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ASTELLAS/MEDIVATION Inc. IIT
CLINICAL RESEARCH PROTOCOL
A Phase II Study of Enzalutamide Plus Dutasteride/Finasteride as First Line Treatment for Vulnerable Patients ≥ 65 Years with Systemic Prostate Cancer

Investigational Products:
Enzalutamide, Dutasteride or Finasteride

Sponsor:
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1.0 BACKGROUND

Prostate cancer (PCa) is the most common non-cutaneous malignancy among elderly men, with over 60% of all PCa cases diagnosed in men over 65 years of age.(1) **It is estimated that men 75 years and older contribute almost half (48%) of all PCa cases presenting with overt distant metastases and more than half (53%) of all PCa deaths.**(2) The estimated prevalence of PCa in men aged 75 years and older is currently over a million and expected to quadruple by 2030, given the long natural history of the disease and aging of the population.(1, 3) Despite the more frequent diagnosis of PCa at an early stage with the widespread use of PSA, many of the patients (1 in 3) without known distant metastases at presentation will subsequently develop systemic disease that would require further treatment.(4) All of these statistics portend an increasing number of older men, including those in the oldest age groups, with a diagnosis of systemic prostate cancer who are likely to experience significant complications from standard treatment. Although the elderly are disproportionately affected by cancer, little attention has been given to the specific management ofcancer in this population. This is primarily due to underrepresentation of older patients in clinical trials, which in turn has greatly hindered our understanding of the effects of cancer treatment in the elderly. (5, 6)

Systemic disease from prostate cancer includes biochemical recurrence (a rise in PSA after definitive treatment with no radiographic evidence of disease elsewhere) as well as overt metastatic disease confirmed by imaging. Once the disease is systemic, the goal of treatments is only palliative and physicians should take into account therapy-related side effects, which can adversely affect quality of life. For several decades the standard of care for the initial management of systemic PCa has been androgen deprivation therapy (ADT) with gonadotropin-releasing hormone (LHRH) agonist or antagonist. Side effects of ADT include but are not limited to weakness, osteoporosis, muscle wasting, metabolic syndrome, hot flashes, increased risk of diabetes, cardiovascular disease, depression, impotence, falls and cognitive/mood disorders.(7-10) While these untoward effects are tolerable in the young fit population, they can have significant adverse consequences in the elderly cancer patients with preexisting co-morbidities and functional impairment.(8, 10, 11) Once ADT is initiated for systemic disease, it is usually continued for life. Since older patients tend to be diagnosed with more indolent cancers and live with PCa as a chronic disease, they experience significant complications from ADT which become worse over time.(8) Some elderly patients may require hospitalizations for complications related to ADT with a few even requiring placement into nursing home facilities. Given the mechanism of ADT, it is postulated that these effects are a direct result of low testosterone. In many elderly men, their testosterone levels do not return to pre-ADT levels after ADT is discontinued. Therefore, even a limited trial of ADT may leave them at risk for long-lasting adverse effects from hypogonadism. **Approximately one-third of patients are deemed high risk for side effects and toxicities from ADT**.(8) **Despite often being asymptomatic from systemic cancer and in the absence of a clear survival benefit withearly**

initiation of ADT, older patients continue to be subjected to substantial side effects from ADT with a decline in quality of life, falls (due to muscle weakness) and exacerbation of underlying chronic diseases (such as heart disease); hence exploration of alternate options in this population is urgently needed.

1.1 Rationale for Peripheral Androgen Blockade

Conventional antiandrogens, such as bicalutamide, bind to androgen receptors and competitively inhibit their interaction with testosterone and dihydrotestosterone (DHT). These agents do not result in a decrease in circulating androgen levels as they do not interfere with the hypothalamic pituitary axis and thereby have less adverse effects compared to ADT. When compared with medical or surgical castration in two randomized trials involving men with advanced PCa, high dose bicalutamide was associated with improvement in symptoms, quality of life (QOL), and lower incidence of hot flashes. However, survival outcomes for metastatic PCa were inferior for patients on bicalutamide monotherapy compared to ADT in both of these trials.(12, 13). Subsequently a meta-analysis of eight trials comparing antiandrogen monotherapy with surgical or medical castration again found a trend towards shorter overall survival (OS) for patients receiving antiandrogens. Based on these data, NCCN recommends against first-line antiandrogen monotherapy for men with systemic disease.(14)

In an effort to increase upon the efficacy of antiandrogen therapy, 5-alpha reductase (5-AR) inhibitors have been evaluated in patients with systemic PCa. These agents block the intraprostatic conversion of testosterone to DHT, which is the more potent form of androgen that is primarily responsible for cell proliferation; thus exerting their action at a different site compared to non-steroidal antiandrogen which blocks the cytoplasmic DHT receptor. 5-AR inhibitors, when used as monotherapy or combination therapy, are well tolerated since serum testosterone levels are maintained during treatment. **The potential synergistic effect of 5-AR inhibitor with antiandrogens provided the rationale for using the combination for treatment of systemic PCa, which is referred to as peripheral androgen blockade (PAB)**.

Several phase 2 trials tested PAB in different settings, including biochemical relapse (in an era in which the concept of PSA doubling time did not exist) and metastatic disease. These studies reported that the majority of patients had a PSA response with good tolerance.(15-17) In one trial, after PSA nadir was achieved with bicalutamide, a second PSA nadir was reached with sequential addition of finasteride, suggesting an additive effect of this combination.(16) In all of these studies, even though the combination was efficacious and well tolerated, the median age was 66 and the patients were fit with very few other medical problems.

In the largest of these trials, CALGB 9782 (N= 99), the role of PAB (bicalutamide and finasteride) was evaluated in patients with biochemical relapse without radiographic

evidence of disease. All patients had undergone prior definitive local therapy, had PSA between 1ng/mL and 10ng/mL, and their PSA doubling time was not calculated prior to enrollment as there was little understanding of the clinical relevance of this concept when the trial was designed.(17) A ≥80% PSA decline was seen in 96% patients, and the median time to PSA progression was 85 months. The toxicities were reported as mild.

1.2 University of Rochester – Peripheral Androgen Blockade Data

Based on the aforementioned clinical data of PAB, we examined retrospective data on elderly PCa patients (≥65 years) who were treated with PAB in lieu of ADT in the geriatric oncology clinic at the University of Rochester. The majority of these patients were treated on this regimen instead of ADT because they were deemed not fit for ADT by their primary oncologists as a result of underlying health status issues (i.e., absolute or relative contraindications to ADT) and these patients had no alternative treatment options. A retrospective analysis was performed subsequently to describe the characteristics and clinical outcomes of 21 elderly patients treated with PAB. The majority of these patients was considered either vulnerable or frail by validated comprehensive geriatric assessment (CGA) and therefore, at a very high risk for adverse effects from standard ADT. Reasons for not receiving ADT included cognitive impairment, multiple falls, and heart disease.

In this retrospective study, prostate cancer patients with asymptomatic hormonal naive metastatic disease or biochemical recurrence with a short PSA doubling time (≤ 6 months) were included. The median age at the start of PAB was 86 years. PSA response was seen in all patients treated with this combination with a median PSA decline of 92% from baseline. This PSA response lasted for a median of 10.5 months. None of the patients reported any major adverse effects or required treatment interruption while on this combination. This data was presented at the 2013 GU ASCO in Orlando, Florida and received general interest from oncologists managing elderly PCa patients.(18) For the first time, these results provide evidence that PAB is not only feasible but also active and well tolerated in the vulnerable/frail older population. **Despite these results, there is still the need to establish a superior regimen with a longer progression-free survival in an attempt to delay or possibly avoid ADT as salvage therapy for these already vulnerable older men.**

1.3 Rationale for Enzalutamide and 5 Alpha reductase inhibitor

Although treatment with bicalutamide and finasteride demonstrated clinical efficacy with good tolerance in the elderly population, the median duration of PSA response was only 10.5 months. **While PAB delayed the time to ADT in fit patients thereby preserving their quality of life; PAB may be the only therapeutic option that many vulnerable or frail patients could tolerate**. Given the relatively brief duration of PSA response

with bicalutamide and finasteride, there is a large unmet need for more effective novel therapies for elderly patients with hormonal naïve systemic prostate cancer.

Enzalutamide, unlike conventional antiandrogens, targets multiple steps in the androgen receptor signaling pathway. It inhibits nuclear translocation of the androgen receptor, binding of androgen to the response elements, and coactivator recruitment. Enzalutamide has greater affinity for the androgen receptor with greater antitumor efficacy in xenograft models as compared to conventional antiandrogens.(19, 20) Based on these data, a randomized phase 3 study (AFFIRM) was conducted to evaluate enzalutamide in patients with castrate resistant metastatic prostate cancer who had progressed after chemotherapy. This study demonstrated a five month improvement in median overall survival in patients receiving enzalutamide compared to placebo.(21) The median age of patients receiving enzalutamide was 69 years with 24.9% of patients aged ≥75 years. Tolerance in all patients was reasonable.

Sternberg et al. presented the outcomes of elderly patients (>75 years) of this study at the GU ASCO 2013 annual meeting and concluded that enzalutamide was well tolerated with the most common adverse events being nausea and fatigue. However, this analysis did not describe underlying health status including falls, cognitive issues, and other complications which are present in many patients in this age range. (22) Recently, the preliminary results of a phase 2 trial that evaluated enzalutamide monotherapy in hormone naïve patients with systemic PCa were presented.(23) The median age in this study was 73 and **all patients had ECOG performance status of 0.** However, underlying health status of these patients again was not described. At 25 weeks of follow-up, the majority of patients had PSA responses- median PSA decrease of 99.6% with good tolerance. The median time to disease progression had not been reached yet.

In the present study, either dutasteride or finasteride will be used as the 5-AR inhibitor for the PAB regimen. Dutasteride due to its higher potency in suppressing conversion of testosterone to DHT (>90%) compared to that of finasteride (~70%) will be preferentially considered. Dutasteride has a dual-enzyme inhibition mechanism that inhibits both type 1 and type 2 5-AR. Additionally, dutasteride has a much longer half-life when compared with finasteride (5 weeks vs. 5-6 hours). Previous studies have shown that dutasteride is well tolerated in older patients when used for chemoprevention.(24) The role of enzalutamide in combination with dutasteride and an LHRH agonist in the neoadjuvant setting is being evaluated in a phase 2 trial (NCT01547299), which recently completed accrual.

In the event, a trial eligible patients is unable to obtain dutasteride due to any reason including financial constraints, finasteride will be used as the 5-AR inhibitor for the PAB regimen. Finasteride is also well tolerated in older patients when used for chemoprevention.(25) Several phase 2 trials also noted the finasteride in combination

with first generation non-steroidal antiandrogens is well tolerated and efficacious in the elderly.(17)

As the population is aging, we will continue to witness a rapid increase in the number of elderly PCa patients with systemic disease for whom the ideal treatment is not yet known. With the changing demographics, many clinical investigators are designing and conducting trials specifically to determine the best treatment for the elderly. The Food and Drug Administration (FDA) also recommends that drugs be studied in all age groups for which they will have significant utility, including the elderly, so that the true risks and benefits can be assessed. **The purpose of adding a 5-AR inhibitor to an already potent antiandrogen is to maximize efficacy and prolong the duration of response, thereby delaying the time to progression**. In the vulnerable and frail population, this combination may offer an opportunity for prolonged disease control as many of them may not be candidates for second line treatment after disease progression.

1.4 Utility of Comprehensive Geriatric assessment

Cancer is primarily a disease of the elderly, with individuals aged 65 years and over accounting for over 60% of all new cancers. Furthermore, 70% of cancer mortality occur in patients over the age of 65.(26) However there are only few evidence based guidelines to help manage these patients. Chronologic age and common assessment instruments in oncology (e.g., Karnofsky performance status) do not address critical geriatric domains that predict morbidity and mortality in the older patient (e.g., functional status, comorbidity, social support). A prospective study of 500 older adults with cancer demonstrated that traditional oncology functional assessment tools, including Karnofsky performance score, could not identify older adults at risk for chemotherapy toxicity. However, a predictive model that includes geriatric assessment questions could identify such individuals.(27) Despite the fact that the majority of cancer patients are in the older age groups, most oncologists have received little to no training in the care of older patients.(28) As a result, common problems facing an aging population of cancer patients may go unrecognized and have serious consequences.(29)

CGA includes a compilation of reliable and validated tools to assess geriatric domains such as comorbidity, functional status, physical performance, cognitive status, psychological status, nutritional status, medication review, and social support.(30-51) CGA can detect unsuspected conditions that may affect cancer treatment in more than 50% of older patients.(52) CGA can help identify the vulnerable older individual who is likely to benefit from and tolerate standard therapy, as well as the seemingly fit older individual who is apt to experience undue side effects and requires a modified treatment plan. Repetto et al. demonstrated that CGA added information to standard oncology performance measures, such as Karnofsky performance score, which is a one item measure of function that was validated in younger patients.(53, 54) CGA has great

potential to identify areas of vulnerability and interventions that could help improve outcomes (e.g., reducing chemotherapy toxicity) in older cancer patients.(50, 55, 56) The initial study of this tool illustrated feasibility as demonstrated by a short mean time to completion of 27 minutes. Furthermore, 90% of patients were satisfied with the questionnaire length and 78% were able to complete the self-administered portion on their own.(57) CGA was also found to be feasible for use by the Cancer and Aging Leukemia Group-B (CALGB 360401).(55) Previous clinical studies, including the FOCUS 2 trial, have demonstrated that incorporating CGA can help better assess toxicities and aid with management decisions.(58) .

A comprehensive health assessment similar to the CGA was utilized in the study. Eligibility for the study was similar to that used in this study; patients were eligible if their physicians deemed them not fit for standard therapy. Treatments were administered with an upfront dose reduction and escalated if the patient tolerated the first treatments.(58). Based on these data, the current study will incorporate CGA to assess the safety profile and toxicities of the proposed PAB regimen in this older, more vulnerable study population.

2.0 OBJECTIVES

2.1 Primary Objective

- To determine the effect of the enzalutamide and 5-AR inhibitor on the time to PSA progression in patients aged 65 or older receiving this combination as first line treatment for systemic prostate cancer

2.2 Secondary Objectives

- To evaluate the absolute PSA nadir as a result of combination treatment
- To determine the time to PSA nadir from the start oftreatment
- To determine the safety and toxicities of the study drug combination

2.3 Tertiary Objectives (Exploratory)

- To determine if the study drug combination affects bone health
- To determine if the study drug combination affects comprehensive geriatric assessment domains
- To determine if the study drug combination affects quality of life

3.0 DRUG INFORMATION

Investigator's Brochures will be provided upon request (Appendix D).

3.1 Enzalutamide

3.1.1 Description

General: Enzalutamide is an androgen receptor inhibitor. The chemical name is 4-{3-[4-cyano-3-(trifluoromethyl) phenyl]-5, 5- dimethyl-4-oxo-2-ulfanylideneimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide. Enzalutamide is a white crystalline non-hygroscopic solid. It is practically insoluble in water.

Molecular weight is 464.44
Molecular formula is C21H16F4N4O2S

3.1.2 Pharmacology

Mechanism of action: Enzalutamide is an androgen receptor inhibitor that acts on multiple steps in the androgen receptor signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors and inhibit androgen receptor nuclear translocation and interaction with DNA. A major metabolite, N-desmethyl enzalutamide, exhibited similar *in vitro* activity to enzalutamide. Enzalutamide decreased proliferation and induced cell death of prostate cancer cells *in vitro* and decreased tumor volume in a mouse prostate cancer xenograft model.

Pharmacokinetics: Data indicate the pharmacokinetics of enzalutamide and its major active metabolite (N-desmethyl enzalutamide) evaluated in patients with metastatic castration-resistant prostate cancer and healthy male volunteers note a linear two-compartment model with first-order absorption. The median time to reach maximum plasma enzalutamide concentrations (Cmax) is 1 hour (range 0.5 to 3 hours).With the daily dosing regimen, enzalutamide steady state is achieved by Day 28, and enzalutamide accumulates approximately 8.3-fold relative to a single dose. Daily fluctuations in enzalutamide plasma concentrations are low (mean peak-to-trough ratio of 1.25). At steady state, enzalutamide showed approximately dose proportional pharmacokinetics over the daily dose range of 30 to 360 mg. A single 160 mg oral dose was administered to healthy volunteers with a high-fat meal or in the fasted condition. A high-fat meal did not alter the AUC to enzalutamide or N-desmethyl enzalutamide.

Enzalutamide is 97% to 98% bound to plasma proteins, primarily albumin. N-desmethyl enzalutamide (active metabolite) is also 95% bound to plasma proteins. Following single

oral administration of 14C-enzalutamide, its metabolites were detected up to 77 days post dose. *In vitro*, human CYP2C8 and CYP3A4 are responsible for the metabolism of enzalutamide. Based on *in vivo* and *in vitro* data, CYP2C8 is primarily responsible for the formation of the active metabolite (N-desmethyl enzalutamide). Enzalutamide is primarily eliminated by hepatic metabolism. The mean terminal half-life (t1/2) for enzalutamide in patients after a single oral dose is 5.8 days (range 2.8 to 10.2days).

3.1.3 Toxicology

Animal studies

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of enzalutamide. Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the *in vitro* mouse lymphoma thymidine kinase (Tk) gene mutation assay or the *in vivo* mouse micronucleus assay. Based on nonclinical findings in repeat-dose toxicology studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at ≥ 30 mg/kg/day (equal to the human exposure based on AUC). In 4 and 13-week studies in dogs, hypospermatogenesis and atrophy of the prostate and epididymitis were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

3.1.4 Adverse Events

Adverse Events with Possible Relationship to Enzalutamide		
Likely (>20%)	Less Likely (≤20%)	Rare but Serious (<3%)
Asthenic conditions	Peripheral edema	Seizure
Back pain	Musculoskeletal pain	PRES
Arthralgia	Muscular weakness	
Diarrhea	Hypertension	
Hot flush	Headache	
	Dizziness	
	Paraesthesia	
	Spinal cord compression and cauda equina syndrome	
	Upper respiratory tract infections	
	Insomnia	
	Neutropenia	
	ALT elevation	
	Elevation in bilirubin	
	Hematuria	

PRES:posterior reversible encephalopathy syndrome

3.1.5 Pregnancy

Enzalutamide can cause fetal harm when administered to a pregnant woman based on its mechanism of action and is contraindicated in women who are or may become pregnant. Sexually active men with partners in child bearing age group are recommended contraceptive use when taking this medication.

3.2 Dutasteride

3.2.1 Description:

General: Dutasteride is chemically designated as (5α, 17β)-N-{2,5 bis(trifluoromethyl)phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide. Dutasteride is a white to pale yellow powder with a melting point of 242° to 250°C. It is soluble in ethanol (44 mg/mL), methanol (64 mg/mL), and polyethylene glycol 400 (3 mg/mL), but it is insoluble in water.

Molecular weight of 528.5
Molecular formula: $C_{27}H_{30}F_6N_2O_2$

3.2.2 Pharmacology

Mechanism of action: Dutasteride inhibits the conversion of testosterone to DHT. DHT is the androgen primarily responsible for the initial development and subsequent enlargement of the prostate gland. Testosterone is converted to DHT by the enzyme 5-AR, which exists as 2 isoforms, type 1 and type 2. The type 2 isoenzyme is primarily active in the reproductive tissues, while the type 1 isoenzyme is also responsible for testosterone conversion in the skin and liver. Dutasteride is a competitive and specific inhibitor of both type 1 and type 2, 5-AR isoenzymes, with which it forms a stable enzyme complex. Dissociation from this complex has been evaluated under in vitro and in vivo conditions and is extremely slow. Dutasteride does not bind to the human androgen receptor.

Pharmacokinetics: Following administration of a single 0.5-mg dose of a soft gelatin capsule, time to peak serum concentrations (Tmax) of dutasteride occurs within 2 to 3 hours. Absolute bioavailability is approximately 60% (range: 40% to 94%). When the drug is administered with food, the maximum serum concentrations were reduced by 10% to 15%. This reduction is of no clinical significance. Pharmacokinetic data following single and repeat oral doses show that dutasteride has a large volume of distribution (300 to 500 L). Dutasteride is highly bound to plasma albumin (99.0%) and alpha-1 acid glycoprotein (96.6%). The maximum effect of daily doses of dutasteride on the reduction of DHT is dose dependent and is observed within 1 to 2 weeks.

In vitro studies showed that dutasteride is metabolized by the CYP3A4 and CYP3A5 isoenzymes. Both of these isoenzymes produced the 4′-hydroxydutasteride, 6-hydroxydutasteride, and the 6, 4′-dihydroxydutasteride metabolites. In addition, the 15-hydroxydutasteride metabolite was formed by CYP3A4. In human serum following dosing to steady state, unchanged dutasteride, 3 major metabolites (4′-hydroxydutasteride, 1,2-dihydrodutasteride, and 6-hydroxydutasteride), and 2 minor metabolites (6,4′-dihydroxydutasteride and 15-hydroxydutasteride), as assessed by mass spectrometric response, have been detected.

Dutasteride and its metabolites were excreted mainly in feces. As a percent of dose, there was approximately 5% unchanged dutasteride (~1% to ~15%) and 40% as dutasteride-related metabolites (~2% to ~90%). Only trace amounts of unchanged dutasteride were found in urine (<1%). Following daily dosing, dutasteride serum concentrations achieve 65% of steady-state concentration after 1 month and approximately 90% after 3 months. Due to the long half-life of dutasteride, serum concentrations remain detectable (greater than 0.1 ng/mL) for up to 4 to 6 months after discontinuation of treatment. The terminal elimination half-life of dutasteride is approximately 5 weeks at steady state.

3.2.3 Toxicology

Animal studies

A 2-year carcinogenicity study was conducted in B6C3F1 mice at doses of 3, 35, 250, and 500 mg/kg/day for males and 3, 35, and 250 mg/kg/day for females; an increased incidence of benign hepatocellular adenomas was noted at 250 mg/kg/day (290-fold the MRHD of a 0.5-mg daily dose) in female mice only. Two of the 3 major human metabolites have been detected in mice. The exposure to these metabolites in mice is either lower than in humans or is not known. Dutasteride was tested for genotoxicity in a bacterial mutagenesis assay (Ames test), a chromosomal aberration assay in CHO cells and a micronucleus assay in rats. The results did not indicate any genotoxic potential of the parent drug. Two major human metabolites were also negative in either the Ames test or an abbreviated Ames test.

Treatment of sexually mature male rats with dutasteride at 0.1-to 110-fold the MRHD (animal doses of 0.05, 10, 50, and 500 mg/kg/day for up to 31 weeks) resulted in dose- and time-dependent decreases in fertility; reduced cauda epididymal (absolute) 17 sperm counts but not sperm concentration (at 50 and 500 mg/kg/day); reduced weights of the epididymis, prostate, and seminal vesicles; and microscopic changes in the male reproductive organs. The fertility effects were reversed by recovery week 6 at all doses, and sperm counts were normal at the end of a 14-week recovery period.

3.2.4 Adverse Events

Adverse Events with Possible Relationship to Dutasteride		
Likely (>20%)	Less Likely (≤20%)	Rare but Serious <3%)
	Impotence	Angioedema
	Libido decreased	Cardiac failure,
	Ejaculation disorders	Depressed mood
	Gynecomastia (including breast tenderness, and breast enlargement)	Dizziness
		Localized hypersensitivity
		Pruritus, rash, skin reactions
		Urticaria
		TSH increased

3.2.5 Pregnancy

Pregnancy Category X. Dutasteride is contraindicated for use in women of childbearing potential and during pregnancy. Sexually active men with partners in child bearing age group are recommended contraceptive use when taking this medication.

3.3 Finasteride

3.3.1 Description:

General: Finasteride is 4-azaandrost-1-ene-17-carboxamide, N-(1,1-dimethylethyl)-3-oxo-,(5α,17β)-. Finasteride is a white crystalline powder with a melting point near 250°C. It is freely soluble in chloroform and in lower alcohol solvents, but is practically insoluble in water

Molecular weight of 372.55.
Molecular formula: C23H36N2O2

3.3.2 Pharmacology

Mechanism of action: Finasteride is a competitive and specific inhibitor of Type II 5α-reductase with which it slowly forms a stable enzyme complex. Turnover from this

complex is extremely slow (t½ ~ 30 days). This has been demonstrated both *in vivo* and *in vitro*. Type II 5α-reductase metabolizes testosterone to DHT in the prostate gland, liver and skin. DHT induces androgenic effects by binding to androgen receptors in the cell nuclei of these organs.

Pharmacokinetics: The mean bioavailability of finasteride 5-mg tablets was 63% (range 34-108%), based on the ratio of area under the curve (AUC) relative to an intravenous (IV) reference dose. Maximum finasteride plasma concentration averaged 37 ng/mL (range, 27-49 ng/mL) and was reached 1-2 hours postdose. Bioavailability of finasteride was not affected by food. Mean steady-state volume of distribution was 76 liters (range, 44-96 liters). Approximately 90% of circulating finasteride is bound to plasma proteins. There is a slow accumulation phase for finasteride after multiple dosing.

Finasteride is extensively metabolized in the liver, primarily via the cytochrome P450 3A4 enzyme subfamily. Two metabolites, the t-butyl side chain monohydroxylated and monocarboxylic acid 10 metabolites, have been identified that possess no more than 20% of the 5α-reductase inhibitory activity of finasteride. In healthy young subjects (n=15), mean plasma clearance of finasteride was 165 mL/min (range, 70-279 mL/min) and mean elimination half-life in plasma was 6 hours (range, 3-16 hours). Following an oral dose of 14C-finasteride in man (n=6), a mean of 39% (range, 32-46%) of the dose was excreted in the urine in the form of metabolites; 57% (range, 51-64%) was excreted in the feces.

The mean terminal half-life of finasteride in subjects ≥70 years of age was approximately 8 hours (range, 6-15 hours; n=12), compared with 6 hours (range, 4-12 hours; n=12) in subjects 45-60 years of age. As a result, mean AUC(0-24 hr) after 17 days of dosing was 15% higher in subjects ≥70 years of age than in subjects 45-60 years of age (p=0.02).

3.3.3 Toxicology

Animal studies

No evidence of a tumorigenic effect was observed in a 24-month study in Sprague-Dawley rats receiving doses of finasteride up to 160 mg/kg/day in males and 320 mg/kg/day in females. These doses produced respective systemic exposure in rats of 111 and 274 times those observed in man receiving the recommended human dose of 5 mg/day. All exposure calculations were based on calculated AUC(0-24 hr) for animals and mean AUC(0-24 hr) for man (0.4 µg•hr/mL).

No evidence of mutagenicity was observed in an *in vitro* bacterial mutagenesis assay, a mammalian cell mutagenesis assay, or in an *in vitro* alkaline elution assay. In an *in vitro*

chromosome aberration assay, using Chinese hamster ovary cells, there was a slight increase in chromosome aberrations. These concentrations correspond to 4000-5000 times the peak plasma levels in man given a total dose of 5 mg. In an *in vivo* chromosome aberration assay in mice, no treatment-related increase in chromosome aberration was observed with finasteride at the maximum tolerated dose of 250 mg/kg/day (228 times the human exposure) as determined in the carcinogenicity studies. In sexually mature male rabbits treated with finasteride at 543 times the human exposure (80 mg/kg/day) for up to 12 weeks, no effect on fertility, sperm count, or ejaculate volume was seen.

3.3.4 Adverse Events

Adverse Events with Possible Relationship to Fuinasteride		
Likely (>20%)	Less Likely (≤20%)	Rare but Serious <3%)
	Orthostatic hypotension	Angioedema
	Dizziness	Cardiac failure,
	Ejaculation disorders	Depressed mood
	Decreased libido	Altered mental status
	Gynecomastia (including breast tenderness, and breast enlargement)	Localized hypersensitivity
		Pruritus, rash, skin reactions
		Urticaria

3.3.5 Pregnancy

Pregnancy Category X. Finasteride is contraindicated for use in women of childbearing potential and during pregnancy. Sexually active men with partners in child bearing age group are recommended contraceptive use when taking this medication.

3.4 Blood Donation

Men being treated with study drugs should not donate blood until at least 6 months have passed following their last dose. The purpose of this deferred period is to prevent administration of study drug to a pregnant female transfusion recipient, for which this drug is not safe.

3.5 Selection of Doses Used in the Study

The recommended dose of enzalutamide is 160 mg/day based on the data from several trials. The durability of disease suppression was similar between the 150 mg/day and the 240 mg/day dose cohorts in post-chemotherapy patients in the Phase 1-2 study.(59) Given this comparable efficacy, with dose-dependent increases of Grade 3 fatigue (0% at 150 mg/day vs. 9% at 240 mg/day), and reports of seizure at high doses (one witnessed event at 360 mg/day and another at 600 mg/day), a dose of 160 mg/day was believed to have the optimal risk/benefit profile and was selected for investigation in a phase 3 randomized double blind trial (AFFIRM). (21) The results of this trial indicated efficacy with good tolerance, therefore based on all the above data, we plan to use the recommended dose of enzalutamide 160 mg/day for the current trial.

The recommended dose of dutasteride is 0.5 mg/day. The current dose is selected based upon the results of a placebo controlled phase III study in patients with benign prostate hypertrophy in which dutasteride 0.5 mg administered once daily.(60) This dose was well tolerated by patients in the study, including those in the older population.

The recommended dose of finasteride is 5mg/day. The current dose is selected based upon the results of placebo controlled study(PLESS) in which finasteride 5mg was administered once daily.(61) Similar dosage was also evaluated in combination with first generation antiandrogens and was noted to be well tolerated and efficacious.(16)

4.0 STAGING CRITERIA

The AJCC Seventh Edition, 2010 will be used in evaluating patients by the treating investigators for staging purposes.

5.0 SELECTIONOF STUDY POPULATION

5.1 Eligibility Criteria

The study population will include men aged 65 years and older with hormonally naïve, progressive, systemic PCa (either biochemical recurrence with a PSA doubling time of $\leq$9 months or hormonal naive metastatic disease confirmed by imaging) who are not candidates for treatment with ADT because the anticipated risk of ADT may outweigh the potential benefits **as determined by the treating physician**. The treating physician will determine whether the patient would have a high risk of side effects from standard ADT. **This eligibility criteria has been incorporated previously in other clinical trials focused on cancer treatment in the elderly, such as the FOCUS-2 trial** which used this eligibility to enroll older patients with advanced colorectal cancer for dose-modified chemotherapy.(58) Physicians in the FOCUS2 trial deemed the patient "not fit" for

standard of care therapy as part of the eligibility criteria for enrollment. In the current trial case report forms (CRF) will be record details as to why each patient was considered for the trial and not ADT.
Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration.

5.2 Inclusion Criteria

Patients must meet the following inclusion criteria:

5.2.1 Disease Related Criteria

1. Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features.
2. Patients with systemic PCa as defined by either a) hormonal naïve metastatic PCa with radiographic evidence of visceral or osseous metastasis or b) biochemical recurrence PCa that fulfills **all** of the following criteria:
   - A minimum of three rising PSA levels with an interval of ≥ 1week between each test.
   - The PSA value at the screening visit should be ≥ 2 ng/ml.
   - PSA doubling time ≤ 9 months.
3. Patients should be 65 years or older.
4. Patients who are deemed "not fit" by CGA or at high risk for side effects from ADT as determined by the treating physician. **A case report form will be used to document the specifics of why each eligible patient is not considered an ideal candidate for ADT.**
5. Serum testosterone level > 1.7 nmol/L (50 ng/dL) at the screening visit (non-castrate)

5.2.2 Prior Therapy Related Criteria

6. Patients could have received hormonal therapy, (ADT), as part of definitive treatment for previous localized PCa. However, they should be off any hormonal therapy for greater than six months prior to entry to clinical trial.

5.2.3 Clinical Criteria

7. ECOG performance status of 0 to 2.
8. Able to swallow the study drug and comply with study requirements.

5.3 Exclusion Criteria

Patients must **NOT** meet any of the following exclusion criteria:

5.3.1 Disease Related Criteria

1. Severe concurrent disease or infection that, in the judgment of the investigator, would make the patient inappropriate for enrollment.
2. Known brain metastases. Brain imaging studies are not required for eligibility if the patient has no neurologic signs or symptoms suggestive of brain metastasis. However, if brain imaging studies are performed, they must be negative for disease.
3. Patient is receiving treatment for another active malignancy excluding localized cutaneous squamous or basal cell carcinoma.

5.3.2 Prior Therapy Related Criteria

4. Prior treatment for systemic prostate cancer with the exception of single agent first generation non-steroidal anti androgen(bicalutamide, flutamide and nilatumade), which they could have taken for up to 2 weeks prior to the start of investigational combination. A washout period is not required.
5. Prior treatment with enzalutamide
6. Treatment with ADT, , ketoconazole, abiraterone, 5-AR inhibitors (finasteride, dutasteride), estrogens, or chemotherapy in an adjuvant setting within 6 months of enrollment (Day 1 visit) or plans to initiate treatment with any of these treatments.
7. Treatment with therapeutic immunizations for prostate cancer (e.g., PROVENGE®) or plans to initiate treatment with any of these treatments during the study period.
8. Use of herbal products that may decrease PSA levels (e.g., saw palmetto) or systemic corticosteroids greater than the equivalent of 10 mg of prednisone/prednisolone per day within 4 weeks of enrollment (Day 1 visit) or plans to initiate treatment with any of these treatments during the study.
9. Radiation therapy within 3 weeks (if single fraction of radiotherapy within 2 weeks) and radioisotope therapy within 8 weeks of enrollment (Day 1 visit).
10. Participation in a previous clinical trial of an investigational agent that blocks androgen synthesis within six months.
11. Participation in a previous clinical trial of enzalutamide.
12. Use of an investigational agent within 4 weeks of enrollment (Day 1 visit) or plans to initiate treatment with an investigational agent during the study.
13. Concomitant use of strong or moderate CYP2C8 or CYP3A4 inhibitors or inducers for subjects receiving dutasteride as the 5ARI (see Appendix F)

5.3.3 Clinical/Laboratory criteria

14. History of seizure, including any febrile seizure, loss of consciousness, or transient ischemia attack within 12 months of enrollment (Day 1 visit), or any

condition that may pre-dispose to seizure (e.g., prior stroke, brain arteriovenous malformation, head trauma with loss of consciousness requiring hospitalization)

15. Clinically significant cardiovascular disease including:
    - Myocardial infarction within 6 months
    - Uncontrolled angina within 3 months
    - Congestive heart failure New York Heart Association (NYHA) class 3 or 4, or patients with history of congestive heart failure NYHA class 3 or 4 in the past, unless a screening echocardiogram or multi-gated acquisition scan (MUGA) performed within 3 months results in a left ventricular ejection fraction that is ≥ 45%
    - Hypotension (systolic blood pressure < 86 millimeters of mercury [mmHg] or bradycardia with a heart rate < 50 beats per minute;
    - Uncontrolled hypertension as indicated by a resting systolic blood pressure of 170 mmHg or diastolic blood pressure > 105 mmHg at the Screening or Study Day 1 visit;
16. Gastrointestinal disorder affecting absorption (e.g., gastrectomy, active peptic ulcer within last 3 months)
17. Major surgery within 4 weeks prior to enrollment (Day 1 visit)
18. Absolute neutrophil count < 1,500/µL, platelet count < 100,000/µL, and hemoglobin < 5.6 mmol/L (9 g/dL) at the Screening visit; (NOTE: patients may not have received any growth factors or blood transfusions within 7 days of the hematologic laboratory values obtained at the Screening visit)

5.4 Regulatory Criteria

Patients or their legally authorized representative must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines. Voluntary written informed consent must be obtained before registration or performance of any study-related procedure not part of normal medical care, with the understanding that the patient may withdraw consent at any time without prejudice to future medical care.

6.0 OVERALL STUDY DESIGN AND PLAN

This study is a phase 2 open label efficacy and safety clinical trial evaluating the combination of oral enzalutamide (160 mg/day) and a 5-ARI either dutasteride (0.5 mg/day) or finasteride (5mg/day)in patients with systemic PCa. The study will enroll patients at two sites: University of Rochester Medical Center and the clinical cancer

center at the Froedtert & Medical College of Wisconsin. Approximately 40 patients will be enrolled.

Patients will receive study treatment until disease progression is documented and confirmed as defined by 1) PSA rise **with or without** radiographic evidence of disease progression or 2) the occurrence of a skeletal-related event. The occurrence of an adverse event, where continued administration of study drug is deemed not in the patient's best interest by the investigator and/or the sponsor, will also result in the removal of the patient from therapy. All patients will be treated with the study drug for a minimum of 12 weeks before assessment for disease progression unless the patient develops significant treatment-related toxicity or worsening symptoms due to rapid disease progression.

The consensus guidelines of the Prostate Cancer Clinical Trials Working Group 2 have been taken into consideration for the determination of disease progression in the study.(62) Disease progression based on PSA is defined as an increase in the PSA that is ≥25% **and** ≥ 2ng/ml above the nadir PSA value. A confirmatory PSA is required three or more weeks later and it should demonstrate persistent elevation. Patients should continue on study treatment until this confirmatory PSA testing is performed to document PSA progression. Radiographic disease progression is defined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (Appendix B) for soft tissue disease or the appearance of two or more new bone lesions on bone scan.

The following assessments will be performed during the course of the clinical trial as detailed in section 8.0: soft tissue and visceral disease on computed tomography (CT) scan or on magnetic resonance imaging (MRI), bone disease on radionuclide bone scans, skeletal related events, analgesics use, Comprehensive Geriatric Assessment, Functional Assessment of Cancer Therapy-Prostate (FACT-P) and PSA. Radiologic studies will be read on site. Each site will ideally designate the same radiologist who will evaluate the images for any one patient for the duration of the trial. Repeat imaging for assessment of radiographic progression is not required once radiographic progression is determined.

Patients without radiographic evidence of metastatic disease at the time of enrollment will obtain repeat imaging only at the time of documented PSA progression or as clinically indicated. For patients with radiographic evidence of metastatic disease at enrollment, disease assessment with radiographic studies should be performed as detailed in section 8.0 and may be performed more frequently if clinically indicated. Chest imaging may include either chest X-ray or CT chest at the discretion of the treating physician.

CGA will be used to capture baseline heath status prior to treatment and repeated at pre-specified intervals to document toxicities related to treatment and to assess any changes in functional status from baseline. A geriatric oncologist or his/her designee at each respective institution will administer CGA.

Forty patients will be recruited and treated until disease progression or meeting any reason for removal from treatment (see section 7.4). The primary efficacy end-point for this trial is PSA progression-free survival (PFS), which is defined as the length of time that a given subject will be alive and free from PSA progression as defined above in section 6.0.

Throughout the study, safety and tolerability of study treatment will be assessed by the monitoring of adverse events, vital signs, physical examinations, and laboratory studies per study calendar. The PI will monitor safety data on an ongoing basis. Patients will have a Safety Follow-up visit 30 days after their last dose of study drug or prior to the initiation of another systemic antineoplastic therapy, whichever occurs first. Serious adverse events will be collected for 30 days after the patient's last dose of study drug. After treatment discontinuation, subsequent antineoplastic therapy and survival status will be assessed.

7.0 TREATMENT PLAN

For treatment or dose modification related questions, please contact Chunkit Fung, MD (E-mail: chunkit_fung@urmc.rochester.edu or Phone: (585) 273-5468)

7.1 Treatment

All patients will receive either a combination of enzalutamide 160 mg oral daily and dutasteride 0.5 mg oral daily or enzalutamide 160 mg oral daily and finasteride 5 mg oral daily until disease progression or other reasons for removal from treatment protocol. (see section 7.4). The type of 5-AR inhibitor used for each patient will depend on insurance approval. Dutasteride will be the 5AR-Inhibitor of choice given its slightly better efficacy. If for any reason dutasteride cannot be obtained, finasteride would be administered.

7.2 Prior and Concomitant Therapy

All concomitant medication(s) including any medications taken within four weeks prior to the Day 1 visit will be collected. Concomitant medications include all vitamins, herbal remedies, over the counter, and prescription medications. Intermittent or as needed (prn) use of any medication during the study indicates the possible occurrence of an adverse event and must be noted as such and be recorded.

7.2.1 Prohibited Medications

The following medications are prohibited within 4 weeks prior to the start of study drug treatment and are prohibited during the course of the study:

- Chemotherapeutic, immunotherapeutic and biologic agents
- Systemic glucocorticoids greater than the equivalent of 10 mg per day of prednisone/prednisolone (unless needed for stress steroids or to treat presumed adrenal insufficiency)
- Estrogens
- Herbal medications that may affect PSA levels (i.e., saw palmetto)
- Androgens (testosterone, dihydroepiandrosterone [DHEA], etc.).

Use of bisphosphates or rank-ligand inhibitor is allowed but doses should be documented during the study period.

The use of strong or moderate CYP2C8 or CYP3A4 inducers or inhibitors (see Appendix F) is prohibited while on study for patients receiving dutasteride.

Patients on therapies known to be weak inhibitors/inducers or narrow-therapeutic-index substrates of CYP2C8 or CYP3A4 should be evaluated for clinically significant drug interactions, but may participate in the study with appropriate monitoring and management.
Deviation from the above guidelines should occur only if absolutely necessary for the well-being of the patient. Any deviations to the medication/treatment guidelines are to be recorded.

7.2.2 Permitted Medications

Patients are allowed to take prescription medications as long as they are not considered to interact with the study drug as listed in the prohibited medication list. All prescription medications should be reported to the study personnel. Patients concomitantly using warfarin will need to have their INR monitored closely.

7.2.3 Non Drug Therapies

Patients are allowed to take over the counter supplements, including multivitamins. All non-prescription therapies should be reported to the study personnel

7.3 Treatment Compliance

Study drug accountability will be performed at pre-specified study visits to document compliance with the dosing regimen. Patients will be asked to bring back all remaining study drug and all study drug packaging at the beginning visit of each cycle for drug

accountability. Treatment compliance will be defined as the number of capsules taken during the study divided by the expected number of capsules, multiplied by 100%. Capsules that are not returned will be considered to have been taken, unless otherwise specified. Compliance will be assessed at each specified visit by review of a pill diary and/or by questioning patients as to compliance. Compliance will be recorded in the source documentation.

7.4 Criteria for Removal from Protocol Treatment

- Disease progression as defined by 1) PSA rise **with or without** radiographic evidence of disease progression or 2) the occurrence of a skeletal-related event (see section 6.0)
- Unacceptable toxicity very likely related to studydrugs
- Off study treatment for ≥ 30 days
- Initiation of new systemic treatment for PCa
- The patient may withdraw from the study at any time for any reason
- Death
- Product not available
- Lost to follow-up
- Decision by sponsor

7.5 Treatment Discontinuation

Patients will be advised in the written informed consent form that they have the right to withdraw from study drug treatment at any time without prejudice, or may be withdrawn at any time at the discretion of the investigator or the sponsor. If medically indicated, the investigator or the sponsor may withdraw study drug from a patient in the event of an intercurrent illness, adverse event, other reasons concerning the health or well-being of the patient, or in the case of lack of cooperation, non-compliance, protocol violation, or other administrative reasons.

Patients removed from therapy for any reason should continue to be followed for the collection of safety data as outlined in the adverse event reporting section and the Safety follow-up visit procedures. For patients who decline further clinic study visits, telephone contact should be attempted to review for adverse events 30 days after the last dose of study drug or prior to the initiation of another systemic antineoplastic therapy, whichever occurs first. All serious adverse events will be followed until resolution, until the event has stabilized and/or become chronic, until it has been determined that the event was caused by an etiology other than the study drug, or through 30 days, whichever comes first.

Reasonable effort should be made to contact any patient lost to follow-up during the course of the study in order to complete study-related assessments and retrieve any

outstanding data and study drug. Following unsuccessful telephone contact, an effort to contact the patient by mail using a method that provides proof of receipt should be attempted. Such efforts should be documented in the source documents. All reasons for discontinuation of treatment must be documented.

7.6 Follow up Period

All patients will be followed until study closure, death, or patient's decision to withdraw consent. Data will be collected at pre-specified intervals as detailed in the study calendar (see section 8.0) to assess safety and efficacy. After treatment discontinuation, subsequent antineoplastic therapy and survival status will be assessed for the duration of follow up.

7.7 Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, or as deemed necessary by the investigator. The date and reason for the unscheduled visit should be recorded in the source documentation. The following activities can be completed at unscheduled visits (other than those exclusively for return or re-supply of study drug):

- 12-lead ECG (if medically indicated);
- Vital signs (blood pressure, heart rate, respiratory rate, temperature);
- Laboratory assessment (hematology and chemistry);
- Enquire from the patient and record the time that study medication was taken on the preceding 2 days;
- Brief history and physical examination; ECOG performance status;
- Record concomitant medications; Record adverseevent

8.0 STUDY CALENDAR@

		Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7		Cycle 8		Cycle 9		β		
Study Day α	PRE STUDY α	W 1	W 3	W 7	W 13	W 19	W 25		W 37		W 49		W 61		W 73		W 85		W 97		FU Prior to Progressionε ∞,	Safety FU Within 30 days after last treatment dose	FU After Progressionφ
REQUIRED STUDIES																							
PHYSICAL																							
History and Physical Exam	X	X	X	X	X	X	X		X		X		X		X		X		X		X	X	
Weight and Performance Status	X	X	X	X	X	X	X		X		X		X		X		X		X		x	X	
Blood Pressure	X	X	X	X	X	X	X		X		X		X		X		X		X		x	X	
Disease Assessment	X				X	X	X		X		X		X		X		X		X		X	X	
Toxicity Notation			X	X	X	X	X		X		X		X		X		X		X		x	X	
Comprehensive Geriatric Assessmentψ	X				X				X				X									x	
LABORATORY																							
Serum PSA	X			X	X	X	X		X		X		X		X		X		X		X	X	
Serum Testosterone	X			X	X				X													X	
Serum Dihydrotestosterone	X								X													X	
CBC/Differential /Platelets/Hemoglobin	X		X	X	X		X		X		X		X		X		X		X		x	X	
Comprehensive Metabolic Panel	X		X	X	X		X		X		X		X		X		X		X		x	X	
X-RAY and SCANS																							
DEXAΩ	X																		X				
CT of Abdomen and Pelvis≠	X						X				X										x≠		
Bone scan≠	X						X				X										X≠		
Chest Imaging≠	X						X				X										X≠		
TREATMENT																							
Enzalutamide€		X			X		X		X		X		X		X		X		X				
5-AR inhibitor€		X			X		X		X		X		X		X		X		X				
Prophylactic Breast Radiation¶	X																						

@ Study visits from the Covid-19 pandemic (starting in March 2020) and moving forward can be performed via telemedicine technology. Study team should adhere to study procedures as outlined by study calendar above except for weight and physical examination, including vital signs (e.g. temperature, heart rate, pulse oximetry, and respiratory rate). We expect subjects to report blood pressure measurements performed by themselves or care providers within +- 7 days of study visit while on study treatment. Study drug may be shipped to patients undergoing a telemedicine visit.

α Except for week 1 visit, there is a window of +/-4 weeks for subsequent follow up visits. Prestudy labs/visit to be no more than 3 weeks prior to cycle 1, Day 1 Pre enrollment scans must be obtained within 28 days of day1 treatment/

Σ Patients off protocol treatment secondary to reasons other than progression will have physical exams and PSA for disease assessment performed every 6 months for first year and as clinically indicated thereafter.

∞ Patients with stable disease and on protocol treatment beyond week 97 will be followed every 12 weeks until disease progression.

Φ After disease progression, follow-up will occur every 6 months (+/- 2 months) for first year after disease progression and as clinically indicated thereafter. Each subsequent antineoplastic therapy and survival status are the only required data point following progression.

Ψ Comprehensive geriatric assessment (CGA) will be performed at baseline, end of cycle 1 and every 24 weeks during the study protocol until week 61 and at the time of progression. FACT-P will be performed along with CGA

Ω DEXA scan must be obtained within 2 years prior to registration for all patients. Follow-up DEXA scans should be obtained after 2 years of protocol treatment for patients not receiving denosumab or bisphosphonates. DEXA scan is not indicated for those who are on treatment with bisphosphonates or denosumab.

≠ For patients without radiographic evidence of metastatic disease at enrollment of study protocol, disease assessment with radiographic studies are not necessary unless there is evidence of PSA progression (see Section 6.0) or clinically indicated. For patients with radiographic evidence of metastatic disease at enrollment of study protocol, disease assessment with radiographic studies should be performed as indicated in the above study calendar and may be performed more frequently if clinically indicated by the same methods used at baseline. Chest Imaging may include either chest X-ray or CT chest at the discretion of the treating physician. After week 97, for patients with stable PSA, scans to be performed at the time of progression or as clinically indicated

€ Treatment will be given daily and will continue until disease progression or other reason for discontinuation of protocol treatment (see Section 7.4) Study drug will be dispensed every 12 +/- 4 weeks and a 120 day supply of medication will be provided at each visit.

¶ This procedure is not mandatory but should be discussed with all patients enrolled in the protocol and can also be considered during the treatment course to prevent further worsening of breast tenderness when considered appropriate..

ʙ Followed until death, study closure, or withdrawal of consent.

9.0 END POINT DEFINITIONS: EFFICACY ASSESSMENT

9.1 Primary Efficacy Assessment

The primary efficacy assessment will be PSA PFS, which is defined as the length of time that a given subject will be alive and free from PSA progression. All patients will be treated with the study drugs for a minimum of 12 weeks before assessment for disease progression unless the patient develops significant treatment-related toxicity or worsening symptoms due to rapid disease progression. PSA progression will be defined according to the consensus guidelines of the Prostate Cancer Clinical Trials Working Group 2. For patients with a PSA decline at week 13 compared to the baseline value at the time of enrollment, the PSA progression date will be defined as the first date (after week 13) when there is a ≥25% increase **and** an absolute ≥ 2ng/ml increase in PSA compared to the PSA nadir. For patients with a PSA rise at week 13, the PSA progression date will be defined as the first date (before week 13) when there is a ≥ 25% increase **and** an absolute increase of ≥ 2 ng/ml in PSA compared to the baseline value at the time of enrollment. A confirmatory PSA is required three or more weeks after the date of PSA progression and it should demonstrate persistent elevation.

9.2 Secondary Efficacy Assessments

9.2.1 Absolute PSA Response

Failure to achieve a PSA of ≤ 4 ng/ml after seven months of combined ADT has been shown to be a negative predictor for survival in the SWOG 9346 trial.(63) We will report the PSA nadir value after initiation of study drugs and measure the absolute and relative PSA declines from the baseline PSA at the time of study enrollment.

9.2.2 Time to PSA Nadir

We will assess the time to PSA nadir, which is defined as the time to achieve the lowest PSA value after initiation of study drugs. The prognostic significance of the time to PSA nadir is yet to be defined but Choueiri et al. suggested that a faster time to reach a PSA nadir after the initiation of ADT was associated with shorter survival duration in men with hormonal naïve metastatic prostate cancer.(64)

9.2.3 Safety and Toxicity

We will assess the safety and toxicity of this drug combination through routine history and physicals as well as serial monitoring of blood work, all of which will be recorded and reviewed periodically. Adverse events will be defined according to CTCAE version 4.0 (Appendix C).

9.3 Tertiary (Exploratory) Efficacy assessments

9.3.1 Change in Bone Health

ADT is known to effect bone strength. Compared to men with prostate cancer who do not receive treatment with ADT, patients with prostate cancer treated with ADT have a 13-30% increased risk of osteoporotic fractures.(65) Loss of lean muscle mass coupled with declined strength from ADT predisposes to a high risk of falls, which in the setting of osteoporosis leads to increased fracture risk. To determine the impact of study treatments of bone health, we will assess changes in bone density by comparing results of DEXA scans prior to and at the end of study treatment. To accurately examine their impact on bone health, only patients who are on the study drugs for at least 1 year will be included for this analysis. Additionally, due to the bone strengthening effects of bisphosphonates and denosumab, patients who receive these therapies will be excluded from this secondary endpoint analysis.

9.3.2 Change in CGA Domains

ADT, which includes orchiectomy or administration of GnRH agonists/antagonists, remains the mainstay of treatment for hormone naïve patients who present with biochemical recurrence or metastatic disease. Testosterone depletion secondary to ADT causes a myriad of side effects, which include decreased libido, muscle strength, increased risk of falls and cognitive changes. All these changes have been well characterized and captured using a CGA in numerous studies. The current trial would be utilizing periodic CGA to capture any side effects related to the study drug combination that would otherwise not be recognized to provide a better understanding of the safety profile of the drug combination specifically in the vulnerable/frail elderly population.

During geriatric assessments, the various domains as listed in the table below will be measured

DOMAIN	TOOL	SCORE SIGNIFYING IMPAIRMENT
Physical function	➢ ADL ➢ IADL ➢ Fall history	➢ Any ADL or IADL impairment ➢ Any history of fall

Objective physical performance	➢ SPPB	➢ ≤ 9
Comorbidity	➢ Average number of comorbid conditions	➢ >5
Nutrition	➢ BMI ➢ MNA	➢ <21 ➢ ≤ 11
Social support	➢ OARS Medical Social Support	➢ Any deficit noted
Polypharmacy	➢ Number of total medications	➢ ≥5 medications
Psychological	➢ GDS	➢ ≥ 5
Cognition	➢ BOMC ➢ MoCA	➢ >10 ➢ <26
Screening	➢ VES-13	➢ ≥3

ADL: Activity of daily living
MNA: Mini nutritional assessment
SPPB: Short physical performance battery
BMI: Body mass index
VES: Vulnerable elderly survey

GDS: Geriatric Depression scale
IADL: Instrumental activity of daily living
BOMC: Blessed orientation-memory-concentration
MoCA: Montreal cognitive assessment

In a study published by Bylow et al., fifty elderly men (>70 years) receiving ADT for systemic Pca(80% with biochemical recurrence), underwent CGA at baseline (while on ADT) and three months later. (10)Fall history in the study population was also recorded. All domains listed in the above table were assessed during these visits. Of the 50 men, 24% had impairment in ADLs, 42 % had impairment in IADLs, 56% had abnormal SPPB findings and 22 % reported falls at the time of first assessment. Among the forty patients who completed the follow up CGA at 3 months, 20% had worsening SPPB scores and falls were common, even in patients with no prior falls. The results of this study demonstrated that a substantial number of of elder patients are vulnerable to frail at baseline, and are at risks of significant functional and physical decline after even short term ADT. This study also reiterates that CGA adds significant information in not only documenting baseline health status but is also instrumental in monitoring toxicities that would otherwise not be captured. More importantly, administration of serial CGA is feasible and hence, the current study will utilize serial CGA besides other tools to monitor adverse events

9.3.3 Quality of life assessments- Functional Assessment of Cancer Therapy - P

The FACT-P is a multidimensional, self-reported quality of life instrument specifically designed for use with prostate cancer patients. It consists of 27 core

items which assess patient function in four domains: Physical, Social/Family, Emotional, and Functional well-being, which is further supplemented by 12 site specific items to assess for prostate related symptoms. Each item is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain, as well as a global quality of life score with higher scores representing better quality of life.

10.0 STATISTICAL CONSIDERATIONS

10.1 Primary End-Point

The primary efficacy end-point for this trial is PSA progression-free survival (PFS) defined as the length of time that a given subject will be alive and free from PSA progression. Median PSA-PFS and 1-year and 2-year PSA-PFS probabilities will be estimated using the Kaplan-Meier method, with 95% confidence intervals constructed based on Greenwood's variance estimator, which is the default approach in SAS 9.3. (66-68) Confidence intervals for the median are given by $\{t : \hat{S}(t) - 0.5\}_2 \leq \chi_2 \hat{V}_\alpha[\hat{S}(t)]\}$, where t represents all time points satisfying the inequality, $\hat{S}(t)$ is the Kaplan-Meier estimate of PSA-PFS, χ^2_α is a chi-square score with one degree of freedom corresponding to the chosen confidence level (for 95% confidence $\chi^2_\alpha = 3.84$), and $\hat{V}[\hat{S}(t)]$ is the Greenwood's variance estimator. [64] Confidence intervals for the 1-year and 2-year survival probabilities will be constructed as $\hat{S}(t) \pm z_{\alpha/2} \hat{V}[\hat{S}(t)]_{1/2}$, where $z_{\alpha/2}$ is the standard normal score. (67)

It should be noted that in the absence of loss to follow-up (i.e., if vital status and PSA-progression status are known for each subject at the end of the study), $\hat{S}(t)$ coincides with the observed proportion of subjects alive and without PSA progression by time t and $\hat{V}[\hat{S}(t)]$ coincides with the usual estimator of the variance of a sample proportion $\hat{V}[\hat{S}(t)] = [\hat{S}(t)][1-\hat{S}(t)]/n$, where n is the number of subjects in the study. [65]

Sample size justification: The median PSA-PFS times under null and alternatives hypothesis are assumed to be 1.44 and 3.04 years (the corresponding 1 year PSA-PFS rates are 50% and 72% respectively). Based on this assumption, the one sample log-rank test shows that a sample size of n=36 has 82% power (two-sided test with significance level 0.05) to reject the null hypothesis if the median survival time is at least 3.04 years. Taking into account of withdrawal or loss to follow-up (no more than 10% for the first year), we plan to recruit 40 patients in the study.

Expected margin of error (one-half of the confidence width) of the 95% confidence intervals for $S(t)$ can be approximated by $1.96\sqrt{[S(t)][1-S(t)]/n}$. For 1-year and 2-year PSA-PFS this gives $1.96\sqrt{0.72\times 0.28/40} = 0.15$, $\sqrt{0.40\times 0.60/40}$

respectively. In addition to the number and percentage of subjects alive and without PSA progression at 1 and 2 years of follow-up, we will report separately numbers and percentages of subjects alive and with PSA progression, dead without PSA progression, and dead with PSA progression. The causes of death and the incidence of clinical progression will also be reported.

10.2 Secondary End-Points

10.2.1 Decline in PSA from Baseline to Nadir

This will be expressed for each subjects in the absolute value and as percentage, displayed for the entire study cohort as a water-fall plot, and summarized with the median (with a 95% confidence interval), first and third quartiles, and the absolute range.

10.2.2 Time to PSA Nadir

This will be expressed for each subjects as the absolute value, displayed for the entire study cohort as a water-fall plot, and summarized with the median (with a 95% confidence interval), first and third quartiles, and the absolute range.

10.2.3 Safety and Toxicity

This will be examined by documenting the type and grade of each adverse event (as defined by CTCAE, appendix C) at baseline and at each follow-up visit.(69) These data will be summarized with counts and percentages. In addition, each grade 3 or 4 adverse event will be described separately, and the plausibility of its causation by the study drug combination will be discussed.

10.3 Tertiary Endpoints

10.3.1 Changes in BoneHealth

This will be expressed as a difference between the mean T scores on bone densitometry at baseline and at 2 years of follow-up (Section 8.0). A 95% confidence interval for the difference will be constructed using the standard approach for paired measurements [67]. We will also compute the frequency and the percentage of subjects with osteopenia (T score = -1.0 to -2.5) and osteoporosis (T score < - 2.5) at baseline and at 2 years of follow-up.

10.3.2 Changes in Comprehensive Geriatric Assessment

Analysis of this aim will be descriptive and will describe mean, median, standard deviations of scores at baseline and at follow up time points. CGA deficits over 6 months will be captured. Each domain will be evaluated individually and scores will be compared between baseline and 6 months. Overall CGA deficits will be examined and the proportion of patients who decline in more than 1 domain will be determined for these time points.

10.3.3 Quality of Life

This will be measured by the FACT-P tool. (70)For each of the 27 core items and 12 site-specific items, mean score for the study cohort will be computed at baseline and at specified follow-up visits (Section 8.0). These means will be plotted against follow-up time and visually assessed for evidence of an upward or a downward trend. For each item, an upward or a downward trend in mean scores over time will indicate improvement or deterioration in a given dimension of quality of life (i.e., the dimension measured by that item). Changes in mean scores from baseline will be calculated at 3 months and at 6 months after therapy initiation and will be reported with 95% confidence intervals.

11.0 Definition of an Adverse Event

An adverse event or experience is defined as any symptom, sign, illness, or untoward experience (including a clinically significant laboratory finding classified as grade ≥ 3 by the National Cancer Institute's Common Terminology Criteria for Adverse Events [CTCAE]; appendix C) that develops or worsens during the course of the study, whether or not the event is considered related to study drug. Any adverse event should be recorded only after the first dose of study drug is taken. Serious adverse events are recorded from the time the informed consent form is signed.

Where a diagnosis is possible, it is preferable to record it rather than a series of terms relating to the diagnosis.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms.
- Requires active intervention.
- Requires interruption or discontinuation of study medication.
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

All adverse events, whether or not related to the study drug, must be fully and completely documented.

Adverse events are detected in two ways:

- Clinical: symptoms reported by the patient or signs detected on examination;
- Ancillary Tests: clinically significant abnormalities of vital signs, ECG, laboratory tests, and other diagnostic procedures.

An adverse event **does not** include:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion); however, the condition that leads to the procedure is an adverse event;
- Pre-existing diseases or conditions present or detected prior to the start of study drug administration that does not worsen;
- Situations where an untoward medical event has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions);
- Overdose of either study drug or concomitant medication without any signs/ symptoms

Relationship to Study Drug: The reasonable possibility of an adverse event's relationship to study drug is to be assessed with careful medical consideration at the time of evaluation of the adverse event. The PI's opinion may be sought in those cases in which the Investigator is unable to make an independent judgment. The following definitions are to be used:

Descriptor	Definition
Unrelated	Adverse event is **clearly not** related to the investigational drug (s)
Unlikely	Adverse event is **doubtfully** related to the investigational drug (s)

Possible	Adverse event is **may be** related to the investigational drug (s)
Probable	Adverse event is **likely** related to the investigational drug (s)
Definite	Adverse event is **clearly** related to the investigational drug (s)

The following criteria will be used as guidelines for determining the attribution of an adverse event to the study drug:

Unrelated	There is no possible relationship to the study drug. The temporal relationship between drug exposure and the adverse event onset/course is unreasonable or incompatible, or a causal relationship to study drug is implausible.
Unlikely	The study drug is believed to be not reasonably related to the adverse event, although a causal relationship cannot be ruled out. While the temporal relationship between drug exposure and the adverse event onset/course does not preclude causality, there is a clear alternate cause that is more likely to have caused the adverse event than the study drug.
Possible	The causal relationship to the study drug is uncertain. The temporal relationship between drug exposure and the adverse event onset/course is reasonable or unknown, dechallenge or rechallenge information is either unknown or equivocal, and while other potential causes may not exist, a causal relationship to the study drug does not appear probable.
Probable	There is a high degree of certainty for a causal relationship between the study drug and the adverse event. The temporal relationship between drug exposure and the adverse event onset/course is reasonable, there is a clinically compatible response to dechallenge, other causes have been eliminated, and the event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
Definite	Causal relationship is certain. The temporal relationship between drug exposure and the adverse event onset/course is reasonable, there is a clinically compatible response to dechallenge, other causes have been eliminated, and the event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge

	procedure if necessary.

In the event that a patient is withdrawn from the study because of an adverse event, it must be recorded. Adverse events will be monitored until resolution or until the event has stabilized and/or reached a new baseline. If an adverse event remains unresolved at the conclusion of the study, a clinical assessment will be made by the investigator to determine whether continued follow-up of the adverse event is warranted.

The investigator must record all directly observed adverse events and all spontaneously reported adverse events. At each visit, the investigator will ask the patient a non-specific question (e.g., "Have you noticed anything different since your last visit?") to assess whether any adverse event has been experienced since the last report or visit. Adverse events will be identified and documented. The severity and the relationship to the study drug will be determined and reported.

Note that any intermittent or as needed use of any medication (and specifically any newly prescribed medication) during the course of a study may indicate the occurrence of an adverse event that may need to be recorded.

Serious adverse events will be collected and reported from the time the patient signs the informed consent form until the Safety Follow-Up visit. Non-serious adverse events will be collected from the time of first study drug dosing until the Safety Follow-Up visit.

11.1 Adverse Events - Severity Rating

Severity describes the intensity of a specific event (as in mild, moderate, or severe chest pain); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria. The severity of an adverse event will be graded following the CTCAE v4.0 (appendix C).

11.2 Disease Progression as an Adverse Event

It is anticipated that a proportion of patients will experience disease progression. **Disease progression per se should NOT be reported as an adverse event.** If there are separate identifiable clinical sequelae that result from disease progression, these sequelae are reportable as adverse events.

11.3 Serious Adverse Events and Unexpected Adverse Events - Definitions

A Serious Adverse Event or reaction is any untoward medical occurrence at any dose that:

- Results in death;
- Is life threatening (i.e., the patient was at immediate risk of death at the time of the event). "Life-threatening" does not include an event that hypothetically might have caused death if it were more severe. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal;

- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of the patient's ability to carry out normal life functions);
- Is a congenital anomaly/birth defect.

In addition, medical and scientific judgment should be exercised in deciding whether other situations should be considered a serious adverse event (i.e., important medical events that may not be immediately life-threatening or result in death, but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above). Examples of such medical events include (but are not limited to): allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse. In this study, a documented seizure should be reported as a medically important serious adverse event.

11.4 Serious Adverse Events - Reporting

The study team should report serious adverse events (SAEs) to the DSMC using the SAE report form on University of Rochester's OnCore platform. If the SAE(s) is related to study medication and is unexpected (SUSARs), the SAE(s) should be reported to the DSMC and RSRB within 5 days and to the FDA within 7 days. If the SAE(s) is unrelated to study medication and/or expected, the SAE(s) report needs to be completed, including all follow up information, prior to the next scheduled review of the study by DSMC. To report SAEs, the Investigator will also submit a SAE report to Astellas by either e-mail or fax, within the same timeframe as required by the DSMC.

For participating sites that do not have access to the University of Rochester's OnCore platform, they can use the MedWatch Form 3500 to report non-SUSAR SAE(s) and the MedWatch Form 3500A to report SUSAR(s) to the sponsor-investigator. Then, the sponsor-investigator team will enter the SAEs/SUSARs into the SAE report form on the University of Rochester's OnCore platform using the same timeline as detailed above.

For all SUSARs, the MedWatch 3500A form should be completed and faxed to Astellas and FDA by either e-mail or fax, within 7 days. If submission of SUSARs to FDA or Astellas or Medivation is not possible within 7 days, the Investigator's local drug safety contact (e.g., DSMC, IRB, etc.) should be informed by phone.

The SUSAR documentation, including the Medwatch 3500A Form and available source records should be emailed or faxed to:

Astellas Pharma Global Development – United States
Email: Safety-us@us.astellas.com
Fax number: (847) 317-1241

The following minimum information is required for the initial report:
Study number/IIT regulatory identifier
Subject number, sex and age
The date of report
The start date of the event
As much information as is known about the event at the time
Suspected causal relationship to the study drug
Whether the event is known to occur in relation to the study drug (i.e., expectedness)

Follow-up information for the event should be sent within promptly (within 7 days) as necessary.

It is the responsibility of the investigator to report serious adverse events to their local IRB/IECs according to their policies.

All serious adverse events should be recorded once the informed consent form is signed and must be reported within the timeframe as discussed above by facsimile to the person listed below

Name: Chunkit Fung
SAE Fax: (585) 276-0350
Email: chunkit_fung@urmc.rochester.edu
Cell: (267) 973-4448

Follow up reports should include the same information as the initial report with any updates or corrections needed. In addition, they should include the details of study drug administration, and as many details of the serious adverse event as are known, including the date of onset, the intensity, the treatment, and the relationship to study drug. SAE reports must include sufficient detail so that the DSMC can determine the CTCAE term, severity, toxicity grade, expectedness, relatedness, treatment required, and a follow up report documenting resolution and whether there are sequelae. If the patient died, the report should include the cause of death and whether or not the death was related to study drug, as well as the autopsy findings if available.

Do not delay reporting a suspected serious adverse event in order to obtain additional information. Any additional information should be reported in a follow-up to the initial report.

All serious adverse events will be followed until resolution or until the event has stabilized and/or reached a new baseline. All serious adverse events continuing at the completion of the study must be followed to determine outcome. All serious adverse events occurring between the times the patient signs the informed consent and 30 days after the patient's last dose of study drug or prior to the initiation of another systemic antineoplastic therapy, whichever occurs first, must be recorded, reported, and followed up by the investigator using the procedure described above.

11.5 Procedure in Case of Pregnancy

The effect of enzalutamide in pregnant and lactating women is not known, and the exposure of a fetus or nursing infant is considered a potential risk. Enzalutamide can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Subjects receiving enzalutamide are advised to use 2 acceptable methods of birth control (one of which must include a condom as a barrier method of contraception) starting at the time of screening for an enzalutamide study and continuing throughout the course of treatment and for at least three months after enzalutamide is discontinued.

Dutasteride is contraindicated for use in women of childbearing potential and during pregnancy. Dutasteride prevents conversion of testosterone to DHT, a hormone necessary for normal development of male genitalia. In animal reproduction and developmental toxicity studies, dutasteride inhibited normal development of external genitalia in male fetuses. Therefore, dutasteride may cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy or if the patient becomes pregnant while taking it, the patient should be apprised of the potential hazard to the fetus

If during the conduct of the clinical trial, a male subject impregnates his partner, the subject should report the pregnancy to the Investigator. The Investigator should report the pregnancy to the Sponsor as an SAE within 24 hours of awareness of the event. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated fertility date, pregnancy result and neonatal data etc., should be included in this information.

The Investigator should report the outcome of the pregnancy (independent of outcome, eg. full term delivery, pre-term delivery, spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly [including anomaly in a miscarried fetus, etc] in accordance with the same reporting procedure as for SAEs. The date of outcome of the pregnancy, gestational age, date of birth and neonatal data etc., should be included in this information.

11.6 Monitoring Plan

This study will be monitored according to the Wilmot Cancer Institute's Data and Safety Monitoring Plan for Clinical Studies. The monitor must be allowed access to all protocol regulatory and source documents to assess compliance with the protocol, federal regulations, and good clinical practices. The monitor will assess data for completeness of source documents and confirm data being recorded in the EDC is accurate. For remote monitoring, the sites will provide source documents as required. The regulatory binder, patient cases, and drug accountability will be reviewed at monitoring visits.

11.7 Safety Analyses

The Data Safety Monitoring Committee (DSMC) at the Wilmot Cancer Institute, University of Rochester, provides oversight of study progress and safety by review of accrual and adverse events semi-annually or more if concerns arise. Any adverse events requiring expedited review per protocol will be submitted to the chair of this committee for determination as to whether further action is required. This committee will meet after 6 patients have been enrolled and received at least one cycle of therapy. If > 3 patients have delays in treatment administration due to toxicity, the protocol will be closed to accrual pending review and discussion with the principal investigators.

The safety coordinator will monitor adverse event rates utilizing the University of Rochester Cancer Center Clinical trial database. If the study has had two or more of the same SAE's reported in a month or more than six of the same SAEs in six months, the DSMC will review the summary of SAEs, discuss events with the study chair, and conduct a detailed review with the study chair. The DSMC will determine if further action is required. A copy of the DSMC report will be sent to all participating sites for review and submission to their local IRB.

12.0 TOXICITY ASSESSMENT AND DOSE REDUCTION/DOSE ADJUSTMENT

All patients will be assessed for safety with frequent history and physical exams along with CGA at pre-specified intervals, and at Unscheduled Visits if necessary, including chemistries and hematology (see Section 8.0).

The study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov.) All appropriate treatment areas should have access to a copy of the CTCAE version 4.0 (appendix C)

General dose modification considerations

- Missed doses are to be omitted rather than made up
- If multiple toxicities are experienced, dose modification will be based on the toxicity requiring the largest dose reduction
- Reductions are based on the dose given in the preceding cycle and are based on toxicities observed since the prior toxicity evaluation
- Dose modifications are required for Grade 3 or Grade 4 adverse events (AEs) or intolerable Grade 2 AE that are considered at least possibly related to enzalutamide or dutasteride
- Toxicities will be assessed and reported as specified in the study calendar

- Dose levels are defined below

Dose Level	Enzalutamide	Dutasteride /Finasteride
0	160 mg daily	0.5/5 mg daily
-1	120 mg daily	0.5/5 mg daily
-2	80mg daily	0.5/5 mg daily

An adverse event, using the common terminology definition, is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of medical treatment that may or may not be related to the treatment. Serious adverse event are defined as grade 3 and 4 toxicities that are believed to potentially impact the safety of the participant. Any patient with SAE that cannot be ameliorated with the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a Grade 2 or lower severity. Once toxicity improves, at the discretion of the treating physician the study combination can be re-started at a reduced dose (-1). Should the patient continue to have intolerable grade 2 or higher toxicity even at a reduced dose (-1), at the discretion of the treating physician the study combination can be further reduced to level -2. Patients with SAE or intolerable grade 2 toxicity Patients with SAE while on dose -2 will permanently discontinue study drug. The study coordinator should be notified of all SAE. Also if the study drug is delayed for more than 4 weeks for any reason or if a dose reduction of enzalutamide below 80 mg daily is required, patients will be removed from the protocol treatment.

Dutasteride/ finasteride is included in this regimen to potentially increase the efficacy of enzalutamide and to prolong the duration of response. Dutasteride is available only as 0.5 mg capsules. Finasteride is available only as 5 mg capsules. In the event grade 3 or grade 4 toxicity occurs and is known to be related to dutasteride or finasteride alone, 5 AR-inhibitor should be held permanently. In the event of an occurrence of a SAE that cannot be attributed directly to either enzalutamide or 5- AR inhibitor, the study combination should be held until toxicity improves to grade 2 or lower and treatment restarted at dose level -1.

For treatment or dose modification related questions, please contact Chunkit Fung, MD at (585) 273-5573 or Deepak Kilari, MD at (414) 805-4600

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patient's enrollment must occur up to 28 days prior to the start of treatment with the study drug combination. All patients must have a signed informed consent prior to registration.

13.2 Investigator/Site requirement

This study is supported by Astellas and Medivation Inc.

Prior to recruitment of a patient for this study, each investigator must have a NCI Investigator number and must maintain an active investigator registration status through the annual submission of a complete investigator registration packet (FDA form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature and Financial Disclosure form with original signature) to the Pharmaceutical Management Branch CTEP, DCTD, NCI.

Each investigator or group of investigators at a clinic site must obtain IRB approval for the protocol and submit IRB approval and supporting documentation to the regulatory office before they can enroll patients.

13.3 Other Registration guidelines

All patients will be registered through the central office/coordinating site which is located at the

James P. Wilmot Cancer Center
University of Rochester Medical Center
Rochester, NY, 14642

Any question regarding eligibility or that may arise during the conduct of the study should be addressed to

Name: Chunkit Fung
SAE Fax: (585) 276-0350
Email: chunkit_fung@urmc.rochester.edu
Cell: (267) 973-4448

14.0 STUDY ADMINISTRATION

Regulatory and Ethical Considerations

14.1 Institutional Review Board or Independent Ethics Committee

Prior to the initiation of the study, the Principle Investigator will obtain written confirmation from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) that the IRB/IEC is properly constituted and compliant with all the local requirements and regulations. A copy of the confirmation will be provided to the sponsor of the study. The investigator will provide the IRB/IEC with all appropriate material,

including the protocol, current Investigator's Brochure, the informed consent document, and other written information provided to the patients. The trial will not be initiated until appropriate IRB/IEC approval of the protocol and the informed consent document and all recruiting materials are obtained in writing by the investigator and copies are received by the sponsor. Appropriate reports on the progress of the study will be made to the IRB/IEC and the sponsor by the investigator in accordance with applicable governmental regulations and in agreement with policy established by the IRB/IEC.

Ethical Conduct of the Study

This study will be conducted under the principles of the World Medical Association (WMA) Declaration of Helsinki under its most recent amendment (by the 52nd WMA General Assembly, Edinburg, Scotland, October 2000, with a Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002 and on

Paragraph 30 added by the WMA General Assembly, Tokyo 2004), and including Good Clinical Practices (GCP) according to International Conference on Harmonisation (ICH) guidelines. Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed and approved

14.2 Patient Information and Informed Consent

All parties will ensure protection of patient personal data and will not include patient names on any reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, the sponsor will maintain high standards of confidentiality and protection of patient personal data. Additional patient confidentiality issues are covered in the Clinical Trial Agreement and in the informed consent form signed by the patient.

A properly executed, written, informed consent, in compliance with the Declaration of Helsinki, ICH GCP, United States (US) Code of Federal Regulations (CFR) for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), and local regulations, will be obtained from each patient prior to entering the patient into the trial. The investigator will prepare the informed consent form (ICF) and provide the documents to the IRB and sponsor for review. The investigator will provide copies of the signed ICF to each patient and will maintain copies in the patient's record file.

14.3 Study Monitoring and Auditing

All aspects of the study will be monitored closely by the site PIs and the coordinating

center. Remote monitoring will be conducted according to GCP and standard operating procedures for compliance with applicable government regulations.

14.4 Drug Supply

Astellas/Medivation Inc. will supply enzalutamide. The drug will be shipped directly to the Investigational Pharmacy at the two recruiting sites, which will in turn dispense the medication through the study coordinator to the patient. Dutasteride/Finasteride would be dispensed from a retail pharmacy through a prescription written by the treating provider.

Storage and Labeling

All study drugs shipped to the investigator will be accompanied by a packaging slip which will detail the contents of the shipment. The investigator or the authorized designee must sign and date the form where indicated confirming receipt of the investigational product shipment as listed. This form should be retained for investigators records.

Study drugs will be stored in a secure location with limited access and within the following temperature range: 59°F to 86°F (15°C to 30°C). Bottles will be labeled with the study protocol number, medication or kit number, contents, directions for use, storage directions, clinical trial statement, and sponsor. Patients will be instructed to store study drug at room temperature out of the reach of children. Only authorized site staff may supply or administer investigational product.

Only subjects enrolled in the study should receive the investigational products, in accordance with the applicable regulatory requirements.

14.6 Selection of Timing of Dose for Each Patient

Enzalutamide is administered orally once daily. Enzalutamide should be taken as close to the same time each day as possible and can be taken with or without food. The capsules should be swallowed whole and not chewed or opened

Dutasteride or Finasteride is to be co-administered with enzalutamide and taken once daily as well. The capsules should be swallowed whole and not chewed or opened, as contact with the capsule contents may result in irritation of the oropharyngeal mucosa. Dutasteride can be administered with or without food. **If dosing of either drug is missed on one day for any reason, double-dosing should NOT occur the following day.** Patients should hold their dose of study drug as instructed by the treating physician.

14.7 Investigational Product Accountability

The investigator must maintain accurate records (including dates and lot numbers) of all study drug supplies received. All study drug supplies issued to, used by, and

returned by each patient must be recorded on a Drug Accountability Log completed by the investigator, study coordinator, or pharmacist. All remaining study supplies, opened or unopened, must be returned to the sponsor (or designee) at the end of the study or destroyed on site according to the site's standard operating procedures only after study drug accountability has been completed and with approval of the study PI. All records must be made available to the sponsor (or designee) and appropriate regulatory agencies upon request.

Clinical Procedures
Members of the study staff or their designee(s) will educate the site personnel about the investigational product, protocol requirements, case report forms, monitoring requirements, and reporting of serious adverse events.

To ensure compliance with all applicable regulatory requirements, the sponsor or any regulatory agency may conduct an inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If such an audit were to occur, the investigator and the institution agree to allow the auditor/ inspector direct access to all documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and relevant issues.

14.8 Retention of Records

The investigator must make study data accessible to the authorized representatives of the sponsor (or designee) and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each patient must be maintained that includes the signed informed consent form and copies of all source documentation related to that patient. The investigator must ensure the reliability and availability of source documents from which the information on the case report form was derived.

Patient identity information recorded will be maintained for 15 years on the Patient Confidentiality Log. Investigators must maintain all study documentation for a period of 2 years following the approval date of the drug combination, or until 2 years after the investigational drug program is discontinued. Study documentation includes the Investigator's Brochure, signed protocol and amendments; signed informed consents; notification of serious adverse events and related reports; any dispensing and accountability logs; shipping records of investigational product and trial related materials; documentation of the financial aspects of the trial, insurance statement, and signed agreement between involved parties; dated and documented IRB/IEC approval, and approval of regulatory authority(ies); normal laboratory values; decoding procedures for blinded trials; initiation visit report; curricula vitae and all correspondence pertaining to the conduct of the study. The sponsor will notify the principal investigator when any records may be discarded.

14.9 Data Management

Clinical data management will be performed by the investigator according to procedures described in a comprehensive Data Management Plan that will be subject to review and approval by the Sponsor. The Data Management Plan will include procedures for all aspects of the processing of the data from this study. In particular, the Data Management Plan will include a list of the Standard Operating Procedures that apply to this study. Adverse events and medications will be coded using MedDRA and the World Health Organization Drug Dictionary (WHO-DD), respectively. The Data Management Plan will

include specific details of which version of these dictionaries has been used.

14.10 Study and Site Closure

Following completion of the study, the investigator will conduct the following activities in conjunction with the site staff, as appropriate

- Return of all the study data as appropriate to the Sponsor
- Data queries
- Accountability, reconciliation and arrangements for unused investigational products
- Review of site study records for completion.

If the study is prematurely discontinued, all study data must be returned to the sponsor. In addition, arrangements will be made for all unused investigational products in accordance with the applicable sponsor procedures for the study to be returned.

15.0 BIBLIOGRAPHY

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16.0 APPENDICES

16.1 Appendix A: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Description	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.

16.2 Appendix B. RECIST 1.1 Criteria

	RECIST 1.1
Measurable Disease: Tumor Lesions	Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded with a minimum size of): - 10mm by CT scan (CT scan slice thickness no greater than 5mm) - 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable) - 20mm by chest X-ray
Measurable Disease: Malignant Lymph Node	Sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) Measure **SHORT** axis: - Target lesion if short axis ≥ 1.5cm - Non-target if short axis 1.0 to <1.5cm or pathological - Normal lymph node if short axis <1.0cm Add **ACTUAL** short axis measurement to sum of longest diameters of non-nodal lesions.
Target Lesions	All measurable lesions: - Up to 5 target lesions max in total - Up to 2 target lesions max per organ
Non-Target Lesions	All other lesions (site of disease). Measurements are not required and these lesions should be followed as: - Present - Absent - Unequivocal progression
New Lesions	The appearance of new malignant lesions denotes disease progression.
Methods for Evaluation of Measurable Disease	All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be done

	rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. *Clinical lesions:* Clinical lesions will only be considered measurable when they are superficial and P10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study. *Chest X-ray*: Chest CT is preferred over chest X-ray, particularlywhen progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. *CT, MRI*: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). *Ultrasound:* Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances. *Endoscopy, laparoscopy:* The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained

	or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint. *Tumor markers:* Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer. *Cytology, histology:* These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease. PET/CT: The low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is **of identical diagnostic quality** to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

16.3 Appendix C: CTCAE Version 4.0

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

16.4 Appendix D: Investigators Brochure

Will be provided upon request

16.5 Appendix E: Comprehensive Geriatric assessment tools

Attached to the protocol

16.6 Appendix F: Prohibited Concomitant Medications

Attached to the protocol

Participant ID

Geriatric Assessment for Older Cancer Patients

Orientation-Memory-Concentration Test

Participant Initials

Directions: Please answer the following questions. DO NOT use a pencil, black pen is preferred. Choose only one answer to each question.

		Maximum Errors	Score	x Weight	=	Final Score
1. What year is it now:		1		x 4	=	
2. What month is it now:		1		x 3	=	

Repeat this phrase after me:

John Brown,
42 Market Street,
Chicago

3. About what time is it (within one hour):	:	1		x 3	=
4. Count backwards 20 to 1:		2		x 2	=
5. Say the months in reverse order:		2		x 2	=
6. Repeat the phrase just given:		5		x 2	=

Total error score = /28

Scoring

Items 1 - 3: response correct = 0, incorrect = 1

Items 4 - 6: subtract 1 point for each error (for 4 and 5 max error is 2, for 6 max error is 5)

Total all scores. Greater or equal to 11 equals cognitive impairment

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Participant ID

Geriatric Assessment for Older Cancer Patients
Vulnerable Elder's Survey -13

Participant Initials

Directions: Please answer the following questions. DO NOT use a pencil, black pen is preferred. Choose only one answer to each question.

1a. Age

1b. In general, compared to other people your age, would you say that your health is:

O Poor O Fair O Good O Very good O Excellent

2. How much difficulty, on average, do you have with the following activities:

	No difficulty	A little difficulty	Some difficulty	A lot of difficulty	Unable to do
a. stooping, crouching, or kneeling	O	O	O	O	O
b. lifting, or carrying objects as heavy as 10 pounds	O	O	O	O	O
c. reaching or extending arms above shoulder level	O	O	O	O	O
d. writing, handling, or grasping small objects	O	O	O	O	O
e. walking a quarter of a mile	O	O	O	O	O
f. heavy housework such as scrubbing floors or washing windows	O	O	O	O	O

Because of your health or physical condition, do you have any difficulty:

3. shopping for personal items (like toilet items or medicines)?

O Yes — If yes, do you get help with shopping? O yes O no

O No

O Don't do — If don't do, is that because of your health? O yes O no

4. managing money (like keeping track of expenses or paying bills)?

O Yes — If yes, do you get help with managing money? O yes O no

O No

O Don't do — If don't do, is that because of your health? O yes O no

5. walking across the room? (Use of a cane or walker is ok.)

O Yes — If yes, do you get help with walking? O yes O no

O No

O Don't do — If don't do, is that because of your health? O yes O no

6. doing light housework (like washing dishes, straightening up, or light cleaning)?

O Yes — If yes, do you get help with light housework? O yes O no

O No

O Don't do — If don't do, is that because of your health? O yes O no

7. bathing or showering?

O Yes — If yes, do you get help with bathing or showering? O yes O no

O No

O Don't do — If don't do, is that because of your health? O yes O no

Total Score:

Participant I.D. | Geriatric Assessment for Older Cancer Patients | Participant Initials

Instrumental Activities of Daily Living

Instructions: Please check one response for each question.

1) Can you use the telephone...

☐ Without help, including looking up and dialing

☐ With some help (can answer phone in an emergency, but need a special phone or help in getting the number or dialing)

☐ Are you completely unable to use the telephone

2) Can you get to places out of walking distance...

☐ Without help (drive your own car, or travel alone on buses, or taxis);

☐ With some help (need someone to help you or go with you when traveling); or

☐ Are you unable to travel unless emergency arrangements are made for a specialized vehicle like an ambulance?

3) Can you go shopping for groceries or clothes (assuming subject has transportation)...

☐ Without help (taking care of all shopping needs yourself, assuming you had transportation);

☐ With some help (need someone to go with you on all shopping trips); or

☐ Are you completely unable to do any shopping

4) Can you prepare your own meals...

☐ Without help (plan and cook full meals yourself);

☐ With some help (can prepare some things but unable to cook full meals yourself);

☐ Are you completely unable to prepare any meals?

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5) Can you do your housework...

☐ Without help (can clean floors, etc.);

☐ With some help (can do light housework but need help with heavy work); or

☐ Are you completely unable to do any housework?

6) Can you take your own medicines...

☐ Without help (in the right doses at the right time)

☐ With some help (able to take medicine if someone prepares it for you and/or reminds you to take it); or

☐ Are you completely unable to take your medicines?

7) Can you handle your own money...

☐ Without help (write checks, pay bills, etc.);

☐ With some help (manage day-to-day buying but need help with managing your checkbook and paying your bills); or

☐ Are you completely unable to handle money?

Participant I.D.

Geriatric Assessment for Older Cancer Patients

Participant Initials

Comorbidity

Instructions: We would like to ask you a few questions about any health problems you might have. Do you have any of the following illnesses at the present time? Please circle the appropriate response (yes or no). If you circle "yes" please tell us how much the illness interferes with your activities: Not at All, Somewhat , or A Great Deal. Circle the appropriate response.

			IF YOU HAVE THIS ILLNESS: How much does it interfere with your activities?		
Illness	No	Yes	Not at All	Somewhat	A Great Deal
1. Other cancer or leukemia	1	2	1	2	3
2. Arthiritis or rheumatism	1	2	1	2	3
3. Glaucoma	1	2	1	2	3
4. Emphysema or chronic bronchitis	1	2	1	2	3
5. High blood pressure	1	2	1	2	3
6. Heart disease	1	2	1	2	3
7. Circulation trouble in arms or legs	1	2	1	2	3
8. Diabetes	1	2	1	2	3
9. Stomach or intestinal disorders	1	2	1	2	3
10. Osteoporosis	1	2	1	2	3
11. Chronic Liver or kidney disease	1	2	1	2	3
12. Stroke	1	2	1	2	3
13. Depression	1	2	1	2	3

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Comorbidity

14a. How is your eyesight (with glasses or contacts)?

☐ Excellent ☐ Poor

☐ Good ☐ Totally blind

☐ Fair

14b. (If Fair to Totally Blind): How much does it interfere with your activities?

☐ Not at all

☐ Somewhat

☐ A great deal

15a. How is your hearing (with a hearing aid, if needed)?

☐ Excellent ☐ Poor

☐ Good ☐ Totally deaf

☐ Fair

15b. (If Fair to Totally Deaf): How much does it interfere with your activities?

☐ Not at all

☐ Somewhat

☐ A great deal

Nutritional Status

1. Have you lost weight involuntarily over the past 6 months? ☐ Yes ☐ No

If yes, how much? ☐☐☐

2. What is your weight now? ☐☐☐

3. What was your weight 6 months ago? ☐☐☐

Participant ID

Geriatric Assessment for Older Cancer Patients
OARS Medical Social Support

Participant Initials

Directions: Please answer the following questions. DO NOT use a pencil, black pen is preferred. Choose only one answer to each question.

1. About how many close friends and close relatives do you have now (people you feel at ease with and can talk to about what is on your mind)?

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
2. someone to help if you were confined to bed	O	O	O	O	O
3. someone you can count on to listen to you when you need to talk	O	O	O	O	O
4. someone to give you good advice about a crisis	O	O	O	O	O
5. someone to take you to the doctor if needed	O	O	O	O	O
6. someone to give you information to help you understand a situation	O	O	O	O	O
7. someone to confide in or talk to about yourself or your problem	O	O	O	O	O
8. someone to prepare your meals if you were unable to do it yourself	O	O	O	O	O
9. someone whose advice you really want	O	O	O	O	O
10. someone to help you with daily chores if you were sick	O	O	O	O	O
11. someone to share your most private worries and fears with	O	O	O	O	O
12. someone to turn to for suggestions about how to deal with a personal problem	O	O	O	O	O
13. someone who understands your problems	O	O	O	O	O

Participant I.D.

Geriatric Assessment for Older Cancer Patients

Social Activities

Participant Initials

Instructions: Please check one response for each question.

1) During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- ☐ All of the time
- ☐ Most of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ None of the time

2) Compared to your usual level of social activity, has your social activity during the past 6 months decreased, stayed the same, or increased because of a change in your physical or emotional condition?

- ☐ Much less socially active than before
- ☐ Somewhat less socially active than before
- ☐ About as socially active as before
- ☐ Somewhat more socially active as before
- ☐ Much more socially active than before

3) Compared to others your age, are your social activities more or less limited because of your physical health or emotional problems?

- ☐ Much more limited than others
- ☐ Somewhat more limited than others
- ☐ About the same as others
- ☐ Somewhat less limited than others
- ☐ Much less limited than others

4) During the last 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- ☐ Not at all
- ☐ Slightly
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely

Physical Activity

Instructions: The following items are activities you might do during a typical day. Does your health limit you in these activities? Please circle the appropriate answer.

Activities	Limited a Lot	Limited a Little	Not Limited at All
1. Vigorous activities, such as running, lifting heavy objects, participating in strenuous activities	1	2	3
2. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
3. Lifting or carrying groceries	1	2	3
4. Climbing several flights of stairs	1	2	3
5. Climbing one flight of stairs	1	2	3
6. Bending, kneeling, or stooping	1	2	3
7. Walking more than a mile	1	2	3
8. Walking several blocks	1	2	3
9. Walking one block	1	2	3
10. Bathing or dressing yourself	1	2	3

Participant ID

Geriatric Assessment for Older Cancer Patients
RAPA Survey

Participant Initials

How physically active are you? (Check one answer on each line)

RAPA 1

		Does this accurately describe you?
1.	I rarely or never do any physical activities.	☐ Yes ☐ No
2.	I do some light or moderate physical activities, but not every week.	☐ Yes ☐ No
3.	I do some light physical activity every week.	☐ Yes ☐ No
4.	I do moderate physical activities every week, but less than 30 minutes a day or 5 days a week.	☐ Yes ☐ No
5.	I do vigorous physical activities every week, but less than 20 minutes a day or 3 days a week.	☐ Yes ☐ No
6.	I do 30 minutes or more a day of moderate physical activities, 5 or more days a week.	☐ Yes ☐ No
7.	I do 20 minutes or more a day of vigorous physical activities, 3 or more days a week.	☐ Yes ☐ No

RAPA 2

1.	I do activities to increase muscle strength, such as lifting weights or calisthenics, once a week or more.	☐ Yes ☐ No
2.	I do activities to improve flexibility, such as stretching or yoga, once a week or more.	☐ Yes ☐ No

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Participant I.D.

Geriatric Assessment for Older Cancer Patients

Participant Initials

Falls

Place an 'X' in one (1) answer to each question.

1. In the past year, have you fallen down?

☐ Yes ☐ Refused
☐ No ☐ Don't Know

If you answered yes to question one, please complete the rest of this page.

2. About how long ago was your most recent fall? ☐☐ months ago

3. In the past year, how many times have you fallen down?

☐☐☐

○ Refused
○ Don't Know

4. In that fall or any of those falls, did you hurt yourself badly enough to get medical help?

☐ Yes ☐ Refused
☐ No ☐ Don't Know

5. Did you talk to a doctor or other medical professional about that fall or any of those falls?

☐ Yes ☐ Refused
☐ No ☐ Don't Know

6. Did the health care provider talk with you to understand why you fell?

☐ Yes ☐ Refused
☐ No ☐ Don't Know

7. Did the health care provider talk with you about how to prevent future falls?

☐ Yes ☐ Refused
☐ No ☐ Don't Know

Participant I.D. | Participant Initials

Geriatric Assessment for Older Cancer Patients

Geriatric Depression Scale

Instructions: Please check one response for each question.

1. Are you basically satisfied with your life?	☐ Yes ☐ No
2. Have you dropped many of your activities and interests?	☐ Yes ☐ No
3. Do you feel that your life is empty?	☐ Yes ☐ No
4. Do you often get bored?	☐ Yes ☐ No
5. Are you in good spirits most of the time?	☐ Yes ☐ No
6. Are you afraid that something bad is going to happen to you?	☐ Yes ☐ No
7. Do you feel happy most of the time?	☐ Yes ☐ No
8. Do you often feel helpless?	☐ Yes ☐ No
9. Do you prefer to stay home, rather than going out and doing new things?	☐ Yes ☐ No
10. Do you feel you have more problems with memory than most?	☐ Yes ☐ No
11. Do you think it is wonderful to be alive now?	☐ Yes ☐ No
12. Do you feel pretty worthless the way you are now?	☐ Yes ☐ No
13. Do you feel that your life is full of energy?	☐ Yes ☐ No
14. Do you feel that your situation is hopeless?	☐ Yes ☐ No
15. Do you think that most people are better off than you are?	☐ Yes ☐ No

Participant ID

Geriatric Assessment for
Older Cancer Patients

Participant Initials

Sarcopenia

How severe are your symptoms? People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms were ***during the last 7 days.*** Please circle the number below from " 0 " (symptom is not present) to " 10 " (as bad as you can imagine it could be) for each symptom.

	No Difficulty										Extreme Difficulty
1. How much difficulty did you have walking at your usual speed?	0	1	2	3	4	5	6	7	8	9	10
2. How much difficulty did you have walking a distance, for example, walking 100 yards or the length of a football field?	0	1	2	3	4	5	6	7	8	9	10
3. How much difficulty did you have walking in a straight line, for example, down a hallway?	0	1	2	3	4	5	6	7	8	9	10
4. How much difficulty did you have walking without stumbling?	0	1	2	3	4	5	6	7	8	9	10
5. How much difficulty did you have going up and down stairs (a flight of stairs or 12 steps)?	0	1	2	3	4	5	6	7	8	9	10

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Sarcopenia

	No Difficulty										Extreme Difficulty
6. How much difficulty did you have standing for 15 minutes without a break?	0	1	2	3	4	5	6	7	8	9	10
7. How much difficulty did you have getting up from a sitting position?	0	1	2	3	4	5	6	7	8	9	10
8. How much difficulty did you have bending to pick up an object off the floor from a standing position?	0	1	2	3	4	5	6	7	8	9	10
9. How much difficulty did you have opening jars that have never been opened?	0	1	2	3	4	5	6	7	8	9	10
10. How much difficulty did you have lifting objects that weigh about 10 pounds, for example, a bag of potatoes?	0	1	2	3	4	5	6	7	8	9	10

Sarcopenia

Please consider the loss of your muscle strength when answering these questions.

If you routinely use devices or aids, please consider your use of those aids when answering the questions; however, please do not consider help from anyone else when answering the questions.

	No Difficulty										Extreme Difficulty
11. How much difficulty did you have doing your usual household activities without resting?	0 ○	1 ○	2 ○	3 ○	4 ○	5 ○	6 ○	7 ○	8 ○	9 ○	10 ○
12. How much difficulty did you have completing a physical activity without resting?	0 ○	1 ○	2 ○	3 ○	4 ○	5 ○	6 ○	7 ○	8 ○	9 ○	10 ○
13. How much difficulty did you have doing social activities outside your home, such as going out to eat with others?	0 ○	1 ○	2 ○	3 ○	4 ○	5 ○	6 ○	7 ○	8 ○	9 ○	10 ○

Participant I.D.

Geriatric Assessment for Older Cancer Patients

Participant Initials

Symptom Inventory

Please tell us about the **severity** of any of the following symptoms that you might have experienced during the last **week** by filling in one circle, from " 0 " (symptom is not present) to " 10 " (as bad as you can imagine it could be), for each of these possible symptoms.

Date ☐☐/☐☐/☐☐

	Not Present										As Bad As You Can Imagine
1. Your pain at its WORST?	O	O	O	O	O	O	O	O	O	O	O
2. Other pain	O	O	O	O	O	O	O	O	O	O	O
3. Your nausea at its WORST?	O	O	O	O	O	O	O	O	O	O	O
4. Your disturbed sleep at its WORST?	O	O	O	O	O	O	O	O	O	O	O
5. Your feelings of being distressed (upset) at its WORST	O	O	O	O	O	O	O	O	O	O	O
6. Your shortness of breath at its WORST?	O	O	O	O	O	O	O	O	O	O	O
7. Your problem with remembering things at its WORST?	O	O	O	O	O	O	O	O	O	O	O
8. Your problem with lack of appetite at its WORST?	O	O	O	O	O	O	O	O	O	O	O
9. Your feeling drowsy (sleepy) at its WORST?	O	O	O	O	O	O	O	O	O	O	O
10. Your having a dry mouth at its worst?	O	O	O	O	O	O	O	O	O	O	O
11. Your feeling sad at its WORST?	O	O	O	O	O	O	O	O	O	O	O
12. Your vomiting at its WORST	O	O	O	O	O	O	O	O	O	O	O
13. Your numbness or tingling at its WORST?	O	O	O	O	O	O	O	O	O	O	O

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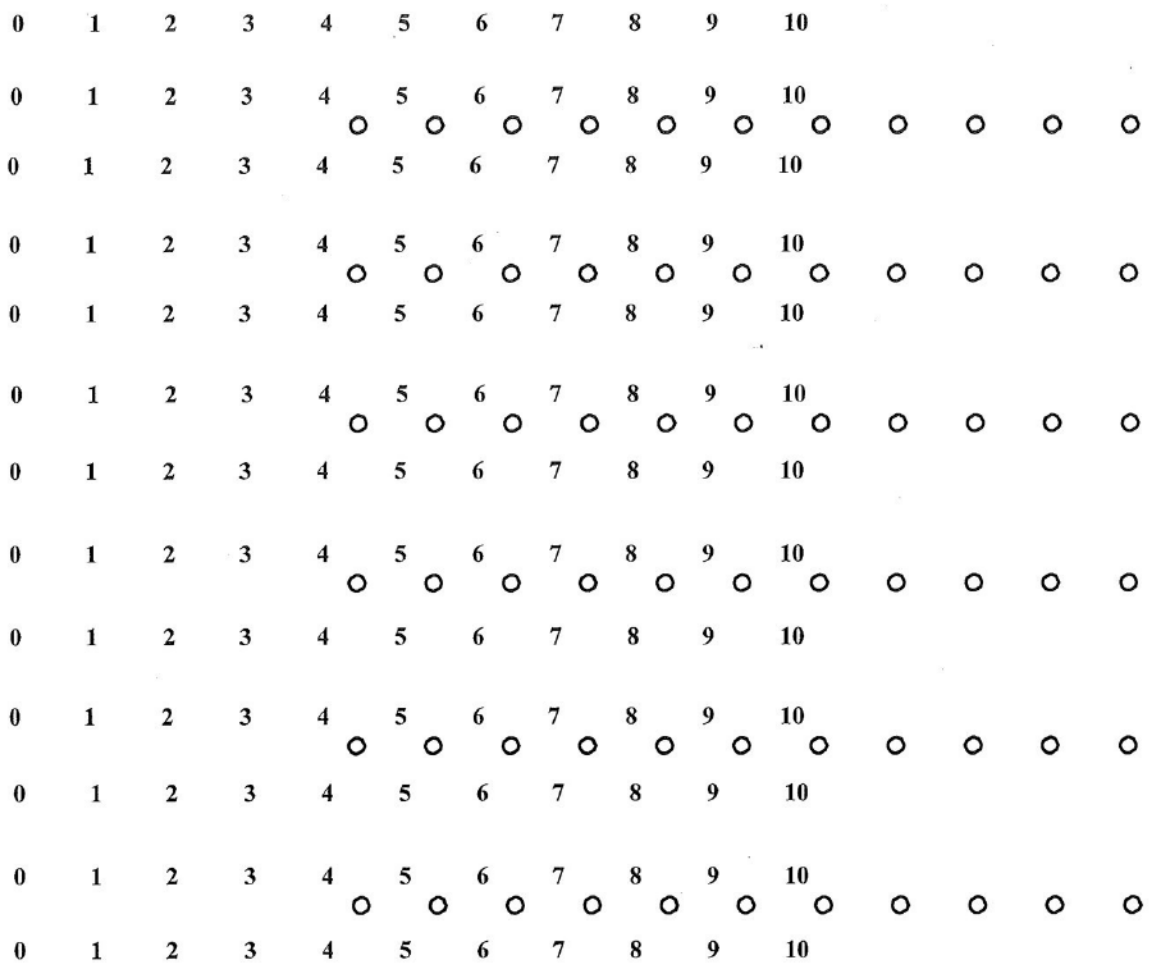

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Geriatric Assessment for Older Cancer Patients

Participant Initials

Symptom Inventory

We want to know if disease or treatment-related symptoms are causing you discomfort or interfere with your lifestyle.

Please rate how much symptoms have interfered with the following items during the last week. Fill in one circle, from " 0 " (did not interfere) to " 10 " (interfered completely), for each item.

1. General Activity	0	1	2	3	4	5	6	7	8	9	10
2. Mood	0 ○	1 ○	2 ○	3 ○	4 ○	5 ○	6 ○	7 ○	8 ○	9 ○	10 ○
3. Work (including work around the house)	0	1	2	3	4	5	6	7	8	9	10
4. Relations with other people	0 ○	1 ○	2 ○	3 ○	4 ○	5 ○	6 ○	7 ○	8 ○	9 ○	10 ○
5. Walking	0	1	2	3	4	5	6	7	8	9	10
6. Enjoyment of life	0 ○	1 ○	2 ○	3 ○	4 ○	5 ○	6 ○	7 ○	8 ○	9 ○	10 ○


ADL.pdf


FACT-P.pdf


Medication List.pdf


MNA_BMI.pdf


MOCA v. 8.1.pdf


SPPB.pdf

APPENDIX F. Strong and Moderate CYP2C8 and CYP 3A4 Inducers and Inhibitors

NOTE: This list may not be comprehensive – review each patient's medications prior to enrollment and at every clinic visit.

CYP2C8 Strong & Moderate INDUCERS	CYP2C8 Strong & Moderate INHIBITORS	CYP3A4 Strong & Moderate INDUCERS	CYP3A4 Strong & Moderate INHIBITORS∞
Carbamazepine Phenobarbital Phenytoin Primidone Rifampin	Efavirenz Gemfibrozil Montelukast Pioglitazone Trimethoprim	Carbamazepine Efavirenz Phenobarbital Phenytoin Primidone Rifabutin	Aprepitant Atazanavir Clarithromycin Conivaptan Darunavir Diltiazem

		Rifampin St. John's Wort	Erythromycin Fluconazole Fosamprenavir Grapefruit Juice Indinavir Itraconazole Ketoconazole Nefazodone Nelfinavir Posaconazole Ritonavir Saquinavir Telithromycin Verapamil Voriconazole

¡ ∞CYP3A4 Strong & Moderate Inhibitors applies to dutasteride/enzalutamide combination therapy only, and not finasteride / enzalutamide combination therapy