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A Phase IIA Exploratory, Randomized, Placebo-controlled Trial of Pomegranate Fruit Extract/POMx™ in Subjects with Clinically Localized Prostate Cancer Undergoing Active Surveillance

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SCHEMA

A Phase IIa Exploratory Randomized, Placebo-controlled, Trial of Pomegranate Fruit Extract/POMx™ in Subjects with Clinically Localized Prostate Cancer Undergoing Active Surveillance (AS)

Eligibility: Men ≥ 21 years of age with organ-confined, low-grade prostate cancer (Gleason score ≤ 3+3 and PSA < 10ng/ml in participants < 70 years old, or Gleason score ≤ 3+4 and PSA ≤ 15 ng/ml in participants ≥ 70 years old) undergoing AS, who have archival tissue available from a prostate biopsy performed ≤ 13 months of randomization

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Baseline Visit (≤ 30 days of randomization)
Inform consent obtained; eligibility labs; total serum PSA (for clinical purposes, this will be processed at the Participating Organization's (PO) clinical laboratory); physical exam; medical and surgical histories; vital signs, height, weight and ECOG performance status; review of baseline symptoms and concomitant medications; collection of blood and urine for research purposes (total serum PSA [done for research purposes only, to be analyzed at the end of study at UWI], serum testosterone; plasma and urine pharmacokinetics* and plasma biomarkers [IGF-I/IGFBP-3 ratio]); review of archival prostate tissue to determine Gleason score and tumor burden; normal and abnormal prostate tissue biomarkers (PSA, IGF-1, IGFBP-3, apoptosis [CASPASE 3], Ki-67, IGF-IR, 8OHdG and androgen receptor).

Registration and randomization to one of the following treatment groups:

- Pomegranate Fruit Extract (PFE) 1000mg (i.e., one (1) 1000mg capsule) each morning, by mouth, x 52 weeks

OR

- Placebo, one (1) capsule each morning, by mouth x 52 weeks

↓

13 Week Visit
Safety labs and total serum PSA (for clinical purposes, this will be processed at the PO's clinical laboratory); vital signs and weight; review of adverse events and concomitant medications; collection of blood and urine for research purposes (total serum PSA [done for research purposes only, to be analyzed at the end of study at UWI]; plasma and urine pharmacokinetics* and plasma biomarkers)

↓

26 Week Visit
Physical exam by physician; safety labs and total serum PSA (for clinical purposes, this will be processed at the PO's clinical laboratory); vital signs and weight; review of adverse events and concomitant medications; collection of blood and urine for research purposes (total serum PSA - done for research purposes only- to be analyzed at the end of study at the UW Carbone Cancer Center Cancer Pharmacology [CP] lab), serum testosterone; plasma and urine pharmacokinetics* and plasma biomarkers)

↓

39 Week Visit
Safety labs and total serum PSA (for clinical purposes, this will be processed at the PO's clinical laboratory); vital signs and weight; review of adverse events and concomitant medications; collection of blood and urine for research purposes (total serum PSA [to be analyzed at the end of study at the CP lab]; plasma and urine pharmacokinetics* and plasma biomarkers)

↓

52 Week Visit (or End of Study Visit)
Physical exam by physician; prostate biopsy (to determine the presence or absence of tumor, the extent of tumor and Gleason scores); safety labs and total serum PSA (for clinical purposes, this will be processed at the PO's clinical laboratory); vital signs and weight; review of adverse events and concomitant medications; collection of blood and urine for research purposes (total serum

PSA [to be analyzed at the end of study at UWI], serum testosterone; plasma and urine pharmacokinetics* and plasma biomarkers), prostate tissue biomarkers (PSA, IGF-1, IGFBP-3, apoptosis (CASPASE 3), Ki-67, IGF-1R, 8OHdG and androgen receptor)

* The following PFE constituents/metabolites will be measured in plasma and urine for evidence of accumulation (trough levels): ellagic acid, dimethyl ellagic acid, dimethyl ellagic acid glucuronide (DMEAG), urolithin A, urolithin A-glucuronide, urolithin B and urolithin B-glucuronide.

NOTE: In addition to doing total serum PSA levels at the PO's clinical lab, serum will be collected to do a total serum PSA test (for research purposes only) at the University of Wisconsin's CP lab. The total serum PSA values done for research only will be used to determine end-of-study PSA doubling time (PSA-DT) results between the active and the placebo group. As a research lab, the CP lab is not CLIA-certified, and only CLIA-certified results can be used for clinical purposes.

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1. OBJECTIVES

1.1. Primary Objective:

The primary objective of the study is to determine the effect of Pomegranate Fruit Extract (PFE) 1000mg, taken daily for 1 year, on the plasma levels of Insulin-like Growth Factor (IGF-1) from baseline to end of study (52 weeks) in participants undergoing Active Surveillance (AS) for early stage prostate cancer.

1.2. Secondary Objectives:

1.2.1. To assess compliance with a once daily oral administration of PFE versus placebo over a 52-week period of time.

1.2.2. To assess the toxicity of PFE vs. placebo when taken daily for 52 weeks (+/- 1 week).

1.2.3. To compare and correlate the effect of 52 weeks of daily dosing with PFE vs placebo on the end of study biopsy results including the presence or absence of tumor, the extent of tumor and Gleason scores.

1.2.4. To compare and correlate biomarker modulation in response to PFE versus placebo in three areas of interest: tissue from a completely benign biopsy core, tumor tissue from a positive core, and normal tissue adjacent to tumor from a positive core. The following biomarkers will be analyzed:

- Plasma: Insulin-like growth factor 1/IGF binding protein 3 ratio (IGF-1/IGFBP-3 ratio)
- Prostate tissue (normal and abnormal). In order of priority:
  - apoptosis (CASPASE 3)
  - Ki-67
  - 8OHdG
  - IGF-1R
  - Androgen receptor
  - IGF-1
  - IGFBP-3
  - PSA

1.2.5. Measure PFE constituents/metabolites in plasma and urine for evidence of accumulation (trough levels): ellagic acid, dimethyl ellagic acid, dimethyl ellagic acid glucuronide (DMEAG), urolithin A, urolithin A-glucuronide, urolithin B and urolithin B-glucuronide.

1.2.6. Measure PSA doubling time (PSA DT) in serum, using the calculation provided on the Memorial Sloan Kettering Cancer Center website: nomograms.mskcc.org/prostate/psadoublingtime.aspx

1.2.7. To assess the feasibility of cancer chemoprevention trials in a population of men undergoing active surveillance for prostate cancer.

1.2.8. Measurement of serum testosterone.

2. BACKGROUND

2.1. Study Disease

Prostate cancer is the most common malignancy and second leading cause of cancer related deaths in American men. Recent estimates report more than 185,000 men will be diagnosed with, and approximately 28,660 men will die from, prostate cancer in 2008 (Jemal et al, 2008). Increasing proportions (30% in 1990, 45% in 2000 with further increases by 2010) of US men diagnosed with prostate cancer each year have early stage, low risk disease (Cooperberg et al, 2004). Despite recent reports of a disease-specific survival advantage for prostatectomy as compared to AS in newly diagnosed prostate cancer patients of varying age and disease stage (Bill-Axelson et al, 2011), multiple prospective and retrospective studies support AS (Warlick et al, 2006; Klotz, 2005; Carter et al, 2002; Wilt and Brawer, 1994) as an acceptable option for men with early stage, low risk disease, especially men who are 70 years of age or older, with low grade early stage disease. Based on the observed lack of overall survival advantage and quality of life data, 50% of men with low risk disease are being unnecessarily treated with surgery or radiotherapy at diagnosis, according to Miller (Miller et al, 2006). Of men diagnosed with early stage, low risk cancer who agree to expectant management, 40-50% will progress (by current clinical standards) or choose to proceed to invasive intervention (without evidence for progression) over 5 years (Warlick et al, 2004, Klotz, 2005). Because of this unmet clinical need for non-invasive interventions for early stage, low risk prostate cancer, and the anxiety of “not doing anything”, many men are choosing to use supplements (Velicer and Ulrich, 2008; Miller et al, 2009). Evaluation of non-invasive interventions for this already large and growing population is needed.

As standard of care, patients undergoing AS will typically undergo periodic PSA testing every 3-6 months and also undergo an annual prostate biopsy to monitor the course of their disease.

The high incidence and lethality of the disease and the morbidity associated with curative therapy strongly support the need for studying prostate chemoprevention (Brawley et al, 2001; Nelson and Wilding, 2001).

Epidemiologic data supporting the preventability of prostate cancer are as follows:

1) widespread geographic variations in prostate cancer incidence and mortality exist throughout the world;
2) risk/incidence of prostate cancer increases with migration shift from low-risk geographic areas to high-risk areas;
3) case-control studies in low and high prostate cancer risk areas implicate dietary factors as modulators of prostate cancer development;
4) autopsy studies of men in the U.S. dying of causes unrelated to prostate cancer suggest the development of life-threatening prostate cancer from small neoplastic lesions may take decades

These data, which implicate environmental influences, such as diet, imply that an intervention might reduce prostate cancer mortality risks in the U.S. Recent epidemiologic studies have identified a number of dietary components and micronutrients as possible prostate cancer preventive or therapeutic agents (Nelson and Wilding, 2001).

There are specific groups of patients who are at high risk of being diagnosed with prostate cancer and who may benefit from chemopreventive agents as a primary cancer prevention strategy. Patients with high grade prostatic intraepithelial neoplasia or a strong family history of prostate cancer are at significant risk for subsequent diagnosis of this disease. Patients with a sustained elevation in PSA but with negative biopsies may also benefit from this strategy. These patients may very well harbor small foci of prostate cancer that have remained undiagnosed due to sampling error on prostate biopsy. Patients at high risk for diagnosis and patients undergoing AS for low grade, localized prostate cancer may represent a continuum of this disease, with AS patients with a detectable volume of cancer at the end of the spectrum. Therefore, patients undergoing AS, an increasingly popular option, may benefit from the evaluation of a relatively non-toxic dietary agent that may be effective in preventing or delaying the progression of prostate cancer (Lieberman, 2001). These patients are eager to try complementary and alternative medicine (CAM) strategies. The standard of care follow up includes periodic clinical monitoring (PSA testing every 3-6 months) and annual prostate biopsies to monitor the course of their disease, which means that additional research procedures and testing are fewer in number in this population than in a population where the standard of care does not include such measures.

2.2. Study Agent

2.2.1. Pomegranate and Cancer

The pomegranate (Punica granatum L.) fruit has been used for centuries in ancient cultures for its medicinal purposes (Longtin, 2003). Pomegranate fruits are widely consumed fresh and in beverage forms as juice and wines (Gil et al, 2000). Commercial pomegranate juice shows potent antioxidant and antiatherosclerotic properties, attributed to its high content of polyphenols, including ellagic acid in its free and bound forms (as ellagitannins and ellagic acid glycosides), gallotannins, anthocyanins (cyanidin, delphinidin, and pelargonidin glycosides), and other flavonoids (quercetin, kaempferol, and luteolin glycosides) (Gil et al, 2000; Fuhrman and Aviram, 2001; Aviram et al, 2004). The most abundant of these polyphenols is punicalagin, an ellagitannin implicated as the bioactive constituent responsible for >50% of the potent antioxidant activity of the juice (Gil et al, 2000). Because of these data, pomegranate has been of increasing interest to the medical community, especially relative to anti-cancer effects (Adhami et al, 2009). The Mukhtar laboratory has been one of the initial groups exploring the anticancer effects of pomegranate (Adhami et al, 2009; Malik et al, 2005). Below are data showing marked in vitro growth inhibitory and pro-apoptotic effects of pomegranate fruit extract (PFE) in prostate cancer cell

lines. In addition, the Mukhtar laboratory has extensively studied PFE in various animal models including data in the TRAMP model (see Figures 1, 2, 3 and 4).

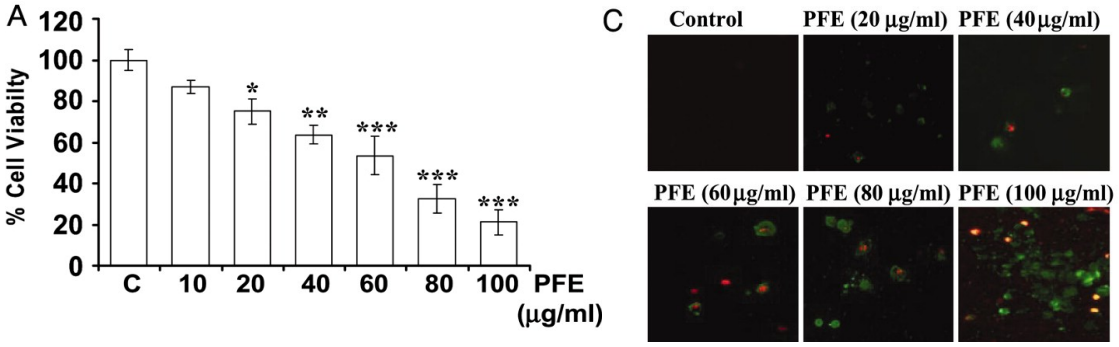


Figure 1: Effect of PFE treatment of PC3 cells on cell growth and apoptosis. (*A*) Effect on cell growth. The cells were treated with PFE for 48 h, and the viability of cells was determined by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide assay. Data shown are mean ± SD of three separate experiments in which each treatment was repeated in 10 wells. * < 0.05; **, *P* < 0.01; ***, *P* < 0.001 vs. control. (*C*) Effect on apoptosis. The cells were treated with vehicle only or specified concentrations of PFE for 48 h. Dose dependent effect of PFE on morphological changes as detected by fluorescence microscopy. Apoptotic cells are stained with annexin V (green fluorescence), and necrotic cells are stained with propidium iodide (red fluorescence).

The Mukhtar data has shown consistent and profound growth inhibitory and pro-apoptotic effects of pomegranate fruit extract (PFE) on prostate carcinoma cells. Whether as a mechanistic effect or associative, perturbation of the IGF axis was also observed (see Figures 3 & 4). They observed a significant decrease in serum and tissue IGF-1 along with a corresponding increase in IGFBP-3 (which sequesters/inactivates IGF-1) (Malik et al, 2005). As a result, the serum ratio of IGF-1/IGFBP-3 was significantly lowered as compared to control mice. As mentioned later, others have also strongly correlated PFE anticancer effects with IGFs. The wide array of cellular and extracellular effects observed with PFE both in cancer and non-cancer-related study further support the potential role IGFs as a common mechanistic theme given the role of the IGF pathway in proliferation and inflammation (Yu and Rohan, 2000).

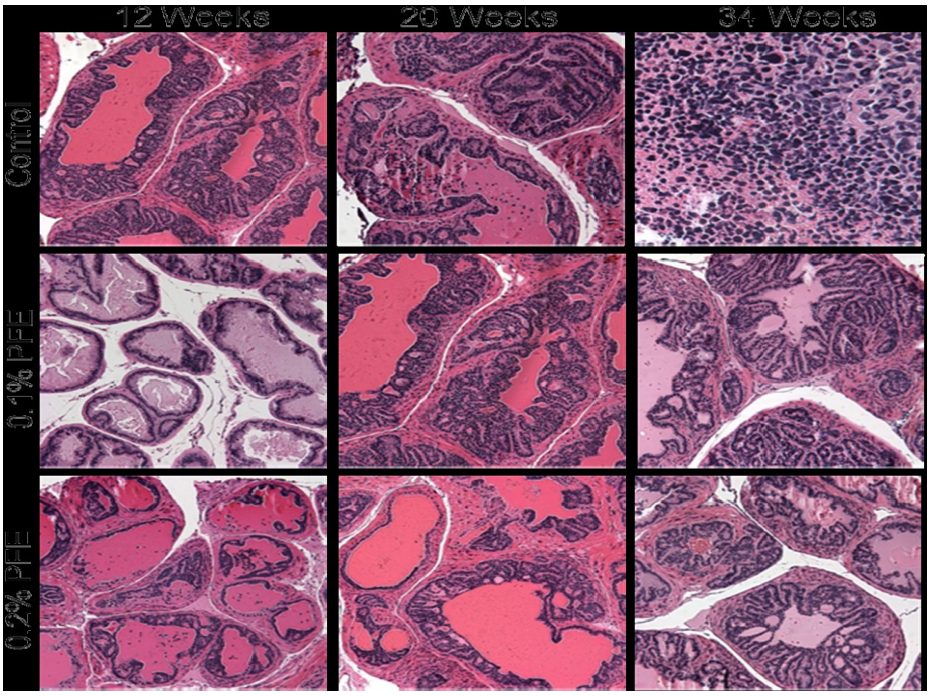


Figure 2: Effect of PFE feeding on prostate histology in the TRAMP mouse model. Representative figures of H&E staining of the dorsal prostate from control and PFE fed TRAMP at 12, 20 and 34 weeks of age. Poorly differentiated tumors at 34 weeks can be seen in the control mice. In PFE fed mice regression of prostate cancer can be seen with well to moderately differentiated tumors at similar age. Most of the animals in the PFE-fed group at 20 and 34 weeks exhibited only early carcinoma lesions with sheets of anaplastic cells.

Figure 3

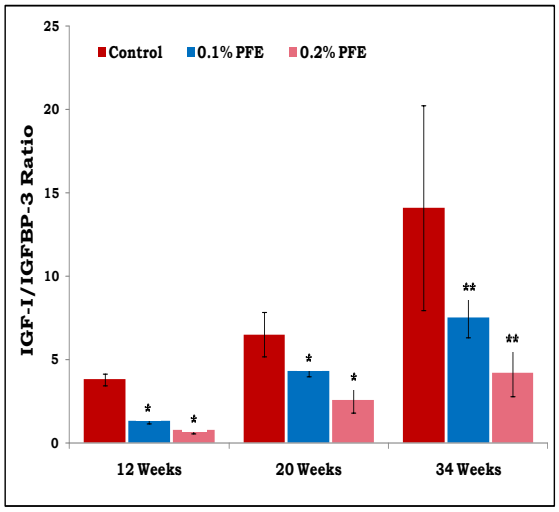
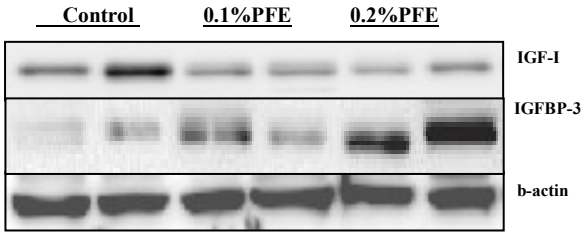


Figure 4



Figures 3 & 4: Effect of PFE on serum and tissue IGF-1 and IGFBP-3 in TRAMP mice fed 0.1%, 0.2% PFE or control for up to 34 weeks. Fig 3 – serum IGF-1/IGFBP-3 ratio at 12, 20 and 34 weeks. Fig. 4 – prostate tissue protein levels of IGF-1 and IGFBP-3 at 20 and 34 weeks.

Researchers from Johns Hopkins University and University of California-Los Angeles have been studying PFE in patients with Stage D_0 recurrent disease after curative therapy (radiotherapy or surgery) (Paller et al, 2012). They have

observed excellent tolerance and an improvement in PSA Doubling Time from 11 months pre-study to 17 months post-study as well as patients with serum PSA declines during study therapy. Carducci and colleagues (Carducci, 2009) recently completed accrual to a randomized, placebo-controlled phase I/II biomarker study of PFE (given as POMx™; 2 capsules; each capsule contains approximately 5-600 mg of polyphenols) in men undergoing prostatectomy for early stage prostate cancer. No preliminary data is available, but endpoints included tissue concentrations of ellagic acids, tissue NFkB, IGF-1/IGFBP-3, Bax/Bcl-2, CASPASE 3 and Ki67.

2.2.2. Pomegranate - Pharmacokinetics and Global Effects

As described above, pomegranate (Punica granatum L.) fruit has been used for centuries in ancient cultures for its medicinal purposes and currently is widely consumed fresh and in beverage forms as juice and wines (Gil et al, 2000). Commercial pomegranate juice shows potent antioxidant and antiatherosclerotic properties attributed to its high content of polyphenols (Fuhrman et al, 2001; Aviram et al, 2004). Because of these data, pomegranate has been of increasing interest to the medical community, especially relative to anti-cancer effects (Adhami et al, 2009).

Although little is known about the metabolism and bioavailability of some of the pomegranate constituents (e.g. ellagitannins) from food sources, there have been some small human trials (Jurenka, 2008). Pomegranate juice (180 ml, containing 318 mg punicalagin; 12 mg of free ellagic acid) was given to 18 adults and serum and urinary concentrations determined for 6 to 24 hours post dose. This study observed rapid absorption (Tmax – one hour) and clearance, mean ellagic acid levels of 0.06 ± 0.01 umol/l, presence of various metabolites (glucuronides and urolithins) and the persistence of urinary metabolites (urolithins) for 48 hours post-dose (Seeram et al, 2006). In another study, 11 healthy men and women were placed on a polyphenol and antioxidant-free diet for three days prior to consuming pomegranate extract (Mertens-Talcott, et al, 2006). Subjects were given 800 mg capsuled PFE daily containing 330.4 mg punicalagins and 21.6 mg ellagic acid (EA). Cmax and Tmax for plasma EA was 33.8±12.7 ng/mL at one hour post-ingestion. This study also demonstrated a significant increase (30-60%) in plasma antioxidant capacity 30 minutes, one and two hours post ingestion.

The potent anti-oxidant and anti-inflammatory effects of pomegranate have led to studying its potential role as a cancer chemopreventive agent. Across various tumor types (prostate, breast, colon, skin, lung) PFE has been observed to have significant growth inhibitory effects with evidence of increased apoptosis, decreased proliferation and effects upon various metabolizing enzymes (Adhami et al, 2009). Purported mechanisms of these observed anticancer effects of PFE include: increased anti-oxidant effects/decreased lipid peroxidation; decreased COX-2, NFkB, cyclin D1, and VEGF; increased apoptosis via increased caspase 3 and Bax/Bcl-2 ratio; inhibition of P450 enzymes; and changes in IGF pathway (Adhami et al, 2009; Bell and Hawthorne 2008).

Studies in prostate cancer started with encouraging preclinical work by Mukhtar and others (Adhami et al, 2009; Malik et al, 2005). The Mukhtar laboratory tested PFE (10-100 ug/ml x 48 hours) against human prostate cancer cells (PC3) and observed dose-dependent growth inhibition, increased apoptosis (induction of Bax and Bak, decreased Bcl-2), decreased cyclins and cdk, and increased p21 and p27 (Malik et al, 2005). Corresponding studies in athymic nude mice elicited similar effects in vivo. Others investigated the effects of PFE on gene expression of key androgen synthesizing enzymes and the androgen receptor observing reduced expression especially in cell lines overexpressing androgen receptor (Hong et al, 2008).

Another explored effect/mechanism is inhibition of phase 1 metabolizing enzymes, Kasimsetty noted PFE inhibited activity and protein expression of CYB1B1 (an activating enzyme of various carcinogens) in prostate cancer cells (Kasimsetty et al, 2009). In addition to the observed effects of PFE on IGFs, Koyama recently observed the growth inhibitory effects of PFE in prostate cancer cells strongly correlated with IGF status (Koyama et al, 2010). Treatment of prostate cancer cells with PFE (10 ug/ml) resulted in significant growth inhibition and corresponding decreased IGF-1 (decreased protein but also a dose-dependent decreased in mRNA expression) and increased IGFBP-3 in prostate cancer cells. Further studies noted the growth inhibition could be blocked by co-treatment with IGF-1 (Koyama et al, 2010).

Initial clinical work with PFE focused on cardiovascular disease (Jurenka, 2008) with a recent example being a prospective, double-blind, placebo-controlled study of pomegranate seed oil capsules (400 mg bid) or placebo for four weeks in 51 subjects observing improvement in some lipid parameters and excellent tolerance in the PFE group (Mirmiran et al, 2010). Whether the effects reported in the study of pomegranate seed oil capsules will be repeated in a study using pomegranate juice remains to be seen. Clinical trials specific to prostate cancer started with researchers at UCLA testing daily pomegranate juice (8 oz., POM Wonderful; 570 mg polyphenol gallic acid equivalents) until disease progression in prostate cancer patients with a rising PSA after surgery or radiotherapy (Pantuck et al, 2006). Eligible patients had a detectable PSA>0.2 and <5 ng/mL and Gleason score ≤7. Clinical end points included safety and effect on serum PSA, serum-induced proliferation, apoptosis of LNCaP cells, serum lipid peroxidation, and serum nitric oxide levels. Forty-eight men enrolled elicited no serious adverse events and the treatment was well tolerated. Mean PSA doubling time significantly increased with treatment from a mean of 15 months at baseline to 54 months post treatment ($P < 0.001$). In vitro assays comparing pretreatment and post treatment patient serum on the growth of LNCaP showed a12% decrease in cell proliferation and a 17% increase in apoptosis ($P = 0.0048$ and 0.0004, respectively), a 23% increase in serum nitric oxide ($P = 0.0085$), and significant ($P < 0.02$) reductions in oxidative state and sensitivity to oxidation of serum lipids at end of study as compared to baseline before pomegranate juice consumption.

Despite the paucity of clinical data and therefore the need for clinical trials to demonstrate efficacy of nutrients like pomegranate in patients with prostate

cancer, the use of alternative and complimentary therapy such as pomegranate is nevertheless a popular strategy for these patients. For instance, surveys suggest that patients with malignant disease frequently resort to nonprescription (or so-called alternative) therapies like green tea because of such purported antitumor effects. A recent survey by Nam et al. found that 25% of patients with prostate carcinoma use these alternative therapies (Nam et al, 1999). Another study has reported that up to 43% of patients in this group utilize alternative and complimentary therapy at some time during the course of their disease (Lippert et al, 2001). Besides the scientific rationale for studying pomegranate fruit extract in prostate cancer the economic impact of alternative therapies demand we study them with the same scientific rigor as a proprietary new compound for prostate cancer.

2.3. Rationale Summary

Despite the commonality of prostate cancer and the uncertain impact on overall mortality of screening and early therapeutic maneuvers, there remains great interest in prevention of prostate cancer (Jemal et al, 2008; Brawley et al, 2001). Epidemiologic studies have consistently correlated prostate cancer incidence with environmental factors, especially dietary nutrient intake (Nelson and Wilding, 2001). The development of prostate cancer chemoprevention compounds has been slowed by the lack of easily accessible tissue endpoints since serum/plasma surrogates have not been identified yet. We and others have increasingly opted for initial phase I or IIa clinical trials of putative prostate cancer chemoprevention agents in a pre-surgical clinical trial design, however a readily available clinical model for performing phase IIb chemoprevention trials was less apparent. Early considerations were to perform studies in men with high-grade prostatic intraepithelial neoplasia (PIN) on prostate biopsies (Bettuzi et al, 2006). However, urologic practice has moved further away from performing follow-up biopsies for PIN. The increasing numbers of men undergoing Active Surveillance (AS) for prostate cancer may provide a clinical model for performing phase II prostate cancer chemoprevention trials.

A rapidly increasing proportion (30% in 1990, 45% in 2000) of the 200,000 men diagnosed with prostate cancer each year have early stage, low risk disease (Cooperberg et al, 2004). Early studies in selected younger prostate cancer patients observed a disease-specific, but not overall, survival benefit for invasive intervention as compared to AS (Bill-Axelson et al, 2011). However, applying these treatments, which deleteriously effect quality of life, to early stage, low risk disease has been questioned (Miller et al, 2006). Most major medical societies now recommend AS for many men with early stage, low risk disease (Horwich, et al, 2009). However, of men who agree to AS, 20-30% will progress and 10-20% will choose to proceed to invasive intervention (without evidence for progression) over 5 years (Warlick et al, 2006; Klotz, 2005). The unmet clinical need for non-invasive interventions for early stage, low risk prostate cancer has led many men to pursue using nutritional supplements (Velicer and Ulrich, 2008; Miller et al, 2009). Therefore, it is highly significant that we explore non-invasive interventions for this already large and growing population and that we carefully use the opportunity that studying this population provides. This can be done by directly evaluating the effects of pomegranate on normal and neoplastic prostate tissue and comparing these results to the planned tissue and plasma biomarkers.

3. SUMMARY OF STUDY PLAN

Study Design

Eligible individuals must be at least 21 years of age or older, with a low-grade, clinically localized prostate cancer. Individuals must have had a prostate biopsy within 13 months of study entry. Use of 5 α reductase inhibitors is prohibited during the study, and for six months prior to the baseline study visit.

Thirty participants will be accrued to this study. Participants will be stratified by tumor volume (≤ 2 positive cores and ≤ 10% of any biopsy core volume is adenocarcinoma vs. >2 positive cores or > 10% of any biopsy core volume is adenocarcinoma). We expect an enrollment duration of 12-18 months. Participants will be randomized, in a 1:1 ratio, to one of two treatment groups:

> PFE (as POMx™) 1000mg (i.e., one (1) 1000mg capsule) taken each morning, by mouth, for 52 weeks ±1 week
>
> Placebo (0mg PFE) one (1) capsule taken each morning, by mouth, for 52 weeks ± 1 week

Following the baseline visit, participants will return for evaluation at 13, 26, 39 and 52 weeks. Scheduled evaluations/procedures are as follows:

- **Baseline Visit**: Eligibility, safety labs and total PSA (to be processed at the PO's clinical lab). Medical history, physical exam, review of concomitant medications and baseline symptom assessment. Blood and urine collection for research purposes (to be batch shipped when a participant completes the study for analysis by the CP lab at UWI. Analysis will include total serum PSA for doubling time, serum testosterone, plasma pharmacokinetics, plasma biomarkers, and urine pharmacokinetics). Review of the pre-study biopsy clinical pathology report for verification of the presence of adenocarcinoma, confirmation that the Gleason grade meets study eligibility criteria, and for stratification by tumor volume. Participants will be stratified by tumor volume and randomized to one of the two treatment groups.

- **Week 13 and 39 Visits:** Safety labs and total PSA (to be processed at the PO's clinical lab), review of adverse events and concomitant medications, pill count and compliance review, blood and urine collection for research purposes (batch shipped to the CP lab at UWI for analysis of total serum PSA , plasma pharmacokinetics and biomarkers and urine pharmacokinetics).

- **Week 26 Visit:** Physician visit, safety labs and total PSA (to be processed at the PO's clinical lab), review of adverse events and concomitant medications, pill count and compliance review, blood and urine collection for research purposes (batch shipped to the CP lab at UWI for analysis of total serum PSA , plasma pharmacokinetics and biomarkers and urine pharmacokinetics).

- **Week 52 ± 1W or End-of-study visit:** Physician visit, safety labs and total PSA (to be processed at the PO's clinical lab), review of adverse events and concomitant medications, pill count and compliance review, blood and urine collection for research purposes (batch shipped to the CP lab at UWI for analysis of total serum PSA, plasma pharmacokinetics and biomarkers and urine pharmacokinetics).

    - Prostate Biopsy – participants will undergo a "standard-of-care" prostate biopsy (8-12 cores from apex, mid-gland, base). Should a study participant elect to undergo surgery, prior to completion of the 12 month study period, (secondary to progression or participant preference) efforts will be made to obtain prostate tissue from the prostatectomy for histology and molecular studies (PSA, IGF-1, IGFBP-3, apoptosis (CASPASE 3), Ki-67, IGF-1R, 8OHdG and androgen receptor), and to obtain all other end of study assessments.

    - If the participant discontinues study therapy and a prostatectomy is not planned, if at all possible, perform a biopsy prior to the participant initiating non-study therapy and obtain all other end of study assessments.

    - Plasma and urine ellagic acid, dimethyl ellelagic acid, urolithin A, urolithin B and their corresponding glucuronides will be evaluated by LCMSMS as previously described by Seeram (Seeram et al, 2006). LCMSMS is a standard analytical technique with improved sensitivity over HPLC.

4. PARTICIPANT SELECTION

4.1 Inclusion Criteria

4.1.1 Participants must have had a standard-of-care biopsy within 13 months of the baseline study visit and must have been diagnosed with low-grade, clinically localized prostate cancer (Gleason Score ≤ 3+3 with a PSA at baseline <10ng/ml in participants <70 years of age, OR Gleason Score ≤3+4 with a PSA at baseline ≤15ng/ml in participants ≥70 years of age). Eligible participants will be those men who are able and willing to undergo AS with PSA monitoring and a scheduled biopsy performed at the end of the study.

4.1.2 No concurrent treatment (hormonal, radiation or systemic chemotherapy) for prostate cancer during study enrollment is planned (unless participants demonstrate clinical evidence of prostate cancer progression such as symptoms, physical exam findings, a rapidly increasing PSA, or radiologic findings that confirm disease progression).

4.1.3 Age ≥21 years. Because no dosing or adverse event data are currently available on the use of POMx™ in participants <21 years of age, children are excluded from this study.

4.1.4 ECOG performance status ≤1 (see Appendix A)

4.1.5 Participants must have normal organ and marrow function as defined below:

4.1.5.1 Hematologic:
WBC ≥ 3000/mm^3;
platelets ≥ 100,000mm^3,
hemoglobin ≥10 g/dL

4.1.5.2 Hepatic:
Total bilirubin ≤ 1.5 x upper limit of institutional normal,
alkaline phosphatase ≤ 1.5 x upper limit of institutional normal,
AST ≤1.5 x upper limit of institutional normal,
ALT ≤1.5 x upper limit of institutional normal

4.1.5.3 Renal:
Serum creatinine within 1.5 x upper limit of institutional normal

4.1.5.4 Electrolytes:
Sodium 135-144 mmol/L (inclusive),
Potassium 3.2-4.8 mmol/L (inclusive),

4.1.6 The effects of PFE on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, participants will be required to use a medically approved method of birth control or abstinence if their sexual partner is of childbearing potential.

4.1.7 Participants must be willing to forego foods, beverages and supplements containing pomegranate for the duration of the study.

4.1.8 Ability to understand, and the willingness to sign, a written informed consent document.

4.2 Exclusion Criteria

4.2.1 Any prior surgery to the prostate within 30 days of baseline procedures. NOTE: Biopsies are not considered surgeries.

4.2.2 Evidence of other cancer(s) (excluding non-melanoma skin cancer) within last 5 years.

4.2.3 Prior pelvic radiation for any reason.

4.2.4 Participants cannot be taking 5-α-reductase inhibitors while on study or within 6 months of the baseline study visit.

4.2.5 Participants may not be taking carbamazepine (tegretol).

4.2.6 Participants may not be receiving any other investigational agents.

4.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to PFE.

4.2.8 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, or psychiatric illness/social situations that would limit compliance with study requirements.

4.2.9 Any significant cardiac event(s) within the 12 months prior to registration, such as episodes(s) of symptomatic congestive heart failure; myocardial infarction; unstable angina pectoris or persistent, stable angina pectoris; or cardiac arrhythmia requiring medication.

4.3 Inclusion of Women and Minorities

Women will not be enrolled in this study of prostate cancer. Members of all races and ethnic groups are eligible for this trial. According to NCI Surveillance Epidemiology and End Results (SEER) 2002 data, the incidence of new prostate cancer diagnosed in the USA during 2002 was distributed ethnically as follows: 5% Hispanic and 94% non-Hispanic; and racially as: 83% white, 12% black, 5% other races. According to SEER the median age at diagnosis for cancer of the prostate is 69 years of age. Approximately 0.0% of those diagnosed are under age 20; 0.0% between 20 and 34; 0.5% between 35 and 44; 8.0% between 45 and 54; 26.1% between 55 and 64; 37.5% between 65 and 74; 23.2% between 75 and 84; and 4.7% 85+ years of age. We expect the age and race distribution to be similar on our study.

The planned distribution of subjects for our study will be men ≥ 21 years old of all racial/ethnic groups with low grade, early stage prostate cancer, who have chosen AS of their prostate cancer. Prostate cancer is only relevant to male gender thus women will be excluded.

It is scientifically and ethically imperative that clinical research into diseases that affect large populations are performed in a way that the knowledge gained can be generalized to the larger population. This means the research subjects need to reflect the population at large. This is especially important in cancer research where data have observed differences in incidence and outcome based upon race/ethnicity or socioeconomic status. Prostate cancer incidence in the United States varies with race/ethnicity, an example being African-Americans, who are at increased risk compared to other races. Therefore, it is critical that adequate representation is achieved.

Because the University of Wisconsin has limited racial/ethnic diversity in our clinical catchment area, we developed a GU prevention group not only focusing on the research expertise of the Urologists involved, but also on achieving more diversity of race/ethnicity and economic status. The University of Wisconsin Carbone Cancer Center serves a multi-county area in southern Wisconsin and northern Illinois that is rural with <5% prostate cancer cases occurring in underserved racial/ethnic populations. In addition, advertisements and contacts with Urologic practices in Milwaukee County, which has a greater proportion of African-Americans, will be targeted. The University of Rochester has a prostate cancer population that is more reflective of the general population with 12-15% of patients being African-American. The University of Minnesota/Minneapolis Veterans Hospital serves both a rural and urban population with approximately 10% of prostate cancer patients being African-

American. The University of Alabama-Birmingham (UAB) serves predominantly an urban population with approximately 35% of prostate cancer patients being African-American. UAB was one of the initial clinical research sites to incorporate community-involvement in their recruitment efforts toward minority populations. In addition to working with community churches that are predominately African-American, they also worked with local barbershops to encourage participation in prostate cancer screening and prevention studies. Urology of San Antonio is a community-based Urologic practice in the city of San Antonio, TX that has been an integral participant in our GU prevention studies. Their participation insures adequate representation of Latino men in our study. Approximately 35% of their prostate cancer patients are Hispanic and 5% are African-American. The Lahey clinic provides another more urban community setting to facilitate diverse representation of subjects. Their distribution according to race/ethnicity is approximately: 83% white, 4% black, 1% Hispanic, <1% Asian, <1% other, and 11% unknown.

4.4 Recruitment and Retention Plan

Subjects will be recruited from Urology clinics at the participating organizations. Study personnel at each PO will be contacted by a patient's Urologist or will contact the PO's Urologists for permission to approach potential subjects they consider appropriate for the study. Local IRB-approved posters or recruitment materials may be placed in Urology clinics identifying the study and directing the potential subjects to notify clinic staff they may be interested in the study. Study personnel would contact the potential subject. When potential subjects are interested, the study will be described by their Urologist and/or study personnel in a private setting. In addition to the study being described, an Informed Consent will be given to the potential subject and family to read and consider. All potential subjects will undergo an informed consent process and will be required to read and sign an Informed Consent form documenting their acknowledgement and desire to be a human research participant.

After the consent form is signed, all procedures and examinations will be done at one visit, including research blood and urine sample collection. Subjects found to be screen failures will not be randomized and the research samples will be destroyed on-site.

Study brochures, posters, protocol fast fact sheets, pocket cards, and other recruitment materials will be developed at the CLO (Consortium Lead Organization – the University of Wisconsin) and made available to the POs for use or modification. The CLO will coordinate with the POs to develop comprehensive site-specific recruitment plans.

5. AGENT ADMINISTRATION

5.1 Dose Regimen and Dose Groups

There will be two treatment groups for this trial. Participants will be randomized in a 1:1 ratio to one of the two groups. The treatment groups are as follows:

Group 1: PFE as POMx™ 1000mg, i.e., one (1) 1000mg capsule, taken each morning, by mouth, for 52 weeks ± 1 week.

Group 2: Placebo, one (1) capsule, taken each morning, by mouth, for 52 weeks ± 1 week.

5.2 Study Drug Administration

Drug will be dispensed by investigational pharmacists or appropriate study staff at the participating organizations and self-administered by the participants. Participants will take one capsule per day, in the morning, by mouth. Study medication may be taken with or without food.

To ensure that study subjects have access to study drug in case of delayed study visit, they will be dispensed four (4) bottles (120 capsules) of study agent at each visit. Tear-off labels will be utilized for unblinding purposes.

5.3 Run-in Procedures

There is no run in phase for this study.

5.4 Contraindications

During study participation, participants may not consume any additional pomegranate, either through dietary sources or through nutritional supplementation.

5.5 Concomitant Medications

As stated in section 5.4, study participants may not consume any additional PFE either in beverage form or as a dietary supplement.

The use of 5-ά-reductase inhibitors (finasteride, dutasteride) is not allowed while on study or within 6 months prior to the baseline study visit. These agents have been shown to affect serum PSA values and may or may not affect prostate cancer biology.

All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participant will be documented on the Concomitant Medications Worksheet and will include: date reported, medication name, start and stop date, dosing regimen, and indication. Medications taken for a procedure (e.g., biopsy) should also be included.

5.6 Dose Modification

The study drug dose modification schema is as follows:

IF	THEN
The participant experiences a grade 2 adverse event that is possibly, probably, or definitely related to study drug	Stop study drug temporarily for up to 4 weeks.
The adverse event resolves to ≤ grade 1 within 4 weeks:	Re-start study drug at 50% dose reduction (1 capsule should be administered every other day).
If the adverse event does not resolve to ≤ grade 1 within 4 weeks:	Stop study drug permanently. Continue to follow participant per the schedule of events in Section 7.1, if participant is willing.
If the participant experiences a grade 2 event after initial dose reduction, and the adverse event is possibly, probably or definitely related to study drug:	Stop study drug permanently and follow until the adverse event is resolved to ≤ grade 1. Continue to follow participant per the schedule of events in Section 7.1, if participant is willing.
In the event a subject had study drug stopped while on the 50% dose reduction, for a grade 2 adverse event that is NOT possibly, probably or definitely related to study drug	Stop study drug temporarily for up to 4 weeks. If the adverse event resolves to ≤ grade 1 within 4 weeks, re-start study therapy at the 50% dose reduction level. If the adverse event does NOT resolve to ≤ to grade 1 within 4 weeks, permanently discontinue study drug. Continue to follow participant per the schedule of events in Section 7.1, if participant is willing.
A grade 3 or 4 adverse event occurs, regardless of relationship to study drug	Stop study drug and call protocol chair to determine if and when drug should be re-started.

5.7 Adherence/Compliance

5.7.1 Ideally, participants will receive 52 ± 1 weeks of treatment. The required compliance rate for evaluability is ≥ 80%. Doses that are missed due to drug holidays (as described in Section 5.6) will not count as non-compliance.

5.7.2 The participant's compliance will be measured by evaluating study calendars and pill counts. Participants will be informed, both verbally and in writing at all visits of the following important compliance points:

- Bring all bottles of study drug (whether or not there is medication in the bottle) to study visits.
- Bring completed pill diary to study visits.

6. PHARMACEUTICAL INFORMATION

6.1 Study Agent (IND #, IND Sponsor)

POMx™ is a pomegranate (Punica granatum L., Wonderful variety) fruit polyphenol extract, which was developed for use as a dietary ingredient. Each capsule contains up to 1000mg of PFE, which delivers pomegranate polyphenols in an amount equivalent to about 8 oz of pomegranate juice. POMx™ powder is produced in a two-step process: (1) extraction of polyphenols from pomegranate fruit, and (2) purification of the extract to produce a highly concentrated polyphenol powder. Extraction is performed during the fruit harvest using pressed pomegranate skins and arils with the seed completely removed. Purification of the extract is performed off-season to meet market demand. Appropriate product specifications have been established, and batch analyses data confirm the product is consistent in quality and free of microbial or chemical contaminants.

The extract is well characterized. It contains the same compounds found in pomegranate juice, and differs only in having lower anthocyanidins, significantly higher proportional content of pomegranate polyphenols, primarily punicalagin and isomers, but the levels in food or supplement products are limited to the amount found in 8 oz of 100% juice. Although punicalagin is unique to pomegranate, its metabolism is known to be like that of other polyphenols. The metabolism of pomegranate polyphenols is reasonably well understood in mice, rats, and humans. Like most dietary polyphenols, pomegranate polyphenols are hydrolyzed in the gut and also metabolized by gut microflora.

POMx™ is a premium grade of pomegranate ellagitannins produced from pomegranate fruits. The extract is from pomegranate skins and arils minus the seeds. POMx™ is standardized to 37% punicalagins, the major pomegranate ellagitannin, and 3.5 % ellagic acid (Seeram et al., 2005; Sartippour et al., 2008). POMx™ is standardized to 60% Gallic Acid Equivalents (GAE) and 85% Total Pomegranate Polyphenols (TPP). POMx™ will be provided by POM Wonderful (Los Angeles, CA, USA).

The investigation product is composed of 1050mg (*Target Fill Weight*) of hygroscopid POM Wonderful pomegranate extract (PWPE) powder blended with 10mg of magnesium stearate (lubricant) and 10mg silicon dioxide (glidant) contained in a size “0” gelatin capsule.

Ingestion of POMx™ results in a level of intake that remains within safe limits established by the history of safe consumption of pomegranate fruit and juice, and is corroborated by published human and animal studies. POMx™ has been sufficiently characterized to assure that it is a safe and wholesome food.

6.2 Reported Adverse Events and Potential Risks

In 21 clinical studies involving 898 human subjects, POMx™ has been very well tolerated. The most commonly reported adverse events have been gastrointestinal effects reported by less than 2% of people taking 1000 mg of POMx™, increasing to

12% at 3,000 mg. Paller et al (2012) in a trial comparing 1000 to 3000 mg of POMx™ over 18 months of intervention reported 12 gastrointestinal events (101 participants, median age 72). These events included diarrhea (1.9% in the 1000 mg group,13.5% in the 3000 mg group – five of these events at this dose level were deemed drug-related); reflux disease (1 participant in the 1000 mg group); nausea (4 participants at 3000 mg); and abdominal pain, constipation, frequent bowel movements, stomach discomfort, and vomiting (1 participant each at 3000 mg). This study also reported several cardiac events including angina pectoris, arrhythmia and congestive heart failure. Three occurred in the 1000 mg group and seven in the 3000 mg group. Most of these events occurred in participants who were diagnosed with cardiac conditions prior to randomization and none of these events were considered to be drug related. The study did not include a placebo control group. There are no other reports in the literature of cardiac events associated with POMx™.

6.3 Availability

POM Wonderful will provide POMx™ to NCI, DCP in sufficient quantities to complete the study. POMx™ will be dispensed to the POs by the DCP repository contractor MRIGlobal.

6.4 Agent Distribution

Agents will only be released by NCI, DCP after documentation of IRB approval of the DCP-approved protocol and consent is provided to DCP and the collection of all Essential Documents is complete (see DCP website for description of Essential Documents).

DCP does not automatically ship study agent; the University of Wisconsin must make a request for agent to be shipped to the PO on a per-participant basis. University of Wisconsin staff will complete the DCP Clinical Drug Request form (NIH-986, to include complete shipping contact information) and fax the form to the DCP agent repository contractor:

NCI-DCP Repository
MRIGlobal
Attn: John Cookinham
1222 Ozark Street
North Kansas City, MO 64116
Fax: 816-753-5359
Phone: 816-360-3805
Email: NCI.DCP@mriglobal.org

DCP does not permit the transfer of agents between institutions (unless prior approval from DCP is obtained).

6.5 Agent Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received from DCP using the NCI "Investigational Agent Accountability Record". The Investigator is required to maintain adequate records of receipt, dispensing and final disposition of study agent. Include on receipt record from whom the agent was received and to whom study agent was shipped, date, quantity and batch or lot number. On dispensing record, note quantities and dates study agent was dispensed to and returned by each participant.

6.6 Packaging and Labels

Study drug (1,000mg PFE/capsule or placebo) will be packaged in standard 100 CC white, pharmaceutical-grade, sealed bottles containing 30 capsules each. DCP will affix a label on each of the bottles; the randomization code will be printed on the label.

6.7 Storage

Investigational product should be stored in dry conditions at room temperature.

6.8 Registration/Randomization

Subjects who are eligible must be randomized by faxing randomization materials to the University of Wisconsin CLO. The PO's study coordinator will complete the Baseline Visit Guide and the Eligibility Questionnaire and fax (608-265-3287) or e-mail (prevention@uwcarbone.wisc.edu) both along with a de-identified copy of the participants Informed Consent form, the clinical lab report and the pathology report from the pre-study baseline prostate biopsy to the CLO central randomization desk. The CLO coordinator at the randomization desk will review eligibility, confirm that the correct consent form version is being used and assign a randomization number.

The CLO will then fax a Clinical Drug Request form to the DCP Drug Repository requesting that drug be shipped overnight to the PO. The Drug Repository will not randomize participants but will maintain a randomization list with treatment assignment codes so they can dispense the correct study product. For next day delivery, the CLO must receive a request for randomization by 12:00 CST on the business day before the drug is needed. Study agent cannot be shipped on a Friday or the day before a holiday. There may be instances where a five-day turn-around is needed (holidays or unusual circumstances). If possible, please randomize a week before the study agent is needed.

As soon as a subject has been randomized, the CLO will email a confirmation of randomization to the PO's study coordinator. If POs do not receive a confirmation within two hours, they should call the CLO to confirm that randomization documents were received. Drug will then be shipped to the PO via overnight courier.

6.9 Blinding and Unblinding Methods

This will be a double-blind study. Neither the participant nor the study personnel will know which treatment arm a participant is on. The Biostatistical Office of the Chemoprevention Program under the guidance of Dr. KyungMann Kim will have the randomization code to unblind subjects. Unblinding of subjects will not occur until the study has been completed by all participants and all data has been collected and analyzed. If a participant experiences a healthcare-related event and unblinding is requested to facilitate their care, the treating physician will contact Drs. Bailey and/or Jarrard with the request to unblind. The request to unblind will be approved upon the agreement of the NCI medical monitor for this protocol. Unblinded participants will be removed from further study participation.

If the request to unblind is approved, the PO will be directed to the product tear-off label which is removed from the study agent bottles at the time they are dispensed and placed in the participant's study chart or other designated research record. The label has a scratch off area that will disclose the treatment assignment.

The PO will immediately notify the CLO of the unblinding by e-mail (prevention@uwcarbone.wisc.edu) and will document the unblinding process in the participant's study chart.

The Medical Monitor must be notified that the blind has been broken.

Howard Parnes, MD
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Division of Cancer Prevention, National Cancer Institute, NIH, DHHS
Shady Grove Campus
9609 Medical Center Dr., Suite 5E-302; MSC9783
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fax 240-276-7828

6.10 Agent Destruction/Disposal

At the completion of investigation, all unused study agent will be returned to the NCI, DCP Repository according to the DCP "Guidelines for AGENT RETURNS" and using the DCP form "Return Drug List".

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events

Evaluation/Procedure	Baseline	Randomization	Week 13 (+/- 1 week)[1]	Week 26 (+/- 1 week)[1]	Week 39 (+/- 1 week)[1]	Week 52 ± 1 Week (or end of study therapy)[1]
Informed consent	x					
Registration	x					
Eligibility Criteria Review	x					
Medical History	x					
Physical Exam	x			x		x
Vital Signs (Temp, BP, Pulse, Respirations) and Weight	x		x	x	x	x
Height	x					
ECOG Performance Status	x					
Assess baseline symptoms	x					
Eligibility/Safety Labs[2]	x		x	x	x	x
Total PSA[3]	x		x	x	x	x
Randomization		x				
Dispense study medication and diary		x[4]	x	x	x	
Pill count and drug calendar review			x	x	x	x
Review concomitant medications	x		x	x	x	x
Assess adverse events						x
Prostate Biopsy	x[5]					x[6]
The samples listed below will be collected locally, and shipped to UWI for analysis:						
Collect one 3ml red top[7]	x		x	x	x	x
Collect a second 3ml red top[7]	x			x		x
Two 10ml green tops[7]	x		x	x	x	x
Urine collection[7]	x		x	x	x	x
IHC analysis of normal and abnormal prostate tissue biomarkers (PSA, IGF-1, IGFBP-3, apoptosis [CASPASE 3], Ki-67, IGF-IR, 8OHdG and androgen receptor)	x[8]					x[9]

[1]The participant must delay his dose of study medication until after blood and urine has been collected, as PK levels need to be assessed approximately 24 hours following the last dose of study medication.

[2]The following lab tests are to be performed: WBC, Hemoglobin, Platelets, Alkaline Phosphatase, ALT, AST, Total Bilirubin, Serum Creatinine, Sodium, Potassium, Chloride, and Bicarbonate. Eligibility labs must be done ≤ 30 days of randomization.
[3]This total serum PSA will be performed at the PO's clinical lab, and used for clinical purposes.
[4]If the participant is unwilling or unable to return to clinic to pick up study medication, it may be sent overnight by a courier service such as UPS or Fed-Ex.
[5] The baseline biopsy must have occurred within 13 months prior to the baseline study visit.
[6]The end of study biopsy performed during week 52 ± 1 week or when participant discontinues study therapy. Participant must take study drug the morning of the biopsy after research blood and urine collection but prior to the biopsy.
[7]These blood and urine samples will be used to determine study objectives (PK and biomarker results) as described in §1.2. See §10.2 for collection and processing instructions.
[8]Tissue will be from a biopsy performed within 13 months of study entry
[9]Tissue will be from the end of study biopsy (or prostatectomy, if applicable)

7.2 Baseline Visit

Baseline evaluations determine if the participant is an eligible candidate for study participation and establish the participant's health status at the time of study entry. Standard-of-care laboratory evaluations or procedures done prior to signing consent will qualify for these baseline evaluations (i.e. physical exams, routine labs, vital signs) if they have been conducted within 30 days prior to study randomization. All baseline evaluations must be completed before a participant is randomized and study agent is dispensed. If a study participant is found to be ineligible, any blood, urine or tissue samples collected for pharmacokinetics or biomarker assessment will be destroyed. The destruction of the blood, urine or tissue samples collected for these evaluations will be clearly documented in the participant's study records.

7.2.1 Informed Consent

At the Baseline visit, written informed consent will be obtained for all potential study participants prior to conducting any research procedures.

- To properly document that informed consent was obtained, the date and time the informed consent was obtained will be documented in the participant's study records.
- A copy of the signed informed consent will be provided to the participant.
- The Registration Source Documents will be sent to the CLO within one business day of obtaining informed consent from any potential study participant, whether or not they are found to be eligible for the study.

7.2.2 Study Registration

Once a participant has signed a consent form, he is assigned a participant ID (PID) number and is considered registered to the study. PID numbers are assigned sequentially and designate the recruitment site, the study and the participant. The CLO will provide each PO with a Participant Identification Number Log at the time of study initiation. Once a participant is registered, the CLO will be notified immediately, to ensure timely and accurate tracking of accrual. Fax (608-265-3287) or e-mail (prevention@uwcarbone.wisc.edu) a copy of the Baseline Visit Guide and the Eligibility Questionnaire to the CLO.

If a consented participant is deemed ineligible (a screen failure), the following documents (provided to PO's at study initiation) must be completed and submitted to the CLO:

- the Baseline Visit Guide
- the Eligibility Questionnaire
- a de-identified copy of the participant's informed consent form
- an Off Study Form
- a Verification Form
- an Adverse Event Tracking Worksheet. If the participant has not experienced an adverse event during the screening process or as a result of baseline study visit procedures, check the box at the top of the page.

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Participants will be registered in the OnCore database by CLO staff.

7.2.3 Medical/Surgical History

Complete medical and surgical histories will be obtained.

7.2.4 Physical Exam

The physical exam will include a general physical assessment; vital signs: blood pressure, temperature, heart rate, and respiratory rate (to be taken after the participant has been in a seated position for 5 minutes); height; weight; and ECOG performance status.

7.2.5 Clinical Safety/Eligibility Laboratory Tests

The following clinical laboratory tests will be performed within 30 days prior to randomization: WBC, hemoglobin, platelets, alkaline phosphatase, ALT, AST, total bilirubin, serum creatinine, sodium, potassium, chloride, bicarbonate and total serum PSA.

7.2.6 Concomitant Medications

Document all prescription and over-the-counter medications; herbal remedies; vitamins and supplements the participant is currently taking. The medication name; date reported; dosing regimen; indication; start (at minimum the estimated start year) and stop dates; will be recorded.

7.2.7 Baseline Symptoms

Any current/active signs and symptoms experienced by the participant will be documented as Baseline Symptoms. This will include any abnormal laboratory values that are deemed clinically significant. A baseline symptom that increases in grade during the course of the study will be documented as an adverse event. The AE onset date is the date on which the increase in severity occurred.

7.2.8 Review of Previous Prostate Biopsy Pathology Report

The participant must have had a prostate biopsy performed within 13 months prior to randomization. This will be the pre-study, baseline biopsy. The Gleason score as reported on the baseline biopsy pathology report will be used to determine eligibility. The pathology report will be submitted to the CLO to determine tumor volume for stratification (see Section 3: Study design).

7.2.9 Collection of Blood and Urine for Research Purposes

Supplies for the collection of research blood and urine samples will be supplied by the University of Wisconsin's CP Lab in a research lab kit. Two 3ml red top tubes and two 10ml green top tubes of blood will be collected in addition to the blood drawn for clinical safety/eligibility labs. In addition, a minimum of 10ml of urine will be collected in a urine collection cup. The cup is not provided in the research lab kit. Instructions for collection, handling and shipping of research blood and urine samples are in sections 10.2 and 10.3 of this protocol.

7.2.10 Eligibility Assessment

The Eligibility Questionnaire, provided by the CLO as part of the Visit Guides for this protocol, will be completed, signed, and submitted to the CLO along with the Baseline Visit Guide, clinical laboratory results, the pathology report from the pre-study baseline prostate biopsy, and a de-identified copy of the participant's informed consent form for review and approval prior to randomization.

7.2.11 Randomization

If the participant is deemed eligible, he may be randomized, per Section 6.8 of the protocol.

7.2.12 Drug Dispensing and Compliance Instructions

Participants will be instructed on the importance of compliance with the study agent dosing instructions (section 5) Participants will be provided with a pill diary and instructed to document daily the date and time they take their dose of study agent, indicate the reason for any missed doses, document any lost capsules of study agent, list any side effects or symptoms noticed, list any new concomitant medications taken and indication for that medication and note any additional information they feel is relevant. The participant will be instructed to initial each day's entry.

All bottles of study agent dispensed to the participant must be accounted for by the PO. Participants will be instructed to return all bottles of study agent (empty, full, or partially full) and all unused capsules of study agent that were previously dispensed to them at their next study visit.

No study agent bottles should be discarded by the participant or by study staff. Returned bottles of study agent will be maintained at the site for review by a study monitor and return to the drug repository (MRIGlobal).

7.3 During Study Intervention

7.3.1 At the week 13 and week 39 study visits the following evaluations will be performed: Safety labs and total serum PSA; vital signs and weight; adverse events assessment; review of concomitant medications; compliance assessment; collection of blood and urine for research purposes (plasma and urine pharmacokinetics and serum and plasma biomarkers). The participant will be instructed to delay his dose of study agent on the day of this visit until AFTER blood and urine samples have been collected to allow for a 24-hour post dose pharmacokinetic assessment.

7.3.1.1 Clinical Safety Laboratory Tests

The following clinical laboratory tests will be performed: WBC, hemoglobin, platelets, alkaline phosphatase, ALT, AST, total bilirubin, serum creatinine, sodium, potassium, chloride, bicarbonate and total serum PSA.

7.3.1.2 Vital Signs and Weight

Vital signs (blood pressure, temperature, heart rate, and respiratory rate) will be assessed after the participant has been in a seated position for 5 minutes. The participant's weight will be recorded.

7.3.1.3 Adverse Event Assessment

The participant will be asked about any symptoms or events he has experienced since initiating study therapy. For each event document a verbatim description of the event, date reported, onset and end dates, CTCAE v4 term and severity grade, the action taken, outcome, whether the event was a Serious Adverse Event or not, whether the participant dropped from the study due to the event and the MD's assessment of attribution of the event to the study agent. Any clinical laboratory results that the M.D. deems clinically significant should be documented as an Adverse Event.

7.3.1.4 Concomitant Medications

The concomitant medication list will be reviewed with the participant. Any new prescription, over-the-counter, herbal remedies, vitamins and supplements the participant has taken will be added to the list. The drug name, indication, dosing regimen date reported, start date (at minimum the estimated start year) will be recorded, and new entries will be initialed and dated.

Any changes to the dosing regimen for medications on the list will be documented as well as stop dates for any medications that the participant is no longer taking.

7.3.1.5 Compliance Assessment

The participant's compliance with study agent dosing will be assessed at each visit. The compliance rate is determined using the following calculation: The number of capsules dispensed – the number of capsules returned = the number of capsules taken in a period. The number of capsules taken in a period ÷ the number of capsules prescribed for that period x 100 = % compliance. The pill diary will be reviewed with the participant to ensure that any missed doses and the reason for the missed dose is documented. A participant must have ≥ 80% compliance to be evaluable for this study. If the participant is having issues with compliance, the importance of taking study agent as prescribed and strategies to improve compliance will be discussed with the participant and documented in the visit notes.

7.3.1.6 Collection of Blood and Urine for Research Purposes

In addition to the blood drawn for clinical safety labs, one 3ml red top tube and two 10ml green top tubes of blood will be collected for research assays using the supplies provided in the research lab kit. A minimum of 10ml of urine will be collected in a urine collection cup. The cup is not provided in the research lab kit. Instructions for collection, handling and shipping of research blood and urine samples are in sections 10.2 and 10.3 of this protocol.

7.3.2 The 26-week visit is identical to the week 13 and 39 visits (as described in section 7.3.1) with the exception of the following two additional evaluations:

7.3.2.1 Physical Exam

The physical exam will include a general overall physical assessment as well as a standard of care prostate examination by a study doctor.

7.3.2.2 Collection of Blood and Urine for Research Purposes

In addition to the blood drawn for clinical safety labs, two 3ml red top tubes and two 10ml green top tubes of blood will be collected for research assays using the supplies provided in the research lab kit. A minimum of 10ml of urine will be collected in a urine collection cup. The cup is not provided in the research lab kit. Instructions for collection, handling and shipping of research blood and urine samples are in sections 10.2 and 10.3 of this protocol.

7.4 Evaluations at Completion of Study Intervention (Week 52±1W or end of study therapy)

The Week 52 Visit (or end-of-study therapy visit, whichever comes first) is identical to the week 13 and 39 visits as described in section 7.3.1 with the following additional evaluations:

- a physical exam
- collection of a second 3ml red top tube for research biomarker assessment
- a prostate biopsy

As for the previous visits, the participant will be instructed to delay his dose of study agent on the day of this visit until AFTER blood and urine samples have been collected to allow for a 24-hour post dose pharmacokinetic assessment. **However, the participant WILL be instructed to take his final dose of study agent immediately following the collection of the research blood and urine samples and prior to the prostate biopsy to allow for the assessment of study agent levels in prostate tissue.**

7.4.1 Physical Exam

The physical exam will consist of a general physical assessment of the participant.

7.4.2. Prostate Biopsy

NOTE THAT THE STANDARD- OF-CARE PROSTATE BIOPSY MUST BE PERFORMED DURING STUDY WEEK 52±1W, OR AT THE TIME THE PARTICPANT DISCONTINUES STUDY THERAPY. If the participant discontinues study therapy to undergo a prostatectomy, tissue samples can be obtained at the time of prostatectomy.

If the participant discontinues study therapy and a prostatectomy is not planned, if at all possible, perform a biopsy prior to the participant initiating non-study therapy.

Prostate biopsies ($\geq$ 8 core samples from all quadrants of the prostate) will be performed at end of study or at the time of study withdrawal and submitted for standard of care histopathologic grading at the participating organization.

If a study participant elects to undergo prostatectomy prior to completion of the 1-year study period (whether or not they have clinical evidence of disease progression) every effort will be made to obtain prostate tissue from the prostatectomy specimen for histology and molecular studies as described above. Data from prostatectomy samples will be viewed as exploratory.

7.4.3 Adverse Event Assessment

If, at the time of the Week 52/end of study therapy visit, the participant has not reported any adverse events, check the box at the top of the Adverse Event

Tracking Worksheet that says, “Check this box if the participant did not have any adverse events during the study”

7.4.4 Concomitant Medications

Place a check mark in the box in the “Check if Continuing at End of Study” column on the Concomitant Medications Worksheet for any concomitant medication the participant is continuing to take as of this visit.

If, at the time of the Week 52/end of study therapy visit, the participant has not reported any concomitant medications, check the box at the top of the Concomitant Medications Worksheet that says, “Check this box if the participant did not take any concomitant medications during the study”.

7.4.5 Collection of Blood and Urine for Research Purposes

In addition to the blood drawn for clinical safety labs, two 3ml red top tubes and two 10ml green top tubes of blood will be collected for research assays using the supplies provided in the research lab kit. A minimum of 10ml of urine will be collected in a urine collection cup. The cup is not provided in the research lab kit. Instructions for collection, handling and shipping of research blood and urine samples are in sections 10.2 and 10.3 of this protocol.

7.5 Post-intervention Follow-up Period

There is no post-intervention follow-up period for this study.

7.6 Methods for Clinical Procedures

Not applicable.

8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

8.1 Primary Endpoint

The primary endpoint of the study is change in plasma IGF-1 from baseline to end of study (12 months).

8.2 Secondary Endpoints

The secondary endpoints are serum PSA doubling time (using results done for research purposes only at the CP lab at the University of Wisconsin), Gleason grade, and tumor volume on prostate biopsy, plasma and tissue biomarkers, toxicity, and compliance. Serum total PSA levels will be collected at baseline and every 3 months while on study. Gleason Grade and tumor volume will be evaluated from pre-study prostate biopsy and end of study (Wk 52) clinical pathology biopsy reports.

Plasma and tissue biomarkers will be compared from baseline to end of study (plasma) or pre-study prostate biopsy materials (within 13 months of study entry) to end of study prostate biopsy (tissue). Toxicity and compliance will be measured throughout the study as appropriate at study visits.

PSA DT will be determined from PSA values obtained during study participation (baseline and weeks 13, 26, 39 and 52). The secondary endpoint of PSA DT is based on the value at study completion (week 52 or at point of early termination). However, PSA DT will be determined starting at week 26 (the earliest time point with 3 values) and week 39 and recorded. For this initial pilot study, we will not specify the parameters for discontinuing study participation due to disease progression, as defined by PSA DT (i.e., PSA DT decreases to <2-3 years).

8.3 Off-Agent Criteria

All participants will be off agent on or before day 364 +/- 7days (52 weeks +/- 1 week) of administration. Participants may stop taking study agent for the following reasons: completed the protocol-prescribed intervention, adverse event or serious adverse event that would compromise the study drug administration or contraindicate the prostate biopsy procedures required in the study, any treatment for prostate cancer between the diagnostic biopsy and end of study biopsy, inadequate agent supply, noncompliance, concomitant medications, or medical contraindication.

8.4 Off-Study Criteria

Participants may go off study for the following reasons: the protocol intervention and any protocol required follow-up period is completed, AE/SAE, lost to follow-up, non-compliance, concomitant medication, medical contraindication, withdrawal of consent, determination of ineligibility, or death. Off study will mean that the investigator will not be able to or does not need to follow the participant to complete any measurements.

8.5 Study Termination

NCI, DCP as the study sponsor has the right to discontinue the study at any time.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Rationale for Methodology Selection

We will perform correlative studies involving the intermediate endpoint biomarkers. As the following will be measured in blood plasma, they will be obtained at baseline and at every 3 months thereafter: Insulin-like growth factor 1 (IGF-1) and IGF binding protein 3 (IGFBP-3) will be measured by immunoassay. PSA will be evaluated in the blood serum.

The following will be measured (using immunohistochemical staining) in benign, normal adjacent to tumor, and tumor tissue obtained from the pre-study and end of study prostate biopsies: PSA, IGF-1, IGFBP-3, apoptosis (CASPASE 3), Ki-67, IGF-1R, and androgen receptor.

9.2 Comparable Methods

We have selected ELISA as a method as it increased sensitivity and quantitation over 2D gels and westerns. **IGF-1.** Assay Summary: IGF-1 in plasma will be measured by a commercially available 96-well plate quantitative sandwich immunoassay from R&D Systems (Minneapolis, MN). The standard curve ranges from 0.188 to 6.0 ng/ml IGF-1. **IGFBP-3**. Assay Summary: IGFBP-3 will be studied in EDTA plasma by a commercially available 96-well plate quantitative sandwich enzyme immunoassay (Quantikine® Human IGFBP-3, R & D Systems, Minneapolis, MN). Findlay et al., (Findlay et al, 2000) recommended precision and accuracy should be in the range of 20-25% for immunoassays and all three assays are well within that range. We have extensive experience with all three assays in human samples.

An important aspect of clinical trials focused on tissue biomarkers is ease and adequacy of tissue acquisition. AS subjects undergo repeat prostate biopsies at intervals of 1-2 years depending on the group and clinical situation. These biopsies are recommended to be 4 quadrant core needle biopsies to a total of 8-12 cores. In an AS population, the majority of the cores will be normal prostate epithelium with scattered amounts of adenocarcinoma and prostatic intraepithelial neoplasia. Therefore, efficiency of use will be paramount. Below are recent technological advances available to UWI consortium studies that improve upon tissue use efficiency (more endpoints assessed with less tissue).

Immunohistochemistry (IHC):
Chromogenic multiplex IHC assay will be used, so the spatial variation of the biomarker expression in the tissue can also be analyzed and compared. Tissue slides will be deparaffinized and stained following standard protocol (Huang, Human Pathology 2013 44(1):29-38). Target markers (PSA, IGF-1, IGFBP-3 apoptosis [CASPASE 3], Ki-67, IGF-1R, and androgen receptor [AR]) will be detected with specific primary antibodies from reputable vendors. The primary antibodies will be paired to perform dual immostaining to minimize waste of biopsy tissue samples. Standard staining agents will be employed.

Biomarker quantitation:
Vectra™ (Perkin Elmer, Waltham, MA will be used for quantitation of the biomarkers. This system includes an automated slide scanner and state-of-the-art softwares (Nuance™ and inForm™). Vectra™ is the most advanced instrument for extracting proteomic and morphometric information from tissue microarray or intact tissue sections. Vectra merges automated slide-handling, multispectral imaging technology, and unique pattern-recognition-based image analysis into a powerful system for discovery and clinical studies. This system accurately measures protein or mRMA/DNA targets and morphometric characteristics in distinct tissue regions of interest on whole slides or tissue microarray (TMA). Sections can be labeled with either immunofluorescent (IF) or immunohistochemical (IHC) stains, or in situ hybridization (ISH) or with conventional stains such as H&E and trichrome. With IF or IHC or ISH, single or multiple proteins or mRNA/DNA targets can be measured on a per-tissue, per-cell, and per-cell-compartment (e.g., nuclear, cytoplasmic) basis, even if those signals are spectrally similar, are in the same cell compartment or are obscured by autofluorescence. Vectra™ processes up to 200 slides in a single run or analyze every spot in a TMA.

The process to quantitate target proteins using the Vectra™ is briefly described as follows:

Image acquisition: Briefly, the stained slides will be loaded onto the Vectra slide scanner. A scanning protocol including a spectral library will be created based on the tissue size, areas of interest and staining complexity (single or multiple staining in a single section). 8-bit image cubes will be acquired for analysis. For setting up the spectral library, three control prostate tissue slides with one dye only (DAB dye, Warp red and hematoxylin, respectively) will be prepared and scanned.

Analysis: Each chromogen has its unique spectral characteristics (curve), which is the basis for building the spectral library. First, we will use the Nuance software and image cubes acquired from the control slides to create a spectral library – defining the spectral curve for each chromogen (DAB, Warp red and hematoxylin) used in this experiment. The spectral library will then be used to unmix the signals on the test slides triple-stained with DAB, Warp red and hematoxylin by recognizing their unique spectral curves for quantitation. By such, signal noises and cross talk are eliminated (Figure 1). Then, using the created spectral library and inForm software to do tissue (epithelium vs. stroma, etc.) and cell (nucleus vs. cytoplasm) segmentations (Figure 2). Then the target signals will be quantitated within the selected subcellular compartment(s) of interest. Continuous signal intensity data will be generated.

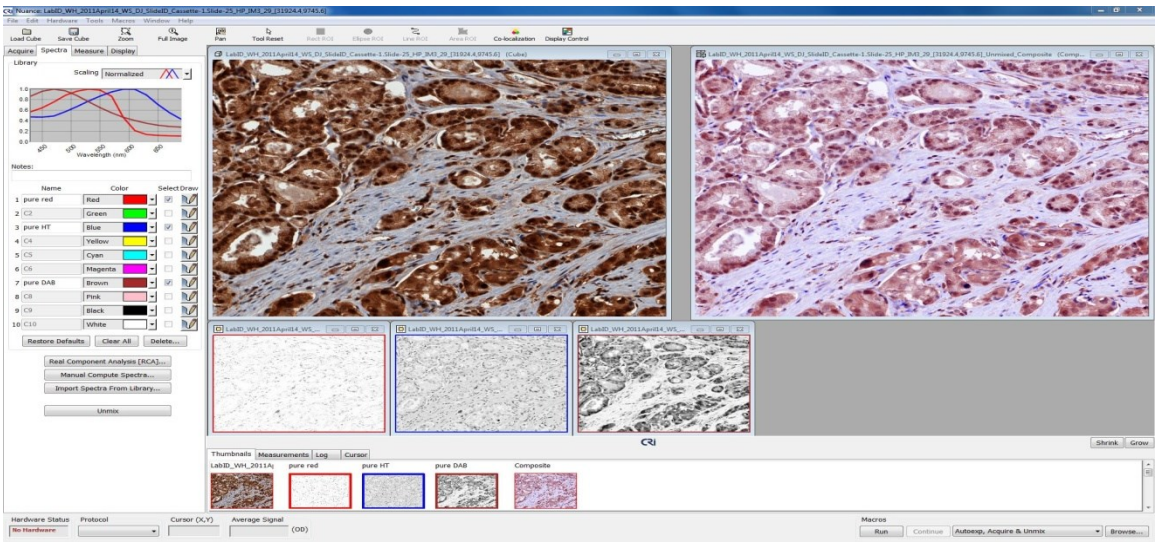

Figure 5. Nuance work area: Left pane shows the spectral library created with pure DAB, pure Warp red and pure hematoxylin slides. Right pane shows an image (top left panel) of prostate adenocarcinoma (PCa) dual immunostained with anti-p27 (brown) and Ki-67 (red)and counter stained with and hemetoxylin (blue), three unmixed gray images of PCa (DAB, Warp red and hematoxylin, respectively) using the spectral library (3 middle panels) and a composite image (top right panel) of unmixed DAB, Warp red and hematoxylin. Target markers (p27 and Ki-67) are quantitated with unmixed pure signals.

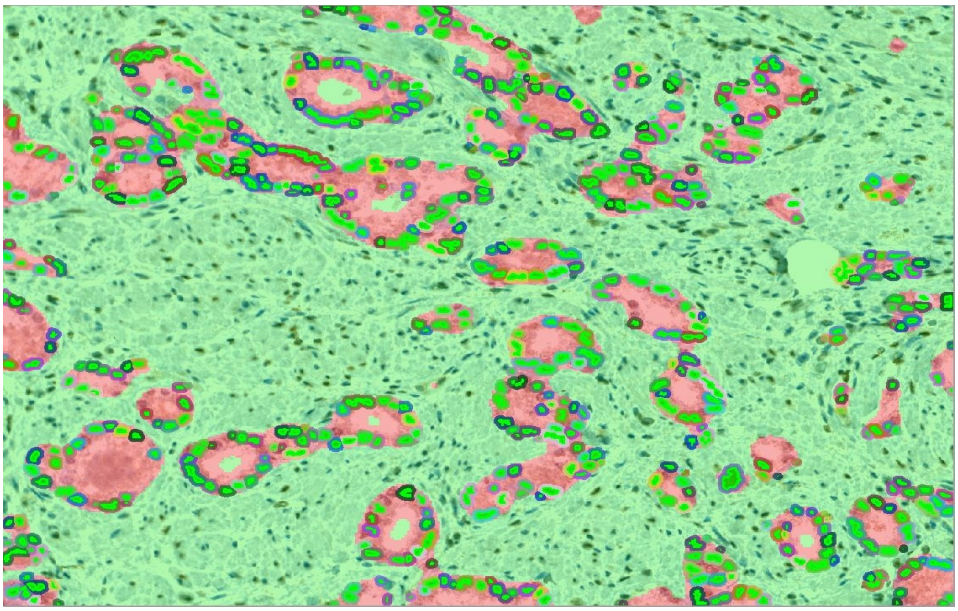

Figure 6. Prostate adenocarcinoma tissue. Epithelium (pink) and stroma (green) are segmented. The nuclear (bright green) and cytoplasmic (purple/blue) compartments in the epithelium are also segmented using inFormTM software. Target markers can be quantitated in the segmented subcellular compartments.

10. SPECIMEN MANAGEMENT

10.1 Laboratories

The UWCCC Cancer Pharmacology Laboratory (The CP lab) will be the central repository for research specimens collected by consortium members. The CP lab will prepare kits for distribution to each PO for use in collection of biomarker data. Upon the receipt of blood, urine, and tissue samples, the CP lab will coordinate the distribution of tissue blocks to the study pathologists for evaluation and biomarker analysis. The CP lab will perform all of the plasma biomarker analyses and perform pharmacokinetic analyses on both plasma and urine specimens, as well as the serum Total PSA levels.

The UWCCC Translational Research Initiatives in Pathology (TRIP) lab will serve as the central pathology analytical facility for the prostate tissue samples acquired for this study. The POs will send paraffin-embedded tissue blocks or unstained slides to the CP lab. The CP lab will be responsible for distributing these blocks or slides to the pathology lab. The pathology lab will be responsible for preparing the pathological specimens for analysis.

10.2 Collection and Handling Procedures

At the baseline visit, we will be performing blood and urine pharmacokinetic analyses, plasma biomarker analyses, and total serum PSA and testosterone levels. Pharmacokinetic analyses, plasma biomarker analyses and total serum PSA levels will be done at all subsequent visits. Serum testosterone levels will be done at baseline and Weeks 26 and 52.

To collect the urine specimen: One (1) urine collection cup and four (4) cryovials are required. Collect at least 10 ml of urine. If the participant has difficulty voiding 10 ml of urine, then collect all of the urine the participant can void at one time. You do not need to collect urine from multiple voids to meet the required minimum volume (10ml). Document the date and time of the void, the void volume and the date and time of the previous void.

To process the urine specimen: Aliquot urine into four (4) cryovials. Dispose of any additional urine. Label the tubes with the participant's initials, PID, sample type, time and date of collection.

To store the urine specimen: Freeze the specimens at -70°C. Store the specimens at -70°C until the participant has completed all of the study visits. See section 10.3 for shipping procedures.

To collect the blood specimens: Basic phlebotomy supplies will be in the lab kit provided by the CP lab: green and red top tubes and cryovials as needed. Draw 9mls of blood into each of the green top tubes. Draw 2.5mls of blood into the red top tube(s).

To process the blood specimens: Centrifuge the green top tubes at ~1000xG for 10-15 minutes. Aliquot the plasma into eight (8) cryovials. Allow the red top tube(s) to clot, then centrifuge at ~1000xG for 10-15 minutes. If <u>one</u> red top tube is drawn,

aliquot serum equally into two (2) cryovials. If two red top tubes are drawn, aliquot serum equally into four (4) cryovials.

Label cryovials with subject initials, PID, time and date of collection, and sample type (i.e., "baseline" or "Week 13 Visit", etc.) Freeze at -70° C.

To store the blood specimens: Store the cryovials at -70°C until the participant has completed all of the study visits. See section 10.3 for shipping instructions.

Prostate biopsy specimens:
The POs will request formalin-fixed, paraffin-embedded tissue blocks from the pre-study baseline and end of study prostate biopsies for submission to the 3P Lab. .The CLO will review each participant's pre- and post-intervention pathology report and select the blocks to be submitted for analysis. This will include location matched blocks of entirely benign cores of prostate tissue, location matched blocks with tumor cores and any additional blocks with tumor cores.

Tissue blocks will be returned to the POs pathology department upon request.

If the pathology department holding the biopsy tissue will not release tissue blocks, 10 unstained slides may be substituted. The slides should be cut in 4-5 um-thick sections and picked up on Super Frost Plus or comparably charged slides. These slides should not be pre-melted or baked. If there is insufficient tissue in the block to cut 10 sections, the remaining sections may be cut from another block containing adenocarcinoma (if another block is available from the same biopsy is available).

If the POs pathology department's policy is not to release blocks immediately after biopsy, the request for blocks may be delayed up to 2 months in order to provide adequate time for pathological processing of the blocks.

Procedure notes and pathology reports: Once the procedure notes and pathology reports are available, blinded copies should be added to the participant's chart. Additionally, copies should be forwarded to the central lab with the shipment of the participant's research kit.*)*

10.3 Shipping instructions

Blood and Urine Specimens

PO's with a –70° C freezer will batch blood and urine samples and ship all research samples for one participant once that participant has completes the study. If a PO does not have access to a -70°C freezer, they should contact the CLO before enrolling participants so special arrangements can be made for the storage and shipping of research samples.

When a participant completes the study and all blood and urine samples are completely frozen at -70^{o} C, place all of the samples in biohazard bags. Place a layer of dry ice on the bottom of the Styrofoam cooler (included in the lab kit). Place the biohazard bags on top of the ice and cover with enough dry ice to fill the cooler.

Complete the Frozen Sample Shipping Inventory. Fax (608-265-3287) or e-mail (prevention@uwcarbone.wisc.edu) a copy of the inventory to the CLO prior to shipping, place a copy on top of the lid of the cooler, and file the original in the participant's study chart. Place the cooler in the cardboard shipping box it arrived in.

Tissue Blocks/Slides (Pre-study/ Baseline and End of Study/Early Termination)

The CLO will send a list of the blocks to be requested to the POs. The PO will request the selected blocks from the pathology department where the biopsy was read. If the pathology department will not release blocks, 10 unstained slides may be substituted (see section 10.2 Collection and Handling Procedures: Prostate biopsy specimens). The PO's will be provided with a Styrofoam shipping container, gel packs and shipping labels and instructions at the time of the request.
For all shipments:

Ship only on a Monday, Tuesday or Wednesday to ensure safe arrival during the week. Do not ship the day before a holiday.

Call (608-263-5369) or E-mail (CPlab@lists.medicine.wisc.edu) the CP Lab to inform them of the shipment.

Use the express courier service indicated by the shipping label contained in the lab kit. Closely follow all special shipping instructions outlined in the kit instruction packet.

Address to:
CP Lab
University of Wisconsin Hospital and Clinics
Room K4/559
600 Highland Avenue
Madison, WI 53792-5669

10.4 Blood, Urine and Tissue Banking

Biologic specimens collected during the conduct of each clinical trial that are not used during the course of the study will be considered deliverables under the contract and thus the property of the NCI. At study completion, NCI reserves the option to either retain or relinquish ownership of the unused biologic specimens. If NCI retains ownership of specimens, the Contractor shall collect, verify and transfer the requested biologic specimens from the PO to a NCI-specified repository or laboratory at NCI's expense.

11. REPORTING AEs

DEFINITION: An AE is any untoward medical occurrence in a study participant. An AE does not necessarily have a causal relationship with the treatment or study participant. An AE can therefore be any unfavorable and unintended sign (including a clinically significant laboratory finding), symptom, or disease temporally associated with participation in a

study, whether or not related to that participation. This includes all deaths that occur while a participant is on a study.

A list of AEs that have occurred or might occur (Reported Adverse Events and Potential Risks) can be found in Section 6.2, Pharmaceutical Information, as well as the Investigator Brochure or package insert.

11.1 Adverse Events (AEs)

11.1.1 Reportable AEs

All AEs that occur after the informed consent is signed (including those that occur prior to the participant starting study agent) must be recorded on the Adverse Event Tracking Worksheet whether or not related to study agent.

11.1.2 AE Data Elements:

- AE reported date
- AE Verbatim Term
- Common Terminology Criteria for Adverse Events v4.0 (CTCAE) AE term
- Event onset date and event ended date
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a serious adverse event (SAE)
- Whether or not the subject dropped due to the event
- Action taken with the study agent
- Outcome of the event
- Comments

11.1.3 Severity of AEs

11.1.3.1 Identify the adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs will be assessed according to the CTCAE grade associated with the AE term. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v4.0. as stated below.

CTCAE v4.0 general severity guidelines:

Grade	Severity	Description
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4	Life-threatening	Life-threatening consequences; urgent intervention indicated.
5	Fatal	Death related to AE.

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, *etc*.

**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.1.4 Assessment of relationship of AE to treatment

The possibility that the adverse event is related to study agent will be classified as one of the following: not related, unlikely, possible, probable, definite.

11.1.5 Follow-up of AEs

All AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed according to good medical practices and documented as such.

11.2 Serious Adverse Events

11.2.1 DEFINITION: Fed. Reg. 75, Sept. 29, 2010 defines SAEs as those events, occurring at any dose, which meet any of the following criteria:

- Results in death
- Is life threatening (Note: the term life threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality/birth defect
- Important medical events that may not result in death, be life-threatening or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed.

11.2.2 Reporting SAEs to DCP

11.2.2.1 The Consortium Lead Organization and all Participating Organizations will report SAEs on the DCP SAE form found at http://prevention.cancer.gov/files/clinical-trials/SAE_form.doc.

11.2.2.2 Contact the DCP Medical Monitor by phone within 24 hours of knowledge of the event.

Howard Parnes, MD
Prostate and Urologic Cancer Research Group
Division of Cancer Prevention, National Cancer Institute, NIH, DHHS
Shady Grove Campus
9609 Medical Center Dr., Suite 5E-302
Rockville, MD 20850
parnesh@mail.nih.gov
(240) 276-7045

Include the following information when calling the Medical Monitor:

- Date and time of the SAE
- Date and time of the SAE report
- Name of reporter
- Call back phone number
- Affiliation/Institution conducting the study
- DCP protocol number
- Title of protocol
- Description of the SAE, including attribution to drug

11.2.2.3 A written SAE report will be faxed to the DCP Medical Monitor within 48 hours of learning of the event using the paper SAE form. PO's will submit their written report to the CLO for review via fax (608-265-3287) or e-mail (prevention@uwcarbone.wisc.edu). Staff at the CLO will review the SAE report form and will return it to the PO if any revisions are required. Once approved, the CLO will FAX the report to the DCP Medical Monitor and to DCP's Regulatory Contractor, CCS Associates, at (650) 691-4410 (phone: (650) 691-4400) or e-mailed to safety@ccsainc.com.

11.2.2.4 The DCP Medical Monitor and regulatory staff will determine which SAEs require FDA submission.

11.2.2.5 The Lead Organization and all Participating Organizations will comply with applicable regulatory requirements related to reporting SAEs to the IRB/IEC.

11.2.2.6 Follow up of SAE
PO staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the

DCP SAE form in the appropriate format. Any information that is added to the report should be circled and dated. Any information that is deleted from the original report should be struck through and dated. Follow-up information should be sent to DCP as soon as available. PO's will submit their follow-up forms to the CLO for review. Once approved, the CLO will submit the follow-up form to the DCP. SAEs will be followed until resolution to baseline, or until the study is closed to accrual, whichever comes first.

12. STUDY MONITORING

12.1 Data Management

All of the procedures outlined in the University of Wisconsin chemoprevention consortium standardized Data Management Plan (approved 06/03/2013) will be followed in this protocol. Please refer to this document for additional details on data management procedures.

This study will report clinical data using the CLO's OnCore database (a web-based clinical trials/database). OnCore will be the database of record for the protocol and subject to NCI and FDA audit. Data entry will be performed at the CLO where staff is trained in OnCore per our DMP and applicable regulatory requirements such as 21 CFR; Part 11.

In order to standardize the collection of information, the CLO will provide POs with protocol specific Visit Guides.

12.2 Case Report Forms

Participant data will be documented in the University of Wisconsin's OnCore database using protocol-specific electronic case report forms (e-CRFs) developed from the standard set of DCP Chemoprevention CRF Templates and utilizing NCI-approved Common Data Elements (CDEs). CLO staff will enter data into OnCore and transfer to Federal Security Compliant formats for transmission to DCP according to pre-established DCP standards and procedures. Amended e-CRFs will be submitted to the DCP Protocol Information Office for review and approval.

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12.3 Source Documents

In order to standardize the collection of study data, the CLO will provide POs with study-specific Visit Guides. These Visit Guides will provide instructions for conducting each study contact and specific details on the data to be collected and reported at each contact. All data reported must be documented either on a clinical primary source document (physician's notes, medication lists, nurse's and study coordinator's notes, pathology reports, operative reports, etc.,)or on the documents provided with the Visit Guides. All source documents must be signed by the staff that collected or elicited the information in the source documents. Source documents will be completed at each PO, then submitted to the CLO (either by fax, e-mail or US mail) for entry into the Oncore database.

12.4 Data and Safety Monitoring Plan

All of the procedures outlined in the University of Wisconsin Chemoprevention Consortium Phase I & II Clinical Trials of Cancer Chemoprevention Agents Data and Safety Monitoring Plan version 2: 01/19/2013 (DCP Approved 02/26/2013) will be followed in this protocol. The UW Chemoprevention Consortium Data and Safety Monitoring Committee will meet approximately every 6 months to review all data from ongoing consortium studies. In open session (may be attended by any member of the Consortium study teams in addition to the Consortium statistician), issues relating to the general conduct and progress of the study will be discussed (e.g. accrual, quality control, compliance with protocol, currency of follow-up, comparability of groups on baseline factors etc.). In closed session DSMC members and the Consortium statistician only review protocol safety data and efficacy endpoint, (if relevant). The data will be presented by coded treatment arm. The codes are accessible to the DSMC at any time if needed.

12.5 Sponsor or FDA Monitoring

The NCI, DCP (or their designee), pharmaceutical collaborator (or their designee), or FDA may monitor/audit various aspects of the study. These monitors will be given access to facilities, databases, supplies and records to review and verify data pertinent to the study.

12.6 Record Retention

Clinical records for all participants, including all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, *etc*.), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with Health Insurance Portability and Accountability Act (HIPAA), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) regulations and guidances, and NCI/DCP requirements, unless the standard at the PO is more stringent. The records for all studies performed under an IND will be maintained, at a minimum, for two years after the approval of a New Drug Application (NDA). For NCI/DCP, records will be retained for at least three years after the completion of the research. NCI will be notified prior to the planned destruction of any materials. The records should be accessible for inspection and copying by authorized persons of the Food and Drug Administration. If the study is done outside of the United States, applicable regulatory requirements for the specific country participating in the study also apply.

12.7 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

This section is not applicable.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a Phase IIA randomized, placebo-controlled, double-blind trial of modulation of intermediate endpoint biomarkers by PFE as POMx™in subjects undergoing AS for low grade, early stage prostate cancer for 12 months. Participants will be randomized to placebo or PFE as POMx™ given for 12 months in a 1:1 ratio stratified by tumor volume.

The primary endpoint for modulation of intermediate endpoint biomarkers will be the change in the plasma levels of IGF-1 by a quantitative assay (ELISA) from pre-study to post-treatment.

The secondary endpoints include compliance and toxicity over the study duration, plasma biomarkers such as IGFBP-3, IGF-1/IGFBP-3 ratio, total PSA (serum), tissue (normal, normal adjacent to tumor, and abnormal prostate) biomarkers such as PSA, IGF-1, IGFBP-3, apoptosis (CASPASE 3), Ki-67, IGF-1R, 80HdG, and AR. Also, the following PFE constituents/metabolites will be measured for evidence of accumulation (trough levels): ellagic acid, dimethyl ellagic acid, dimethyl ellagic acid glucuronide (DMEAG), urolithin A, urolithin A glucuronide, urolithin B and urolithin B glucuronide.

The primary analysis will be a comparison of change in IGF-1 plasma levels from pre-study to post-study, based on two-sample t-test with normalizing transformation if necessary or Wilcoxon rank-sum test.

13.2 Sample Size/Accrual Rate

The sample size for each group is based on comparing the change in IGF-1 levels between the PFE and placebo arms. According to ELISA assay analysis, this primary endpoint can be considered a continuous random variable. The sample size justification is thus based on a two-tailed two-sample t-test of the difference between the two groups at a significance level of 0.05. In order to detect an effect size of 1.10, i.e. the difference in the mean change between the two groups of 1.10 standard deviations, with power 0.80, or an effect size of 1.17 with power 0.85, the trial requires an effective sample size of 14 per group. Assuming a random dropout of up to 5%, 15 subjects per group will be enrolled for a total of 30 subjects for this exploratory study.

There will be six organizations participating in the study. With each PO randomizing one participant per month, a conservative estimate, the study will enroll the target accrual goal of 30 subjects within 6 months. Considering the usual delay due to start-up, it may take up to 18 months. Each randomized participant will be treated with study medication for one year. We will allow for a study duration of two-three years.

13.3 Randomization and Stratification

The randomization will be based on a permuted block of size 4 with stratification by tumor volume (≤ 2 positive cores and ≤ 10% of any biopsy core volume is adenocarcinoma vs. >2 positive cores or > 10% of any biopsy core volume is adenocarcinoma). The decision was made not to stratify by PO to avoid problems with sparse data. After random permutation of numbers from 1 to 4 in each block, incoming subjects in sequence will be randomized to treatment corresponding to the permuted numbers in sequence according to the following: placebo for odd number and PFE for even number, separately among subjects in the lower and higher tumor volume groups. This process will be repeated after every 4 subjects.

13.4 Primary Endpoint(s)

The primary endpoint of the study is the difference in plasma levels of Insulin-like Growth Factor (IGF)-1 from baseline to end of study (12 months) in subjects undergoing AS for early stage prostate cancer. For the primary comparison, the difference between the placebo group and the PFE group will be tested using a two-sample t-test with normalizing transformation if necessary or Wilcoxon rank-sum test.

13.5 Secondary Objectives

For the secondary objectives, we will compare compliance and toxicities for a once daily oral administration over a 12-month period of time between the PFE and placebo groups. We will compare the modulation of the following biomarkers with response to PFE versus placebo: plasma biomarkers, including IGF-1/IGFBP-3 ratio, total serum PSA and normal and abnormal prostate tissue biomarkers, including PSA, IGFBP-3, apoptosis (CASPASE 3), Ki-67, IGF-1R, 80HdG and androgen receptor. We will also compare PFE constituents/metabolites for evidence of accumulation (trough levels): ellagic acid, dimethyl ellagic acid, dimethyl ellagic acid glucuronide (DMEAG), urolithin A, urolithin A glucuronide, urolithin B and urolithin B glucuronide between the treatment groups. Serum testosterone levels will also be measured.

For secondary objectives, all measurements and changes in measurements of interest will be summarized by treatment arm (and, if applicable, by visit) with appropriate descriptive statistics. Compliance, in terms of the number of pills missed, will be summarized by treatment arm with descriptive statistics, and tested for imbalance using Wilcoxon rank-sum test. Patient toxicity throughout the study will be summarized in several ways; the presence or absence of any toxicities, worst CTCAE grade, and strongest investigator-defined relationship will all be examined and characterized by treatment arm, and analyzed appropriately (Wilcoxon rank-sum for ordinal data, Fisher's exact test for dichotomous data, and log rank test for time to event data). We will examine the differences between the groups for the change from baseline for serum biomarkers, tissue biomarkers, and PFE constituents/metabolites with the appropriate tests; for dichotomous data we will use Fisher's exact test, for ordinal data we will use Wilcoxon rank-sum test, and for continuous data, and a two-sample t-test with normalizing transformation if necessary or Wilcoxon rank-sum test.

We are also interested in the correlation of the markers and expression data with plasma IGF-1 and serum PSA doubling time. These will be tested with Pearson and Spearman correlation coefficients as appropriate; regression models will be developed to test if there is a significant relationship in the presence of treatment effect. Beyond the correlations with the primary endpoint, we are interested in exploratory analyses of the interplay various markers have with each other, and quantifying the individual contributions each make, along with baseline characteristics toward IGF-1 and PSA doubling time: we are interested in examining the complex pathways associated with the chemopreventive activities. In working toward the goal of obtaining an understanding of these relationships, we will explore the correlations and characterize the relationships among the plasma levels of the various biomarkers, the tissue biomarker measurements in normal and malignant tissue and the levels of genetic expression. Where possible, these analyses will be performed on location-matched pre- and post-treatment tumor and benign cores. When there is not a location match, we will select a post-treatment core from the nearest possible location in the prostate. In all cases, the post-treatment tumor core selected for match analysis will be of the same Gleason grade as the pre-treatment core. In addition to analyzing the expression of the selected biomarkers in pre- post-treatment matched tumor and benign cores, we will further characterize the expression of these markers across the prostate by analyzing all biopsy cores that contain cancer. Statistical techniques that may be used include, but are not limited to, Pearson and Spearman correlation analysis and multivariate regression techniques with possible transformation of the data if necessary.

13.6 Reporting and Exclusions

As the nature of this study is exploratory, intent-to-treat should not be used as a principal analysis criterion. Nevertheless, no subjects will be excluded from the analysis and reporting, except for obvious random dropouts and for those who never took the protocol treatment.

Compliance with the protocol treatment will be measured in the form of pill counts, but the information will not be used for the primary analysis. There will be no imputation of missing data for both the primary and the secondary endpoints.

13.7 Evaluation of Toxicity

All participants receiving any protocol treatment will be evaluated for toxicity from the time of their first dose of placebo or PFE up to the time of biopsy according to the NCI's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

13.8 Evaluation of Response

For the primary analysis comparing the change in the IGF-1/IGFBP-3 ratio from pre-study to post-study biopsies, the as-treated analysis will be used. All of the participants who met the eligibility criteria, with the exception of those who did not receive study agent, will be included in the main analysis. Random dropouts will be excluded.

13.9 Interim Analysis

Interim analysis will be performed at a regular schedule to document study progress and to review safety data. This will be performed by an unblinded statistician who is not connected with the day-to-day operation of the study; the regular study staff will not be unblinded. There is no plan for interim analysis for efficacy data. Results of interim analyses of safety data will be reported to the Consortium's data and safety monitoring board for review at approximately six month intervals. They will be in charge of reviewing safety information, including adverse events, serious adverse events, and death data, and making a judgment as to the advisability of continuation. There will be no hard and fast criteria set for the safety analysis.

13.10 Ancillary Studies

No ancillary studies are planned.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Form FDA 1572

Prior to initiating this study, the Protocol Lead Investigator at the Lead and Participating Organization(s) will provide a signed Form FDA 1572 stating that the study will be conducted in compliance with regulations for clinical investigations. All investigators at the organization that will participate in the protocol will be listed on the Form in addition to all personnel directly involved in the performance of procedures required by the protocol and the collection of data.

14.2 Other Required Documents (each organization participating in this protocol, including the Lead Organization, must submit the following before their site can be opened to accrual)

14.2.1 Signed and dated current (within two years) CV or biosketch for all staff listed on the Form FDA 1572 and Delegation of Tasks Form.

14.2.2 Current medical licenses for all study personnel listed on Form FDA 1572 and the Delegation of Tasks Form whose position requires they hold a current medical license (ex. physician, dentist, nurse, pharmacist).

14.2.3 Lab certification (*e.g.*, CLIA, CAP) and lab normal ranges for all labs listed on Form FDA 1572.

14.2.4 Documentation of training in “Protection of Human Research Subjects” for all study personnel listed on the FDA Form 1572 and Delegation of Tasks Form.

14.2.5 Documentation of Federalwide Assurance (FWA) number.

14.2.6 Signed Investigator’s Brochure/Package Insert acknowledgement form.

14.2.7 Delegation of Tasks Form signed by the Lead Investigator for each site and initialed by all study personnel listed on the form.

14.2.8 Signed and dated NCI, DCP Financial Disclosure Form for all study personnel listed on Form 1572.

14.2.9 IRB Membership list/letter.

14.3 Institutional Review Board Approval

Prior to initiating the study and receiving agent, the Investigators at the Lead Organization and the Participating Organization(s) will obtain written approval to conduct the study from the appropriate IRB. Should changes to the study become necessary, protocol amendments will be submitted to the DCP PIO according to DCP Amendment Guidelines. The DCP-approved amended protocol must be approved by the IRB prior to implementation

14.4 Informed Consent

All potential study participants will be given a copy of the IRB-approved Informed Consent to review. Study staff will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the Informed Consent document. The study agent(s) will not be released to a participant who has not signed the Informed Consent document. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

Participants will be provided the option to allow the use of the blood and urine samples collected at each study visit, and tissues obtained during prostate biopsies or prostate surgery for further research purposes. Statement of this option is included in the informed consent document.

Prior to study initiation, the informed consent document will be reviewed and approved by NCI, DCP, the Consortium Lead Organization, and the IRB at each Organization at which the protocol will be implemented. Any subsequent changes to the informed consent must be approved by NCI, DCP, the Consortium Lead Organization's IRB, and then submitted to each organization's IRB for approval prior to initiation.

14.5 Submission of Regulatory Documents

All regulatory documents will be collected by the CLO and reviewed for completeness and accuracy. Once the CLO has received complete and accurate documents from a participating organization, they will forward the regulatory documents to the DCP Regulatory Contractor:

<u>Paper Document/CD-ROM Submissions:</u>
Manager, Regulatory Affairs
CCS Associates

1923 Landings Drive
Mountain View, CA 94043
Phone: 650-691-4400
Fax: 650-691-4410

E-mail Submissions: regulatory@ccsainc.com

Regulatory documents that do not require an original signature may be sent electronically to the CLO for review. The CLO will forward the documents electronically to the DCP Regulatory Contractor.

14.6 Other

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

15. FINANCING, EXPENSES, AND/OR INSURANCE

The following procedures/tests are considered standard of care. The associated fees will be billed to the participant or his insurer:

- The clinical total serum PSA tests performed at the baseline, Week 13, Week 26, Week 39 and Week 52 or end of study therapy visits.
- The Baseline, Week 26, and Week 52 clinic visits with physical examination by a study doctor.
- The pre-study biopsy and the Week 52 (or end of study therapy) biopsy or prostate surgery.

The following costs will be paid for by the study contract. These are not billed to the participant or his insurer:

- The study agent/placebo
- The Week 13 and Week 39 study visits
- Clinical safety labs
- Blood draws for research purposes

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APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B
Informed Consent Form Template

Site Name

Research Subject Information and Consent Form

Study Title: **UWI2013-00-01: A Phase II Exploratory, Randomized, Placebo-controlled, Trial of Pomegranate Fruit Extract/POMx™ in Subjects with Clinically Localized Prostate Cancer Undergoing Active Surveillance**

Study Investigator: Name

Invitation/Summary

This is a clinical trial, which is a type of research study. Your doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part in the research. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

Why is this study being done?

We are looking for ways to prevent prostate cancer in the future. This study involves taking a substance found in pomegranates, called Pomegranate Fruit Extract (PFE)/POMx™. We hope to learn more about what effects, good and/or bad this medication may have on the body, and what effects it may have in preventing prostate cancer. In this study, we want to find out if there is a difference in the level of PFE found in the blood, urine and prostate tissue between people taking a placebo ("sugar pill") versus those taking POMx™.

You are eligible to take part in this research study because you have been diagnosed with prostate cancer and have decided to choose observation as your treatment option.

How many people will take part in this study?

Thirty people will take part in this study. About 8-12 people will take part in this study at the University of Wisconsin and about 18-22 people will take part at other sites across the country.

What will happen if I take part in this research study?

In this study we will compare the effects of POMx™ with the effects of a placebo. A placebo is sometimes called a "sugar pill". The placebo looks like POMx™ but has no active ingredients. If you take part in this study, you will be randomly assigned (by chance, like flipping a coin) to take either POMx™ or the placebo. No one, including you, your doctor, and the study staff, will

know if you are taking POMx™ or the placebo. However, if we need to know what someone is taking, we can find out right away.

Before you begin the study…

You will need to have some exams and tests at the *Clinic Name* to find out if you can be in the study.

- Blood samples will be taken with a needle from a vein in your arm. About three tablespoons of blood will be taken.
    - Some of this blood will be used to find out if you are healthy enough to be in the study; it will be used to look at the health of various organs in your body
    - Some of this blood will be used for research purposes, so we can later compare how much PFE is in your system after taking the study medication
    - A Prostate-Specific Antigen (PSA) test will be done. A PSA test is a blood test commonly used in men with prostate cancer to see if the cancer is responding to treatment.
- Urine will be collected for research purposes, so we can later compare how much PFE is in your system after taking the study medication.
    - A doctor or nurse will ask you questions about your medical history and health, ask you about any medications you are taking, and measure your height, weight, blood pressure, pulse and temperature.
    - A doctor will do a physical exam.
    - The doctor will review previous biopsy results to see if you are eligible to be in the study.

If the results of your blood tests, physical exam and review of previous biopsy results show that you are eligible, and you agree to take part in the study, you will then be assigned to take either POMx™ or a placebo every morning, by mouth, for 52 weeks (that is, about one year). You will take one capsule every morning.

Along with the study capsule, you will be given a calendar. We ask that you use this calendar to write down what time you take your study capsule each morning and to write down any side effects or health changes you might notice. You can use this calendar to let us know if you missed taking any capsules or if some of the capsules were lost. We ask you to return this calendar and any unused medication and the study medication bottles (even if they are empty) when you come back to the clinic at your next visit.

During the study …

After taking the medication for 13 weeks (about three months), you will return to *Clinic Name.* At this visit, the study nurse will take your vital signs (pulse, heart rate and temperature) and record your weight. You will be asked about any changes in your medication, and any side effects that you may have had. Your diary will be reviewed to see if you have been taking the

medication correctly. You will again have about 3 tablespoons of blood taken from a vein in your arm. Some of the blood will be used to see how the medication is affecting your organs, some is for research purposes, and some will be used to do a PSA test. Urine will be collected and used for research purposes (to see how much PFE is in your system). You will be given a new bottle of medication and a new diary. If there are any signs or symptoms concerning for worsening cancer, you will be referred to your doctor.

After taking the medication for 26 weeks (about six months), you will return to *Clinic Name.* At this visit, the doctor will perform a physical exam, to make sure that the prostate cancer is not getting worse. Your vital signs (pulse, heart rate and temperature) will be recorded, as will your weight. You will be asked about any changes in your medication, and any side effects that you may have had. Your diary will be reviewed to see if you have been taking the medication correctly. You will again have about 3 tablespoons of blood taken from a vein in your arm. Some of the blood will be used to see how the medication is affecting your organs, some is for research purposes, and some will be used to do a PSA test. Urine will be collected and used for research purposes (to see how much PFE is in your system). You will be given a new bottle of medication and a new diary. If there are any signs or symptoms concerning for worsening cancer, you will be referred to your doctor.

After taking the medication for 39 weeks (about nine months), you will return to *Clinic Name.* At this visit, the study nurse will take your vital signs (pulse, heart rate and temperature) and record your weight. You will be asked about any changes in your medication, and any side effects that you may have had. Your diary will be reviewed to see if you have been taking the medication correctly. You will again have about 3 tablespoons of blood taken from a vein in your arm, and urine will be collected. Some of the blood will be used to see how the medication is affecting your organs, some is for research purposes, and some will be used to do a PSA test. The urine will also be used to see how much PFE is in your system. You will be given a new bottle of medication and a new diary. If there are any signs or symptoms concerning for worsening cancer, you will be referred to your doctor.

At the end of the study….

You will continue to take the medication until the last day of the study, that is, for 52 weeks (about twelve months). On the last day of the study, you will return to *Clinic Name.* At this visit, the doctor will perform a physical exam, to make sure that the prostate cancer is not getting worse. Your vital signs (pulse, heart rate and temperature) will be recorded, as will your weight. You will be asked about any changes in your medication, and any side effects that you may have had. Your diary will be reviewed to see if you have been taking the medication correctly. You will again have about 3 tablespoons of blood taken from a vein in your arm, and urine will be collected. Some of the blood will be used to see how the medication is affecting your organs, some is for research purposes and some will be used to do a PSA test. The urine will also be used to see how much PFE is in your system.

At this visit, your doctor will also perform a yearly prostate biopsy. This is considered standard of care, and is not part of the study. However, we will collect any left-over prostate tissue to see

if taking POMx™ or placebo has affected the prostate tissue, and how the prostate tissue has been affected.

Study Calendar

The study calendar below shows what will happen during the study.

Visit	*What you do*
Clinic Visit 1	Read and sign the study consent form. Have blood drawn and a PSA test. Answer questions about your medical history, current health and medications. Have a physical exam done and height and weight, temperature, pulse and blood pressure measured. Random assignment to POMx™ or placebo
Clinic Visit 2 (13 Week Visit, or after about 3 months)	Return to clinic for blood tests, urine collection, and a PSA test. Have blood pressure, pulse, temperature and weight measured. Bring your study calendar, your study medication bottles and any medication that you did not use. Bring the empty medication bottle if you used all the medication. Tell the study staff about any medication changes you have had. Tell the study staff about any symptoms, side effects or health changes you have noticed.
Clinic Visit 3 (26 Week Visit, or after about 6 months)	Return to clinic for blood tests, urine collection, and a PSA test. Have blood pressure, pulse, temperature and weight measured. Doctor will perform physical exam Bring your study calendar, your study medication bottles and any medication that you did not use. Bring the empty medication bottle if you used all the medication. Tell the study staff about any medication changes you have had. Tell the study staff about any symptoms, side effects or health changes you have noticed.
Clinic Visit 4 (39 Week Visit, or after about 9 months)	Return to clinic for blood tests, urine collection, and a PSA test. Have blood pressure, pulse, temperature and weight measured. Bring your study calendar, your study medication bottles and any medication that you did not use. Bring the empty medication bottle if you used all the medication. Tell the study staff about any medication changes you have had. Tell the study staff about any symptoms, side effects or health changes you have noticed.
Clinic Visit 5 (52 Week Visit, or after about 12 months)	Return to clinic for blood tests, urine collection, and a PSA test. Have blood pressure, pulse, temperature and weight measured. Doctor will perform physical exam Bring your study calendar, your study medication bottles and any medication that you did not use. Bring the empty medication bottle if you used all the medication. Tell the study staff about any medication changes you have had. Tell the study staff about any symptoms, side effects or health changes you have noticed. Your doctor will perform the yearly prostate biopsy.

How long will I be in the study?

You will be in the study for about 12 months.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely. If you decide to stop taking the study drug, you may still participate in other parts of the study. You will be asked if we can still use your medical information, blood and prostate tissue. It is your choice whether you want us to use your information or blood and prostate tissue. If you decide that you do not want us to use your information or blood and prostate tissue, we will destroy all of your research records and samples.

The study doctor may stop you from taking part in this study at any time if he/she believes stopping is in your best interest; if you do not follow the study rules; if the study itself is stopped; or if it appears that the prostate cancer is worsening.

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

If you choose to take part in this study, there is a risk that you may:

- Lose time at work or home and spend more time in the clinic than usual attending study visits.
- There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

The POMx™ used in this study may affect how different parts of your body work, such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common side effects that we know about POMx™, some of which may be serious. There might be other side effects that we do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

RARE, SOME MAY BE SERIOUS In 100 people receiving POMx™, 3 or fewer may have:
• Diarrhea • Nausea or vomiting • Abdominal pain • Constipation • Stomach and intestinal problems (mild to moderate)

POSSIBLE, SOME MAY BE SERIOUS The frequency of some individual side effects has not yet been determined:
• Chest pain • Irregular heart beat • Heart failure • Respiratory infections

Because your doctors and you have chosen not to treat your prostate cancer at this time, it is possible that, over the course of this 12-month trial, taking POMx™ may lower your PSA blood levels without preventing the prostate cancer from worsening. This potential effect could alter or delay a decision by your doctor to recommend getting a repeat prostate biopsy prior to your scheduled end-of-study prostate biopsy and possibly delay your doctor recommending prostate cancer treatment while participating in this study.

Reproductive risks: You should not father a baby while on this study because it is not known how POMx™ can affect an unborn baby. It is important you understand that, if you can father a child, you need to use an effective method of birth control, or abstinence, if your sex partner is a woman who can become pregnant. Each of the following is considered to be an effective method of birth control:

- Partner's use of a combined oral contraceptive pill if used for more than 30 days
- Partner's use of an implanted hormone if in place for more than 30 days
- An implanted device such as an intrauterine device (IUD) used for the purpose of contraception
- Vasectomy
- 2 barrier methods used together
    - partner's use of a cervical cap + spermicidal foam
    - partner's use of a diaphragm + spermicidal foam
    - condom + spermicidal foam

Effects of other drugs you may be taking: It is important to tell the doctor or study staff if you are taking any prescription or over the counter drugs or herbal supplements. We will need this information to make sure that there is no interaction with the study agents.

Tests done for research only: During the study, blood and prostate tissue will be taken for research purposes only. We will use these samples of blood to test how much PFE is in the blood after taking study medication for about 12 months. At the end of this form, you will be asked if we could use any samples that are left over after this study is done for future research projects. This is optional.

At the end of the study, when the prostate biopsy is performed, we will take left-over prostate tissue to test how much PFE is in the prostate tissue, and how it has affected the prostate tissue.

Are there benefits to taking part in the study?

Taking part in this study is not expected to make your health better. While doctors hope that POMx™ will be useful in cancer prevention, there is no proof of this. We do know that the information from this study will help doctors learn more about POMx™ as an agent in cancer prevention. This information could help improve the public health.

What other choices do I have if I do not take part in this study?

If you do not take part in this study, your choice is to proceed with observation without participating in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Personnel from the University of Wisconsin Comprehensive Cancer Center in charge of quality assurance.
- The Institutional Review Board (IRB) – a group of people who review the research with the goal of protecting the people who take part in the study.
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people.
- The National Cancer Institute will obtain information for this clinical trial under data collection authority Title 42 U.S.C. 285.Contractors hired by the government to review study files.
- Data will be stored on computer files at the University of Wisconsin and the National Cancer Institute's statistical center.

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

You may call the National Cancer Institute's Cancer Information Service at l 1-800-4-CANCER (1-800-422-6237). You may also visit the NCI web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask y our study doctor.

We will ask you if you would like other doctors informed of your participation in this research. If you do, we will inform them of your participation.

What are the costs of taking part in this study?

The NCI is supplying the study drug/placebo at no cost to you. Laboratory tests required for study participation will be done at no cost to you or your insurance company.

The clinic visits with the doctor, physical exams, PSA tests and the biopsies at the beginning and end of the study would be done whether or not you are in the study. The fees for the clinic visits with the doctor, physical exams and biopsies will be billed to you or your insurer. The visits with the study nurse will be paid for by the study. Although it is not expected, taking part in this study may lead to added costs to you or your insurance company. If you have any concerns about possible costs, please discuss them with your insurer.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

Will I be paid for taking part in this study?

You will receive *$X* after each study visit.

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

In the event that you are physically injured as a result of participating in this research, emergency care will be available. You will, however, be responsible for the charges for the emergency care. There is no commitment to provide any compensation for research-related injury. You should realize, however, that you have not released this institution from liability for negligence. Please

contact your study doctor or the study investigator, *Insert P.I. Name, at Insert PI phone number* if you are injured or for further information.

It is important that you tell your study doctor or the study investigator, Dr. Insert Name, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at Insert phone number if you are injured or wish further information.

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

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

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

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor or the study investigator about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor *(insert name of study doctor(s)* at *Insert Phone Number.*

For questions about your rights while taking part in this study contact *Insert IRB contact information or the IRB's designated Patient Relations/Rights Representative's contact information*.

AUTHORIZATION TO PARTICIPATE IN THE RESEARCH STUDY:

I have been given a copy of all pages of this form. I have read it or it has been read to me. I have had my questions answered. I agree to take part in this study.

Signature of Participant	**Date**
Signature of Person Obtaining Consent	Date

Please note: This section of the informed consent form is about additional blood, urine, and prostate tissue banking that is being done with people who are taking part in the main study. You may take part in the blood, urine and prostate tissue banking if you want to. You can still be a part of the main study even if you say "no" to taking part in any of the blood, urine and prostate tissue banking.

ADDENDUM FOR OPTIONAL BLOOD, URINE AND PROSTATE TISSUE BANKING
Invitation/Summary

You are going to have blood drawn, and urine and prostate tissue collected removed as part of this research study. Most of this blood, urine and prostate tissue will be used for research purposes (to see how much PFE is found in the blood and prostate).

We would like to keep (or "bank") some of the blood, urine and prostate tissue that is left over for future research. If you agree, this blood, urine and prostate tissue will be kept and may be used in research to learn more about cancer and other diseases, such as diabetes or heart disease. You do not have to agree to donate any leftover blood, urine and prostate tissue. You can still take part in the main study without donating leftover blood, urine and prostate tissue.

Why is this blood, urine and prostate tissue banking being done?

The National Cancer Institute (NCI) saves blood, urine and prostate tissue leftover from participants on many of their studies. They will use the blood, urine and prostate tissue in future research to study cancer and other diseases. The blood, urine and prostate tissue may also be used for genetic research.

The research that may be done with your blood, urine and prostate tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your blood, urine and prostate tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

What will happen if I take part in this blood, urine and prostate tissue banking?

Blood, urine and prostate tissue samples left over in the research laboratory after the primary study has been completed will be saved securely at the University of Wisconsin Carbone Comprehensive Cancer Center until NCI researchers develop new studies and wish to use human blood, urine and prostate tissue. NCI researchers and other researchers funded by the NCI will request the samples from the cancer center. If you choose not to participate, the left over blood, urine and prostate tissue will be destroyed.

Can I change my mind/What are my rights if I take part in this blood, urine and prostate tissue banking?

The choice to let us keep the left over blood, urine and prostate tissue for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your blood, urine and prostate tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your blood, urine and prostate tissue. Then any blood, urine and prostate tissue that remains will no longer be used for research, however, any data that has been obtained from samples that were already used will continue to be used. No matter what you decide, there will be no penalty to you and you will not lose any of your regular benefits. Refusing blood, urine and prostate tissue banking will not affect your medical care. You can still get your medical care from our institution.

Who can answer my questions about this blood, urine and prostate tissue banking?

For questions about the blood, urine and prostate tissue banking or to inform us that you no longer wish to participate, contact your study doctor or the study investigator, *Insert Name and Phone Number.*

Are there benefits to taking part in the blood, urine and prostate tissue banking?

You will receive no direct benefit from this blood and prostate tissue banking. The benefits of research using blood, urine and prostate tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

What risks can I expect from being in the blood, urine and prostate tissue banking?

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information accidentally will be given to someone else is very small.

In some cases, a new federal law call the Genetic Information Nondiscrimination Act (GINA) makes it illegal for health insurers and employers to discriminate against you based on your genetic information. But you should know that there are limitations to this law; for example, it does not apply to businesses that employ fewer than 15 people or life insurance, disability insurance or long term care insurance. An abnormal genetic test could result in denial or much higher rates for life insurance, disability insurance, or long term care insurance if your genetic test results were to become known.

Will commercial products be made from my sample?

Commercial products may be developed from the samples you provide for this research study. However, it is not expected that you will be able to share in the profits from commercialization of products developed from your blood, urine and prostate tissue.

Will my medical information be kept private?

Blood, urine and prostate tissue samples will be coded when submitted to the NCI. The University of Wisconsin investigator holds a link to the code, but the NCI does not have access to that link. The link will be kept on a password-protected computer in a locked office.

In the future, people who do research may need to know more about your health. While the University of Wisconsin Comprehensive Cancer Center may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood, urine and prostate tissue is used for genetic research (about diseases that are passed on in families). Even if your blood, urine and prostate tissue is used for this kind of research, the results will not be put in your health records. Gene research will be limited to genes available in the banked blood and prostate tissue samples. Research on these genes generally provides information about diseases that are specific to a type of tumor or cancer.

Your blood, urine and prostate tissue will be used only for research and will not be sold. The research done with your blood, urine and prostate tissue may help to develop new products in the future.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions about the blood and prostate tissue banking, please talk with the study doctor or study staff. If you have questions about the rights of research subjects please callInsert appropriate phone number.

No matter what you decide to do, it will not affect your care.

1. My blood, urine and prostate tissue may be kept for use in research to learn about, prevent, or treat cancer.

Yes No

2. My blood, urine and prostate tissue may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No

3. Someone may contact me in the future to ask me to take part in more research.

Yes No

AUTHORIZATION TO PARTICIPATE IN THE RESEARCH BLOOD, URINE AND PROSTATE TISSUE BANKING:

I have been given a copy of all pages of this form. I have read it or it has been read to me. I have had my questions answered. I agree to take part in this blood, urine and prostate tissue banking.

_____ _____

Signature of Participant **Date**

_____ _____

Signature of person obtaining consent **Date**