the plasma levels of AGEs in patients with prostate cancer.

2.2 Primary Objective.

The primary objective is to determine if the test agent reduces AGE levels by 30% (or greater) in 50% or more of test subjects.

2.3 Secondary Objectives.

- Identify correlations between AGE level changes and baseline, changes in clinical parameters (BMI, PSA, insulin resistance (HOMA-IR), A1C, testosterone, lipids, diet) and quality of life measures (AUA symptom index, FACT-P).

- Identify toxicities of the test agent in PCa subjects.

- Identify correlations between AGE level changes and baseline, changes in laboratory parameters of inflammation (plasma IL6, leptin, CRP), oxidative stress (MDA, oxLDLs), and sRAGE. Identify the spectrum of protein species that are modified by AGEs, and the changes in levels of these modified proteins to treatment.

3 SUBJECT SELECTION

3.1 Inclusion Criteria

1. Confirmation of adenocarcinoma of the prostate that is documented by one of the following: pathology report or clinic note with documented history of prostate cancer.
2. Subjects must be receiving ADT with a GnRH agonist or antagonist, with or without an anti-androgen, with a current testosterone level documented to be <50ng/dL at enrollment. Subjects whose ADT is interrupted may enroll or continue on study as long as the testosterone is documented to remain <50ng/dL for the entire duration of study participation. Subjects who have undergone orchiectomy are also eligible.
3. Subjects must have adequate hematologic, renal, and hepatic function at baseline, as follows:
    - Hematology parameters: ANC >1000/mcL, platelets > 100,000/mcL, Hgb >8.0gm/dL
    - Renal Function: eGFR of > 45mls/min using Cockkroft and Gault formula (see appendix C).
    - Liver Function: Total bilirubin ≤ULN, AST and ALT <1.5xULN

4. Able to swallow and retain oral medication
5. ECOG performance status of 0 – 2
6. Ability to sign written informed consent
7. Testosterone level <50ng/dL

3.2 Exclusion Criteria

1. Known allergy to grapes or grape seed
2. History of receiving more than 2 classes of ADT.
3. Prior cytotoxic chemotherapy for metastatic prostate cancer; prior treatment with genomically-targeted agents, or Provenge is allowed.

3.3 Study Registration

The SIS Unit will provide patient registration services for this study. The SIS unit will conduct a patient eligibility audit review of all redacted eligibility source documents prior to patient registration. These procedures are outlined in the study's Operations Manual. After obtaining signed informed consent and completion of required baseline assessments, eligible subjects will be registered. A unique subject number will be assigned to each patient. The SIS Unit will issue a patient registration confirmation email to the enrolling study team at the time of registration. This confirmation will include the patient's study ID number. Patient registrations may occur between 8AM and 5PM EST, Monday through Friday.

4 DRUG ADMINISTRATION

During the course of the study, subjects will continue to receive ADT therapy per subject's primary oncologist. Changes to ADT administration will be made at the discretion of the primary oncologist.

Study drug capsules may be taken with or without food. Capsules lost through vomiting will not be made up.

4.1 Arm 1: OPC only.

Subjects will take OPC at the same time each morning and evening, approximately 12 hours apart from day 1 to day 85 (12 weeks).

Agent	Duration	Administration
OPC	Weeks 1-12	500 mg PO BID

4.2 Medication Compliance Assessment.

Patients will be required to track daily doses of study drugs by maintaining a daily medication diary.

4.3 Dose Modifications.

There will be no reduction or escalation of OPC dose. The patient will either take 500mg BID or go off study. Interruption of dosing for more than 14 consecutive days will result in the patient being taken off study.

4.4 Discontinuation of Therapy

Participation in this study should be discontinued for any of the following reasons:

- Change in anti-cancer therapy
- Procedures requiring general anesthesia.
- Development of any medical condition that, in the opinion of the treating physician, requires discontinuation of the study intervention
- Withdrawal of consent by the subject
- Evidence of allergic reaction to any component of the treatment regimen
- Any grade 3-4 hematologic or non-hematologic toxicity (other than diarrhea) that does not resolve to grade 1 or less in 14 days of treatment interruption.
- Interruption of study drug for more than 14 consecutive days.

4.5 Restricted Therapies During Study Therapy

None

4.6 Supportive Care during Therapy

It is unlikely that specific supportive care interventions will be needed for the study interventions. General supportive care for the subjects will be at the discretion of the treating physician, except as limited as described in Section 4.2 Drug Administration.

5 SCHEDULE OF INTERVENTIONS AND ASSESSMENTS

5.1 General Considerations

- Informed consent must be signed prior to any study-specific assessments being done
- Screening assessments may be done up to 28 days prior to registration. Screening assessments completed within 28 days of day 1 do not have to be repeated.
- Day 85 or End of Study Assessments may be done +/- 7 days, but all efforts should be made to complete this visit within 24 hours of last dose of study drug
- All research blood samples must be collected while the subject is fasting.

5.2 Assessments and Procedures

The following clinical assessments are made at the times designated in the study calendar.

- History and physical examination to review patient medical history, medication list, overall health and any side effects they may be experiencing.
- CBCD
- Fasting CMP (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, albumin, alkaline phosphatase, AST, ALT, calcium). The CMP to confirm eligibility does not need to be fasting, but a fasting CMP does need to be collected prior to day 1 drug administration.
- PSA, testosterone, A1C, and BMI

While on study, documented testosterone level must be maintained during treatment <50ng/dL

5.3 Disease assessment

Disease response will be obtained by the assessment of PSA at enrollment and at the time the patient comes off study. Imaging studies will be done if clinically indicated and/or at the discretion of the subject's primary oncologist.

5.4 Correlative Research

After consent and prior to drug administration on day 1 and at day 85 (or end of study) the following research procedures will be completed:

- Quality of Life Questionnaires (FACT-P, AUA).
- Fasting research blood will be taken to participating research labs for analysis of the correlative studies to look at AGE levels, CRP, insulin levels and other biomarkers.
- Research samples for correlative studies will be linked using the study ID issued at registration.
- Food intake assessment using the NIH "Eating at America's Table Study Quick Food Scan" and the NCI "Quick Food Scan."

5.5 Schedule of Assessments

See Appendix A.

6 STUDY DRUG INFORMATION

There are no clinical studies describing interactions between commonly used prostate cancer therapy and OPC. A search of the drug.com database for interactions reveals no citations.

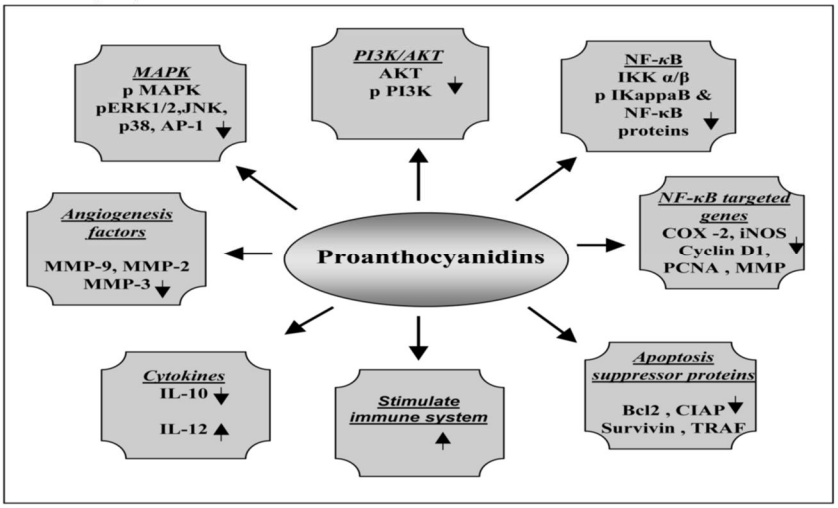
6.1 Oligomeric Procyanidin Complex (OPC)

6.1.1 Agent Description. OPC is a form of plant-derived polyphenols. OPC may be also called oligomeric flavanols. The three richest OPC sources are grape seed, pine bark and red wine. Grape seeds contain lipid, protein, carbohydrates, and 5-8% polyphenols depending on the variety. Polyphenols include gallic acid, the monomeric flavan-3-ols catechin, epicatechin, gallocatechin, epigallocatechin, and epicatechin 3-O-gallate, and dimers, trimers, or higher order polymers of these monomers.

Grape seeds and skins are obtained as by-products of wine production. Grape seeds and skins are ground, then extracted with either hot water or a water:ethanol mixture, followed by spray drying to produce GSE. GSEs typically contain 80% or more OPCs, with smaller amounts of procyanidin monomers and their gallic acid esters. In this protocol, a characterized and standardized GSE will be used as a source of OPC for patient treatment. This material, manufactured by Polyphenolics Inc., as MegaNatural® Gold Grape Seed Extract, has been described extensively in patents and used in human clinical trials.

6.1.2 Pharmacology. In vitro studies have shown GSE or the more-purified OPC to have anticancer effects (see (58-61) for recent reviews) and synergistic effects with doxorubicin (59) in inhibiting cancer cell growth and chemotherapy drug cardiotoxicity. GSE was found to down-regulate the NF-kB and MAPK pathways, along with related downstream pathways such as cyclin D1, iNOS, and COX also linked to inflammation (Fig. 1). Procyanidins found in GSE also inhibit xanthine oxidase activity and non-competitively inhibit the proteolytic enzymes collagenase and elastase and the glycosidases hyaluronidase and beta-glucuronidase.

Fig.1: Molecular targets of proanthocyanidins in prevention or therapy of cancers. (66)



Multiple biologic effects have been ascribed to OPCs, as a result of their potent antioxidant effects. The phenotypes potentially resulting from OPC administration to animals include altered capillary permeability, inhibition of cardiotoxicity from anthracyclines, improved glucose tolerance, prevention of weight gain, and atherosclerosis. In some cases these phenotypes were accompanied by a reduction in levels of proinflammatory cytokines such as TNF□ and IL-6. Small human trials have shown possible efficacy in decreasing LDL and increasing total serum antioxidant activity. Additionally, topical application of GSE has been shown to accelerate wound contraction and closure. Orally administered GSE was not effective for reducing breast induration following radiotherapy in patients with breast cancer. These protective effects theoretically come from its ability to modulate anti-apoptotic genes and modify molecular targets such as DNA damage and repair, lipid peroxidation and intracellular calcium homeostasis.

The bioavailability of OPCs derived from GSE or other sources is variable and controversial. Higher molecular weight (polymeric) polyphenols tend to be very poorly bioavailable. Thus, preparations skewed toward lower molecular weight compositions are likely to be more efficacious. A GSE used in previous studies has been molecularly profiled by LC-MS analysis, and shown to consist of catechin and epicatechin monomers (15%); epicatechin dimmers, trimers, tetramers and their gallates (80%); and higher-order polymers and their gallic acid esters (5%).

Procyanidin multimers are cleaved in the gut and absorbed primarily as catechin and epicatechin monomers. The detection of proanthocyanidin dimers B1 and B2 in human plasma was reported in 2 studies. The absorption of these dimers was ~100-fold lower than that of the monomeric flavanols. However, these compounds were found to have direct effects on the intestinal mucosa and protect it against oxidative stress or the actions of carcinogens. 70% of GSE is eliminated within the first 24 hours, most through the urine and feces although some through the bile.

6.1.3 Adverse reactions and Toxicology. GSE side effects have not been reported in the medical literature, but very few human studies have been done. In one study normal volunteers were given the particular GSE preparation proposed for this study at 100 mg three times a day orally for 6 months, no major side effects were reported (62). A similar dose was used in a study of radiation-induced skin toxicity in breast cancer patients (63). According to a GSE summary document published by the U.S. Department of Health and

Human Services and National center for Complementary and Alternative Medicine, Grape Seed Extract side effects may include dry, itchy scalp, dizziness, headache, high blood pressure, hives, indigestion and nausea.

GSE inhibits CYP3A4 and can affect the intracellular concentration of drugs metabolized by this enzyme. Due to its anticoagulant (antiplatelet) effects, GSE could possibly enhance the activity of warfarin. GSE modulates UGT enzymes in vitro and can increase the side effects of drugs metabolized by them.

6.1.4 Sources. We will use MegaNatural Gold® brand of OPC manufactured by Polyphenolics, Inc. This is incorporated into capsules by Swanson Health Products (Fargo, ND) as "Characterized Grape Seed Extract", 500mg (product SWH093). Capsules will contain 500mg of OPC. MegaNatural Gold® brand of OPC has been extensively characterized in terms of the quantity of monomers, oligomers, and polymers of catechins and epicatechins, and is on the FDA's GRASlist. The dose of OPC has been shown to be safe from an unpublished Phase I study conducted at HCC/MUSC (M. Lilly, unpublished, 2015). The MTD was more than 3000mg daily. MUSC IDS will supply OPC capsules to subjects at MUSC.

7 ADVERSE EVENTS

7.1 Definitions

Adverse Events (AE). An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drugs, whether or not is it causally related. During clinical trials, adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events.)

Serious Adverse Event (SAE). An SAE is any untoward medical occurrence that at any dose**:**

- results in death,
- is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalization or causes prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- results in the development of drug dependency or drug abuse,
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

Overdoses. An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. Overdoses should be following the same reporting requirements as SAEs.

7.2 Reporting of SAEs

Following the subject's registration, all SAEs should be collected and reported, including those thought to be associated with clinical trial procedures. SAE terminology and severity grading will be based on CTCAEv4. The following categories and definitions of causal relationship to study drug should be used:

Definitely related:	An adverse event occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible. The event must be definite pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary and feasible.
Possibly related:	An adverse event with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Not related:	An adverse event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying diseases provide plausible explanations.

Adverse events classified as "serious" require expeditious handling and reporting to the coordinating center and Sponsor-Investigator. SAEs must be reported to all of these entities within 24hrs of becoming aware of the event, *whether or not the event is related to the study drugs or procedures*. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.

SAEs should be reported on the 102508 SAE eCRF via REDCap at redcap.musc.edu. The coordinating center will be responsible for submission to the Sponsor-Investigator, HCC-DSMC and FDA as applicable. SAEs should be reported to the site's IRB per institutional standards.

The site should receive confirmation from MUSC that the SAE report was received. If not, please contact the SIS Unit immediately.

Collection of complete information concerning SAEs is extremely important. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.

AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious. This also applies to subjects experiencing AEs that cause interruption or discontinuation of study drugs, or those experiencing AEs that are present at the end of their participation in the study; such subjects should receive post-treatment follow-up as appropriate. All SAEs must be collected which occur within 30 days of discontinuation of dosing or completion of the patient's participation in the study if the last scheduled visit occurs at a later time.

8 DATA SAFETY MONITORING

8.1 Responsible Individuals and Organizations.

The Principal Investigator will be responsible for monitoring the safety and efficacy of the trial, executing the DSM plan, and complying with all reporting requirements. This will be accomplished under the oversight of the HCC DSMC.

The HCC DSMC is responsible for monitoring data quality and patient safety for all interventional IITs at HCC. The HCC DSMC will have oversight of this protocol. The HCC DSMC will meet at a minimum on an annual basis to discuss the investigator-initiated trial. Also, the IIT will be audited by the DSMC auditor or external agency at least once a year.

The DSMC reviews all IRB reportable serious adverse events, monitoring/ auditing reports, and protocol deviations and has the authority to recommend closure and/or suspension for trials on which there are safety or trial conduct issues and may submit recommendations for corrective actions. The DSMC recommendations for modifications to the trial (if requested) are forwarded to the principal investigator. The principal investigator is notified of this recommendation in order that he/she may alert all investigators involved in the trial with regard to the potential action. At this time the principal investigators may submit to the DSMC additional information that could affect the Committee's decision.

All IRB reportable serious adverse events, monitoring/ auditing reports will be reviewed by the HCC DSMC for review during the DSMC monthly meetings. The SIS Unit will forward the event report to the HCC DSMC so that the information can be reviewed at the next available DSMB meeting. During the DSMB review, the DSMB can make recommendations for any further study action. The SIS Unit will maintain a copy of the DSMB approval letters for each event review within this study's central file.

8.2 Data Collection

Electronic CRF's will be provided for the recording of data and reporting that requires expedited review, such as SAE submissions. All data should be substantiated by clinical source documents organized within a patient research record. ICH Good Clinical Practices are to be followed. Data submission guidelines are outlined in the 102508 Operations Manual.

Electronic data for on study and follow-up patient data is submitted via the electronic system called REDCap. REDCap is managed from MUSC as a consortium partner under their CTSA. REDCap CRF is a secure, Web-based application designed to capture and manage research study data.

The system has been reviewed for 21CFR Part 11 compliance and has been deemed "21CFR 11 Capable." Users of the REDCap system are limited to members of the IRB approved research team who are delegated data management responsibilities, typically the study coordinator and data manager.

9 STATISTICAL METHODS AND POWER ANALYSIS

This is a non-randomized single arm Phase II study enrolling 20 patients. Patients will be considered evaluable for the primary objective if they have both a baseline and 12 week measure of AGEs. Patients who drop out of the study for any reason before the week 12 visit will be replaced. All patients who receive at least one dose of study treatments will be considered evaluable for toxicity.

9.1 Primary endpoint:

The primary endpoint will be a binary indicator of a 30% or greater decrease in plasma AGE level between baseline and week 12 specimens. An active agent for further study will be one that induces a 30% or greater decrease in total AGE levels in at least 50% of treated subjects. Total AGEs, CML-AGEs (carboxymethyllysine (CML)), and the AGE precursor methylglyoxyl (MG) will be measured using a 96-well competitive ELISA (Cell Biolabs).

9.2 Secondary endpoints:

Secondary clinical endpoints will include a description of the toxicity profile of the test agent in prostate cancer patients, and recording changes in BMI, fasting glucose, insulin resistance (HOMA-IR), anthropomorphic measurements as well as testosterone and PSA levels. Changes in the analytes will be assessed with respect to age (in years), duration of ADT, extent of cancer, personal or family history of diabetes mellitus, race, and BMI.

9.3 Statistical analysis and sample size justification for Primary Objective

The primary endpoint will be a binary indicator of a 30% or greater decrease in plasma age level between baseline and week 12 specimens. With a sample size of 20 patients, we can estimate the percentage of patients with a 30% or greater decrease in AGE levels based on a 90% confidence interval with a half-width of no greater than 0.19 (e.g., if the observed proportion is 0.20 or 0.50, then the 90% CI would (0.05, 0.35) or (0.31,0.69), respectively). If at least 8 of 20 subjects in a cohort achieve this degree of AGE reduction we will conclude that the agent has interesting activity for AGE suppression based on the lower limit of the 90% confidence interval exceeding 0.20. This analysis assumes that an agent in which only 20% of patients demonstrate 30% or greater decrease in plasma AGE would not be sufficiently active for further study. An exact binomial test will be performed based on a null hypothesized true proportion of 0.20 (i.e., only 20% of patients have a 30% or greater reduction in AGE levels). With an alternative of 0.50 and a sample size of 20 patients, assuming a one-sided test with a significance level of 0.05, the power to detect this difference is 0.87.

9.4 Statistical analyses for Secondary Objectives

Toxicities will be tabulated per arm by type and grade, and the proportion of patients with grade 3 or grade 4 toxicities, or an SAE will be estimated with a 90% confidence interval. Changes in continuous secondary endpoints will be graphically displayed and summarized per treatment arm with summary statistics. Associations between AGE level changes and other clinical and demographic characteristics and laboratory parameters will be explored using graphical displays (e.g. scatterplots, boxplots) and evaluated using linear regression with change in AGE as the outcome, and clinical/demographic characteristic as the independent variable.

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APPENDIX A. SCHEDULE OF PROCEDURES AND ASSESSMENTS

		Timepoint		
	Procedure	**Screening[a]**	**Day 1[a]**	**Day 85/ End of study[c]**
Study Procedures	H & P	X	X	X
	AE assessment			X
	CBCD	X	X	X
	CMP (fasting)[a]	X	X	X
	PSA	X	X[f]	X
	Testosterone	X	X	X
	BMI	X	X	X
RX	OPC		X----------X	
	Drug diary review[d]			X
Correlative Research	Informed consent	X		
	FACT-P Quality of Life Questionnaires	X[e]		X
	Research Blood (fasting)[b]	X[e]		X

a. Screening assessments may be used for the Day 1 assessments if they were completed within 28 days of day 1. The CMP used for eligibility confirmation does not have to be fasting, but a fasting CMP will need to be collected prior to day 1 drug administration. Fasting is defined as nothing containing calories since the previous midnight.

b. Recommended tubes: 1x7mL sodium heparin, 1x7mL lithium heparin, 1x7mL EDTA, 1x7mL serum (Clot). Fasting research blood will be taken to participating research labs for analysis for of the for correlative studies to look at AGE levels, CRP, insulin levels and other biomarkers.

c. Day 85 visit may be done +/- 7 days. If the subject goes off-study less than 2 weeks after start of dosing, "end of study" labs and questionnaires will not be done.

d. The drug diary will be given to each subject on day 1 to be completed during the study. The subject should return the drug diary and pill bottle at the end of study visit to review study compliance.

e. Research blood and FACT-P QOL Questionnaires may be done at any point after consent and prior to day 1 drug administration.

f. If clinically indicated

APPENDIX B: CALCULATION OF CREATININE CLEARANCE

Estimation of creatinine clearance using Cockroft and Gault method:

Cl_{CR} for males (mL/min) = $\frac{[140 - \text{age (years)}] \times [\text{weight (kg)}]}{(72) \times [\text{Serum creatinine (mg/dL)}]}$

For SI units:

Cl_{CR} for males (mL/min) = $\frac{[140 - \text{age (years)}] \times [\text{weight(kg)}] \times (1.23)}{[\text{Serum creatinine (µmol/L)}]}$