COMIRB PROTOCOL #: **14-0909**

PROTOCOL VERSION: **April 27, 2018**

PROTOCOL TITLE: An open label, randomized, Phase II trial of Metabolic complications in patients treated with enzalutamide vs standard ADT for the treatment of hormone sensitive prostate cancer

NCT02278185

COORDINATING CENTER: *University of Colorado Cancer Center*

LEAD PRINCIPAL INVESTIGATOR: *Elizabeth Kessler, MD*

University of Colorado Denver, Division of Medical Oncology

12801 East 17th Avenue, MS 8117

Aurora, CO 80045

Phone: 720-848-0402

Fax: 303-724-3889

Elizabeth.kessler@ucdenver.edu

Statistician:

Dexiang Gao, PhD

Protocol Summary

An open label, randomized, Phase II trial of Metabolic complications in patients treated with enzalutamide vs standard ADT for the treatment of hormone sensitive prostate cancer	
Primary Objective	To determine the incidence of metabolic syndrome within 12 months, as defined by the Adult Treatment Panel III, in patients treated with enzalutamide compared to standard androgen deprivation therapy.
Secondary Objectives	In patients on enzalutamide versus traditional ADT: - To determine the incidence of metabolic syndrome within 6 months, as defined by the Adult Treatment Panel III, in patients treated with enzalutamide compared to standard androgen deprivation therapy. - To assess bone health, as measured by a DXA scanner - To assess body composition (sarcopenic obesity), as measured by cross sectional CT analysis - To assess QOL, as measured by the FACT-P and SHIM - To assess time to PSA progression and time to radiographic progression. Progression will be defined as lack of clinical benefit in the setting of either rising PSA, growth of visceral or soft tissue metastasis, or development of new bone metastasis as defined per protocol - To assess the incidence of developing individual risk factors, or components, which comprise metabolic syndrome - To assess the safety and tolerance of enzalutamide or ADT - To assess the change in hs-CRP as a marker of inflammation - To assess the change in physical function as measured by the Short Physical Performance Battery
Study Population	Patients with biochemically recurrent disease, metastatic disease, and patients offered ADT as primary therapy if they are not candidates for local therapy.
Other Participating Site (enrolling subjects)	University of Colorado Health - Poudre Valley Hospital (UCH-North) Site Principal Investigator: Steven Schuster, MD
STUDY DESIGN	
Multi-center, open label, randomized, phase II trial evaluating the incidence of metabolic syndrome within 12 months in patients treated with enzalutamide in comparison with androgen deprivation therapy for treatment of advanced prostate cancer. Enzalutamide 160mg orally daily versus standard androgen deprivation therapy. Acceptable forms of ADT will be specified and this therapy must result in castrate levels of testosterone. Patients will be treated for a 12-month period and assessed for the development of metabolic syndrome at 3 month intervals. Patients with continued clinical benefit beyond the 12-month endpoint may continue on their assigned treatment through standard of care prescribing methods.	

TABLE 1: Schedule of Events	**Screening** Day 0	**Start of Treatment** Month 1, Day1[2]	Month 2, Day1	Month 4, Day 1	Month 7, Day 1	Month 10, Day 1	Month 13, Day 1 End of Treatment	End of study[6]
Informed Consent	X							
VISIT ASSESSMENTS								
Adverse events assessment	X	X	X	X	X	X	X	X
Review medication list	X	X	X	X	X	X	X	X
Physical Exam and history	X	X	X	X	X	X	X	X
Vital signs, including weight, waist circumference	X	X	X	X	X	X	X	X
Height	X							
Performance Status	X	X	X	X	X	X	X	X
LABORATORY STUDIES								
CBC, Comprehensive metabolic panel (fasting for glucose)	X[1]	X	X	X	X	X	X	X[8]
PSA	X	X[7]	X	X	X	X	X	
Lipid Profile (including triglycerides and HDL)	X			X	X	X	X	
N-Telopeptide, Bone specific alkaline phosphatase, hs-CRP, estradiol		X		X	X	X	X	
Testosterone	X		X	X	X	X	X	
25-OH Vitamin D	X				X		X	
IMAGING								
Fill out QOL questionnaires (FACT – P and SHIM)		X		X	X	X	X	
Bone densometry (DXA)		X[9]		X			X[9]	
CT scan of chest, abdomen, pelvis[3, 4]	X				X		X	
Nuclear Bone scan[3,4]	X				X		X	
TREATMENT								
Enzalutamide dosed at 160mg po daily		X	X	X	X	X		
GNRH agonist/antagonist (Standard of care)		X	X	X	X	X		
Calcium/Vitamin D[5]		X	X	X	X	X		
OTHER								
Short physical performance battery		X		X	X	X	X	
Optional biomarker blood testing (3 tubes, see lab manual)		X		X	X	X	X	

1 May be performed from day -14 to 0. Screening is day 0.
2 Day 1 Month 1 must occur with 21 days of screening. Visit days of the remaining months must occur +/- 5 days to date on the calendar.
3 May be performed Day - 28 - Day 0
4 Also to be performed during treatment to evaluate a rising PSA. CT chest combined with MRI of the abdomen/pelvis is also accepted.
5 At least 1000mg of calcium and 800 International Units (IU) of vitamin D

6. Safety visit to be performed within 30 days from last study drug dose, or prior to starting a new treatment, whichever is sooner
7 If screening PSA is within 5 days of Day 1, repeat testing is not necessary
8 Glucose does not have to be fasting
9 Please see protocol for windows as DXA and NM bone scan need 14 days of separation if bone scan is performed first

Table of Contents

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
ADT	Androgen deprivation therapy
AE	Adverse event
AUC	Area under the plasma concentration versus time curve
$AUC_{0\text{-}inf}$	Area under the plasma concentration versus time curve zero to infinity
CRPC	Castrate resistant prostate cancer
CBC	Complete blood count
CI	Confidence interval
hs-CRP	C-reactive protein
CrCL	Creatinine clearance
CL/F	Apparent oral clearance
C_{max}	Maximum plasma concentration
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P_{450}
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
DXA	Dual-energy x-ray absorptiometry scan
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOS	End of study
FACT-P	Functional assessment of cancer therapy-prostate
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
FSH	Follicle stimulating hormone
GABA	Gamma-aminobutyric acid
GnRH	Gonadotropin releasing hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
HDL	High density lipoprotein
HIPAA	Health insurance portability and accountability act
HR	Hazard ratio

Abbreviation	Term
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational new drug
IRB	Institutional Review Board
IU	International units
LDL	Low density lipoprotein
LH	Leutinizing hormone
LHRH	Leutinizing hormone releasing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse
NYHA	New York Heart Association
PI	Principal investigator
PD	Progressive disease
PFS	Progression-free survival
PSA	Prostate specific antigen
PCWG2	Prostate Cancer Working Group 2
QOL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SPPB	Short physical performance battery
SRE	Skeletal related event
SUSAR	Serious Unexpected Suspect Adverse Reaction
SHIM	Sexual Health Inventory in Men
$T_{1/2}$	Terminal half life
UCH-North	University of Colorado Health – Poudre Valley Hospital
ULN	Upper limit of the normal range
V/F	Volume of distribution
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Prostate cancer

Prostate cancer is the most common non-cutaneous cancer in men in the United States, and the second leading cause of cancer death in US men[1]. As many as three-quarters of prostate cancer patients present with localized disease yet a good proportion have recurrent or metastatic disease requiring systemic treatment with androgen deprivation therapy (ADT).

1.2 Androgen deprivation therapy and metabolic syndrome

While many new agents have been developed for the treatment of prostate cancer, these focus on treatment in the metastatic, castrate-resistant setting. Patients requiring systemic therapy for prostate cancer continue to be initially treated with traditional gonadotropin hormone analogues, despite advances in therapeutic development. The treatment is very effective with survival results mainly impacted by disease state at initiation. The average time from biochemical recurrence, or prostate specific antigen (PSA) relapse, to development of metastatic disease is approximately 8 years [2] and survival for patients with metastatic disease on ADT is approximately 30 months. The median time of response for patients with biochemically relapsed disease treated with ADT is 10.8 months [3]. Thereafter, patients remain on ADT in combination with other therapies for the duration of their anti-cancer therapy, which may be years. Men treated with ADT experience long-term adverse effects such as fatigue, loss of muscle mass (i.e. sarcopenia), loss of bone density, increased adiposity, development of metabolic syndrome, depression, sexual dysfunction and poor quality of life (QOL)[4-13]. Men treated with ADT had lower levels of self-reported physical function and QOL in comparison to age-matched controls [8,10,14-17]. These effects are profound for any patients but may be felt to a larger degree in the standard older patient population afflicted with prostate cancer, already dealing with the changes of decreasing functional reserve.

1.3 Metabolic syndrome

One of the long term sequelae of ADT is the development of metabolic syndrome. While many definitions exist, "metabolic syndrome" broadly encompasses reduced insulin sensitivity and increasing body mass. The syndrome itself imposes a higher risk of cardiovascular disease and diabetes which subsequently impact mortality risk [18]. Metabolic syndrome is a common health problem in the United States with a distant evaluation of the prevalence estimated at over 40% for persons over the age of 60 with more recent updates suggesting that the incidence is increasing [19]. This is the same age group most likely to be affected by prostate cancer. A long term hypogonadal state, such as is induced by prostate cancer therapy, has been shown to independently predict the development of metabolic syndrome, and patients with metabolic syndrome have a 3 times greater risk of death from cardiovascular disease than healthy counterparts [20,21]. There are data supporting the role of hypogonadism in independently increasing the risk of many of the components of metabolic syndrome such as dyslipidemia, hypertension, alterations in body mass and glucose intolerance, and that these parameters may change as early as 3-6 months after the initiation of therapy [7,22-25]. Population-based analyses have shown a higher incidence of diabetes and coronary disease in patients treated with ADT [26,27]. Cross sectional studies have shown that men with prostate cancer treated with ADT are twice as likely to meet the criteria for metabolic syndrome in comparison to matched prostate cancer patients or healthy controls[7]. Unlike many cancer treatments, patients remain on ADT for years, allowing for the development of long-term sequelae, which impact a patient's global health and quality of life during survivorship and may contribute to overall mortality in equal parts as the cancer.

1.4 Rationale for study design

Improved understanding of the biology of prostate cancer has allowed for the development of agents, which more effectively manipulate the androgen axis even under castrate conditions. Not only reduction in circulating testosterone, but also improved blockade of the androgen receptor has led to an improvement in survival for patients with metastatic castrate resistant prostate cancer (CRPC). The development of a new generation of agents, such as enzalutamide, that preserve circulating testosterone levels while acting on the androgen receptor, provide new therapeutic opportunities for an active single agent with the potential for a reduction of the long term effects associated with ADT. Single agent data of enzalutamide reveals an excellent PSA response and tolerance profile[28] Preservation of these hormone levels may delay the adverse effects associated with long term ADT that contribute to development of metabolic syndrome.

The influence of the adverse events associated with newer agents on a patient's QOL is increasingly used to guide cancer care [29], and understanding the comparative effectiveness of agents is important. Men with prostate cancer have higher rates of noncancerous mortality than men in the general population, perhaps due to the contribution of the hypogonadal state in worsening common causes of death such as heart disease and diabetes. The clustering of cardiovascular risk factors, which occurs with ADT, may not be found in patients treated with enzalutamide due to its preservation ofsystemic testosterone levels. There has not been a longitudinal analysis of the development of metabolic syndrome in patients on ADT, nor a structured evaluation of the development of metabolic syndrome, or metabolic changes in patients treated with enzalutamide. This protocol will evaluate the effect of androgen blockade via enzalutamide versus traditional ADT on development of metabolic syndrome, changes in body composition, changes in quality of life, and changes in physical function in patients with advanced prostate cancer.

1.5 Enzalutamide

Enzalutamide is a non-steroidal anti-androgen that blocks the ability of testosterone to signal through the androgen receptor. Enzalutamide has no known agonistic properties even when the androgen receptor is overexpressed as supported in preclinical models of CRPC. Enzalutamide is currently approved by the FDA for treatment of men with metastatic prostate cancer that have previously been treated with docetaxel chemotherapy. In the AFFIRM trial, which led to this approval, patients received enzalutamide 160mg/day orally or placebo [30]. The study showed a survival advantage for patients treated with enzalutamide of 18.4 months in comparison to 13.6-months (hazard ratio (HR) 0.631 [95% CI: 0.529-0.752], $p< 0.0001$). Other endpoints of radiographic progression free survival (PFS), 8.3 versus (vs) 2.9 months; hazard ratio (HR) 0.40, $p< 0.001$ and PSA response 54% vs 2%, $p< 0.001$were also significantly improved in those receiving enzalutamide. The AFFIRM trial also supported an improved QOL in the enzalutamide treated group as well as improvement in time to first skeletal-related event (SRE) (16.7 vs 13.3 months; HR 0.69, $p< 0.001$). In addition, the PREVAIL trial is studying enzalutamide versus placebo in men with metastatic castrate resistant prostate cancer that have not yet been treated with chemotherapy and has reported promising results that will likely lead to its approval [31].

Ongoing studies of enzalutamide are evaluating its efficacy earlier in the treatment spectrum. The Phase II, STRIVE trial is evaluating the efficacy of enzalutamide for patients that may have castrate resistant disease with metastatic and non-metastatic CRPC (NCT01664923). In addition, there was a relatively small phase II trial evaluating the use of enzalutamide prior to the initiation of traditional testosterone-lowering agents [32]. This single agent trial was conducted in 67 men without previous exposure to ADT with a primary endpoint of PSA response defined as an 80% decline from baseline. Monotherapy with enzalutamide was highly effective, with a median PSA decrease of 99.6% seen,

and 92.5% of patients achieving the primary endpoint at week 25. The trial enrolled patients with and without metastatic disease at baseline.

In the randomized clinical trial in patients with metastatic castration-resistant prostate cancer who had previously received docetaxel, 1200 patients were enrolled. The most common adverse drug reactions (≥ 5%) reported in patients receiving enzalutamide in the randomized clinical trial were asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension [33]. Severe, grade ≥3 adverse events, were reported in 47% patients receiving enzalutamide and 53% of patients receiving placebo. The most common adverse reaction leading to treatment discontinuation in the enzalutamide treated group was seizure, which occurred in 0.9% of the enzalutamide-treated patients compared to none (0%) of the placebo-treated patients. In the Phase III trial, 7 of 800 patients treated with enzalutamide experienced a seizure in comparison to 0 events in the placebo arm. The seizures occurred days 31-603 after drug initiation. No further seizures occurred after patients discontinued enzalutamide. Patients were never readministered enzalutamide while on study, and patients with a history of seizure have been excluded in additional studies. It is thought that the mechanism of seizure may be the inhibition of the GABA-gated chloride channel. It is suggested that enzalutamide may lower the seizure threshold but not directly contribute to these events. This trial will exclude patients with a predisposition to seizure, as the exclusion of this subset of patients should not have a known impact on altering the incidence of metabolic syndrome. Another notable adverse event associated with the enzalutamide treatment arm is fall and fall-related injuries. This occurred in 4.6% of patients enrolled in the randomized trial and assigned to the enzalutamide treatment group in comparison to 1.3% of patients treated with placebo. The mechanism of fall is not clear. Fall-related injuries are described as joint injuries, non-pathologic fractures, and hematomas.

Very few laboratory abnormalities were seen in patients treated with enzalutamide. Neutropenia of all grades occurred in 15% of patients on enzalutamide (1% Grade 3-4). The incidence of thrombocytopenia was similar in the treatment and placebo arms (0.5% on enzalutamide v 1% on placebo). Elevation in transaminases occurred in 10% of patients on enzalutamide (0.3% Grade 3-4) and 18% of patients on placebo (0.5% Grade 3-4), with elevations in bilirubin occurring in 3% v 2 % on placebo.

1.6 Androgen deprivation therapy

Standard androgen deprivation therapy is a broad term encompassing any agent, or method, which invokes a castrate state for the treatment of prostate cancer. Medical therapy generally includes a gonadotropin releasing hormone (GnRH) analogue (agonist or antagonist) with a lowering of testosterone to castrate levels as the primary result of treatment. The agonists bind to the GnRH receptors in the pituitary to alter release of luteinizing and follicle stimulating hormones (LH and FSH) and eventually alter the feedback loop. A GnRH antagonist suppresses testosterone while avoiding the initial flare in testosterone seen with the administration of GnRH agonist. Examples of currently available formulations include: degarelix, goserelin, leuprolide, triptorelin, and histerelin. Surgical castration by means of an orchiectomy also reduces overall testosterone production. Hormone therapy is palliative in nature but has been shown to have a significant effect on the morbidity and mortality of prostate cancer. Notable side effects include sexual dysfunction, osteoporosis, sarcopenic obesity, increase in cardiovascular risk factors and diabetes, vasomotor symptoms, fatigue and alterations in cognition.

1.7 Nonclinical Experience

1.7.1 Drug Metabolism and Pharmacokinetics

Enzalutamide alters the functioning of the androgen receptor-signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors and to inhibit the translocation of the receptor to the nucleus and subsequent DNA binding. The phase I, first-in-human trial of enzalutamide (or MDV3100) enrolled 140 patients with CRPC [34]. Dosing ranged from 30 to 600 milligrams (mg)/day with the maximum tolerated dose (MTD) determined as 240 mg orally per day. The recommended phase II dose was 160 mg/day.

The major active metabolite of enzalutamide is N-desmethyl enzalutamide. The pharmacokinetics of enzalutamide and this metabolite have been evaluated in healthy male volunteers or men with castrate-resistant metastatic prostate cancer [33]. A linear two-compartment model with first-order absorption adequately described. Following oral administration, the median time to reach maximum plasma enzalutamide concentrations (C_{max}) is 1 hour. The mean steady state C_{max} values are 16.6 μg/mL for enzalutamide and 12.7 μg/mL for N-desmethyl enzalutamide. The mean predose trough values are 11.4 μg/mL and 13.0 μg/mL, respectively. With the approved dosing schedule, steady state is reached in 28 days due to the long half-life ($t_{1/2}$) of 5.8 days. At steady state, enzalutamide showed approximately dose proportional pharmacokinetics. The mean apparent volume of distribution (V/F) of enzalutamide in patients after a single oral dose is 110 L. Enzalutamide is 98% bound to plasma proteins. N-desmethyl enzalutamide is 95% bound to plasma proteins.

Plasma samples were analyzed after a single oral administration of 160mg of carbon-labeled enzalutamide. Enzalutamide, N-desmethyl enzalutamide, and an inactive carboxylic acid metabolite accounted for 30%, 49%, and 10%, respectively, of the total AUC. Based on *in vivo* and *in vitro* data, CYP2C8 is primarily responsible for the formation of N-desmethyl enzalutamide, but *in vitro* data suggests the CYP3A4 is partially responsible for metabolism.

Enzalutamide is primarily eliminated by hepatic metabolism. The majority of elimination is through the urine (71% from one study) with 14% through feces. The mean apparent clearance (CL/F) of enzalutamide in patients after a single oral dose is 0.56 L/hour.

Based on limited data, the apparent clearance of enzalutamide is similar in patients with pre-existing mild and moderate renal impairment (CrCL 30 to < 90 mL/minute) compared to patients and volunteers with normal renal function. There are insufficient data to describe the potential effect of more severely impaired renal function on the clearance of enzalutamide. Hepatic function abnormalities of mild or moderate grade do not affect the area under the curve (AUC) of enzalutamide or its active metabolite.

1.8 Toxicology

1.8.1 Drug-Drug Interaction Risk Assessment

In a drug-drug interaction trial in healthy volunteers, a single 160 mg oral dose of enzalutamide was administered alone or after multiple oral doses of a strong CYP2C8 inhibitor and the AUC was increased 2.2 times with minimal effect on C_{max}. When administered with a single dose of a strong CYP3A4 inhibitor, the $AUC_{0\text{-}inf}$ increased by 1.3 times [33].

2. STUDY OBJECTIVES

2.1 Primary Objectives

To determine the incidence of metabolic syndrome within 12 months, as defined by the Adult Treatment Panel III, in patients treated with enzalutamide compared to standard androgen deprivation therapy.

2.2 Secondary Objectives

In patients treated with enzalutamide versus traditional ADT:

- To determine the incidence of metabolic syndrome within 6 months, as defined by the Adult Treatment Panel III, in patients treated with enzalutamide compared to standard androgen deprivation therapy
- To assess bone health, as measured by a DXA scanner
- To assess body composition (sarcopenic obesity), as measured by measurements of fat on CT
- To assess QOL, as measured by the FACT-P and SHIM
- To assess time to PSA progression and time to radiographic progression. Progression will be defined as lack of clinical benefit in the setting of either rising PSA, growth of visceral or soft tissue metastasis, or development of new bone metastasis as defined per protocol
- To assess the incidence of developing individual risk factors, or components, which comprise metabolic syndrome
- To assess the change in hs-CRP as a marker of inflammation
- To assess the safety and tolerance of enzalutamide or ADT
- To assess the change in physical function as measured by the Short Physical Performance Battery (SPPB)

3. STUDY ENDPOINTS

3.1 Primary Endpoints

Incidence of metabolic syndrome within 12 months as defined by the ATP III, in patients treated with enzalutamide versus patients treated with standard testosterone-lowering ADT.

3.2 Secondary Endpoints

- Incidence of metabolic syndrome within 6 months, as defined by the ATP III, in patients treated with enzalutamide versus patients treated with standard testosterone-lowering ADT
- Change in bone density, as measured by a DXA scanner
- Change in bone turnover as measured by bone-specific alkaline phosphatase and N-telopeptide
- Change in body composition (fat distribution as measured on CT)
- Change in QOL, as measured by the FACT-P and SHIM
- Time to PSA progression and time to radiographic progression. Progression will be defined as lack of clinical benefit in the setting of either rising PSA, growth of visceral or soft tissue metastasis, or development of new bone metastasis as defined per protocol
- Incidence of developing individual risk factors, or components, which comprise metabolic syndrome
- Change in inflammatory markers as measured by serum hs-CRP

- Safety and tolerability as assessed by regular recording of toxicities via physical exam and laboratory analysis using the CTCAE v4.1 guidelines
- Change in physical function as measured by the Short Physical Performance Battery

4. STUDY DESIGN

4.1 Overview of Study Design

This study is a multi-center, open label, randomized, phase II trial of the incidence of metabolic syndrome within 12 months in patients treated with enzalutamide in comparison with androgen deprivation therapy for treatment of advanced prostate cancer. This will include patients with biochemically recurrent disease, metastatic disease, and patients offered ADT as primary therapy if they are not candidates for local therapy. Fifty-six patients will be 1:1 randomized to one of two treatment arms with metastasis as a stratification factor. Patients will be treated for a 12-month period continuously and assessed for the development of metabolic syndrome at 3-month intervals.

Treatment will be administered for a 12-month period. Enzalutamide will be taken orally on each day of the cycle. Androgen deprivation therapy will be administered according to standard of care; however, there will be no intermittent dosing of this treatment. Acceptable forms of ADT must result in castrate levels of testosterone (<50ng/dL), and may include: leuprolide, goserelin, histerelin, triptorelin, degarelix, and surgical castration. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.1 [35]. Metabolic syndrome will be diagnosed by assessing a patient's blood pressure, waist circumference, fasting glucose, high density lipoprotein (HDL), and triglyceride level and determined according to the Adult Treatment Panel III criteria [36].

Analysis of bone turnover will include measurement of urinary N-telopeptide and serum bone-specific alkaline phosphatase. A dual-energy x-ray absorptiometry scan (DXA) will also be performed at enrollment, month 3 and EOT. This scan will provide information on bone density changes induced by treatment.

Quality of life questionnaires will be administered at each study visit. Physical function changes will be assessed via the Short Physical Performance Battery; the SPPB incorporates 3 validated portions to assess a patient's balance and mobility. Changes in systemic inflammation will be assessed via circulating hs-CRP levels. Additional collection of complete blood counts and chemistries will provide safety information. This testing will occur in the clinic setting every 3 months as well.

Adverse events (AEs) will be assessed; and laboratory values, vital signs, and physical exam will be obtained in order to evaluate the development of metabolic syndrome in patients treated with either enzalutamide or standard androgen deprivation therapy. In addition, we will obtain a PSA every 3 months and radiographic imaging at baseline, 6 months, and 12 months. Patients may remain on study as long as they are deriving clinical benefit, until there is clear progression of disease (per protocol), unacceptable toxicity, or withdrawal of consent.

4.2 Duration of Study

Patients will continue therapy until disease progression, development of unacceptable toxicities, non-compliance, intercurrent illness that prevents treatment continuation, withdrawal of consent, or change in subject condition that render the subject unacceptable for further treatment. If a patient develops

metabolic syndrome, but the patient has at least stable disease and ongoing clinical benefit, then the patient may be allowed to continue on their assigned treatment. The End of Study (9) visit will occur within 30 days after the last dose of study drug, or prior to the start of subsequent anti-cancer therapy. Patients will be assessed for metabolic syndrome over a 12-month period of treatment, as this allows adequate time in which to see the emergence of the metabolic syndrome parameters as well as time for patients to derive a potential clinical benefit from the respective treatment agent. Patients with continued clinical benefit beyond the 12-month endpoint will have the option of remaining on their current therapy with additional follow up visits every 3 months for safety and tolerability assessment. Patients receiving enzalutamide will no longer receive this as a study medication beyond the 12-month time point but may potentially obtain the medication through standard prescribing methods. It is estimated this trial will take 36 months to complete.

4.3 Overview of treatment

During the trial, patients will be assigned to treatment with either enzalutamide or standard of care ADT. For patients randomized to the ADT arm, the choice of type of ADT will be at the discretion of the treating provider. Patients that are in the enzalutamide arm may not also be treated with ADT. In addition, patients on the ADT arm may not also be treated with an androgen-receptor blocker. Anti-androgen therapy may be administered as a single agent $\leq$14 days prior to and 14 days following medical castration with a GnRH agonist in order to cover the potential testosterone surge. Intermittent dosing of ADT is not acceptable. Enzalutamide will be dosed at the approved dose of 160mg orally daily. ADT will be administered according to the standard prescribing information for the agent. All subjects should also take at least 1000mg of calcium and 800 International Units (IU) of vitamin D. This treatment will allow protection against bone density loss caused by metastasis or ADT. All subjects will receive this treatment to avoid confounding data, as it is a non-toxic, non-prescription supplement.

4.4 Criteria for Dose Administration

4.4.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented prior to drug administration. Enzalutamide or ADT will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s).

Patients should be instructed to take their study medication at approximately the same time each day. Enzalutamide can be taken with or without food, patients must swallow capsules whole without chewing, opening or dissolving the capsule. If a patient misses a dose, then they should take it as soon as they remember. If they forget an entire day's dose, they should take their normal dose the next day. They should not take more than their prescribed dose per day.

For any depot-injections of ADT, the site of injection and name of the agent will be recorded. Patients on depot-injections may only be treated with formulations given every 4, 8, or 12 weeks.

4.4.2 Clinical Benefit

Continuation on the trial is dependent on toxicities, as well as evidence of clinical benefit. Patients must not have evidence of radiographic or PSA disease progression as per protocol section 7. Efficacy assessments will be performed via provider assessment. Imaging studies will be obtained every 6 months, or sooner at the discretion of the treating provider. PSA values will be assessed every 3

months, or sooner at the discretion of the treating provider. Patients with progressive disease per section 7 will be ineligible to receive further study treatment.

4.5 Dose Modification Guidelines

Patients will be assessed for toxicities at each study visit, every 3 months. Patients may be evaluated more frequently at the discretion of the treating provider. Toxicities are to be assessed according to the NCI CTCAE, version 4.1. Each AE should be assessed for potential contribution by the study drug. If a patient experiences a grade≥3 toxicity on enzalutamide or an intolerable side effect, withhold dosing for one week or until symptoms improve to grade≤2. Dosing may resume at the same, or a reduced dose, (per treating physician discretion) for a maximum dose reduction to 80mg daily. Once a dose reduction has occurred, the patient may not re-escalate to a higher dose.

There are no dose modifications for ADT. As stated, this therapy must be dosed continuously and may not be given on an intermittent basis.

4.6 Study specific biomarker collection

Plasma samples will be obtained and stored for future correlative analysis regarding potential identified biomarkers important in the development of metabolic syndrome or prostate cancer progression. Approximately 3 7mL tubes of blood will be drawn. De-identified tubes will be processed and stored for future analysis. See lab manual for processing instructions.

5. STUDY POPULATION

5.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Histologically or cytologically proven adenocarcinoma of the prostate. If pathology is unavailable, the PI may also make a determination of prostate cancer based on unequivocal clinic data.
2. Patients with advanced prostate cancer suitable for systemic treatment defined as: having metastatic disease, a biochemical relapse after primary therapy, or patients in whom primary therapy is not appropriate or feasible. Patients without metastatic disease will need evaluation for local therapy and deemed inappropriate or have refused this treatment option
3. ECOG 0-2
4. Age > 18 years old
5. Must use a condom if having sex with a pregnant woman
6. A male patient and his female partner who is of childbearing potential must use 2 acceptable methods of birth control (one of which must include a condom as a barrier method of contraception) starting at screening and continuing throughout the study period and for 3 months after final study drug administration
7. Life expectancy estimated at >12 months
8. Ability to understand and willingness to provide written informed consent document

5.2 Exclusion Criteria

The following are criteria for exclusion from participating in the study:

1. A history of androgen deprivation therapy.

   a. Patients receiving hormonal therapy in the adjuvant and/or neoadjuvant setting must have discontinued therapy at least 6 months prior to day 1 of treatment
   b. AND have a serum testosterone level ≥50ng/dL
   c. AND cannot have received more than 18 months of previous ADT.
2. A history of orchiectomy
3. Previous androgen blockade (e.g. antiandrogens) given for greater than 2 weeks in the last 3 months. Anti-androgens used during the initiation of ADT to avoid a flare phenomenon are acceptable for up to 4 weeks.
4. Patients already meeting the criteria for metabolic syndrome as defined by the Adult Treatment Panel III Criteria which requires 3/5 parameters below.. *Patients with 2 of the parameters at baseline will be allowed enrollment provided that one of those risk factors is hypertension (≥130/≥85 mm Hg).*
   a. Abdominal obesity, defined as a waist circumference >102 cm (>40 in)
   b. Serum triglycerides ≥150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides
   c. Serum HDL cholesterol <40 mg/dL (1 mmol/L) or drug treatment for low HDL
   d. Blood pressure ≥130/≥85 mmHg or drug treatment for elevated blood pressure
   e. Fasting plasma glucose (FPG) ≥100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose
5. Baseline hypogonadism as defined as a testosterone <50 ng/dL
6. PSA <0.5ng/dL
7. Serum Vitamin D 25, OH <12 ng/mL
8. Active Hepatitis C virus
9. Use of corticosteroids as defined by a daily dose of prednisone (or equivalent) of 5mg or greater for more than 1 month continuously within 3 months of screening
10. Corrected calcium >10.6 mg/dL
11. Absolute neutrophil count <1500/uL; platelet count <100, 000/uL, hemoglobin <9g/dL
12. Total bilirubin ≥1.5xULN (unless documented Gilbert's); alanine aminotransferase or aspartate aminotransferase ≥ 2.5xULN
13. Creatinine >2mg/dL
14. Clinically significant cardiovascular disease as evidenced by: Myocardial infarction within 6 months of screening; uncontrolled angina within 3 months of screening; New York Heart Association (NYHA) class 3 or 4 congestive heart failure; clinically significant ventricular arrhythmia; Mobitz II/2nd degree/or 3rd degree heart block without a pacemaker in place; uncontrolled HTN (systolic >180mmHg or diastolic >105mmHg at screening)
15. Previous exposure to enzalutamide
16. Use of an investigational therapeutic within 30 days
17. History of gastrointestinal disorders (medical disorders or extensive surgery) that may interfere with the absorption of the study agent
18. Known or suspected brain metastasis or active leptomeningeal disease
19. History of seizure or any condition that may predispose to seizure (e.g., prior cortical stroke, significant brain trauma) at any time in the past. Also, history of loss of consciousness or transient ischemic attack within 12 months of Day 1 visit
20. Have any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or prevent the subject from meeting or performing study requirements

6. STUDY PROCEDURES AND ASSESSMENTS

The schedule of assessments is summarized in **Table 1**

6.1 Informed Consent

Enrollment in the study requires that all inclusion and exclusion criteria have been met. A patient may be enrolled into the study when the written informed consent has been obtained and the patient's eligibility per all inclusion and exclusion criteria has been confirmed.

6.2 Randomization

Randomization will occur using the GraphPad QuickCalcs randomization service.

6.3 Study Visits

Patients will be evaluated at scheduled visits over the following study periods: Screening, Treatment, and end of study (EOS). Tests and procedures should be performed on schedule for all visits during Cycle 1. During all subsequent cycles, occasional changes are allowable (± 5 days) with permission for holidays and other administrative reasons. If extenuating circumstances prevent a patient from completing a scheduled procedure or assessment within this time, the patient may continue the study only with the permission of the Principal Investigator (PI). All EOS evaluations should occur within 30 days after the last dose of study drug, or prior to the start of subsequent anti-cancer therapy.

6.3.1 Physical Examination

A complete physical examination will be performed before dosing on Day 1 of each cycle and at the end of treatment. Vital signs (temperature, blood pressure, pulse rate, respiratory rate, weight, waist circumference) will be performed at each visit. ECOG performance status will be evaluated at day 1 of each cycle and end of study. Clinically significant AEs will be captured as well.

6.3.2 Schedule of Events

Screening/Baseline Day -21 - 0

- Informed consent and HIPAA release
- Study eligibility per inclusion/exclusion criteria
- Medical history/baseline conditions
- Physical examination
- Vital signs, including height and weight, waist circumference
- ECOG performance status
- Blood samples for hematology, comprehensive metabolic panel (fasting), lipid profile
- Serum Testosterone
- Serum PSA
- 25-OH Vitamin D
- CT scan and assessment of tumor burden, may use imaging study within 28 days of day 1
- Bone scan, may use imaging study within 28 days of day 1
- Collection of concomitant medications
- Collection of adverse events

Month 1 Day 1

- Physical examination
- Vital signs, including weight and waist circumference
- ECOG performance status
- Blood samples for CBC, Comprehensive metabolic panel (fasting), PSA, N-telopeptide, bone specific alkaline phosphatase, estradiol, hs-CRP
- Optional tubes of blood for future biomarker testing
- FACT-P, SHIM completed
- DXA scan (+/-14 Days of Day 1 Dosing); note that there must be a 14 day separation of bone scan and a DXA scan
- Short Physical Performance Battery
- Collection of concomitant medications
- Collection of adverse events
- Dosing of medication, or documentation of continued dosing
- Verification of calcium/vitamin D administration

Month 2 Day 1 +/- 5 days

- Physical examination
- Vital signs, including weight and waist circumference
- ECOG performance status
- Blood samples for CBC, Comprehensive metabolic panel (fasting), PSA, testosterone
- Collection of concomitant medications
- Collection of adverse events
- Dosing of medication, or documentation of continued dosing
- Verification of calcium/vitamin D administration

Month 4 Day 1+/- 5 days

- Physical examination
- Vital signs, including weight and waist circumference
- ECOG performance status
- Blood samples for CBC, Comprehensive metabolic panel (fasting), testosterone, PSA, N-telopeptide, bone specific alkaline phosphatase, lipid profile, estradiol, hs-CRP
- Optional tube of blood for future biomarker testing
- FACT-P, SHIM completed
- DXA scan (+/-14 Days of Day 1 Dosing); note that there must be a 14 day separation of bone scan and a DXA scan
- Short Physical Performance Battery
- Collection of concomitant medications
- Collection of adverse events
- Dosing of medication, or documentation of continued dosing
- Verification of calcium/vitamin D administration

Month 7 Day 1+/- 5 days

- Physical examination
- Vital signs, including weight and waist circumference
- ECOG performance status

- Blood samples for CBC, Comprehensive metabolic panel (fasting), testosterone, PSA, N-telopeptide, bone specific alkaline phosphatase, lipid profile, estradiol, hs-CRP, 25-OH Vitamin D
- Optional tubes of blood for future biomarker testing
- FACT-P, SHIM completed
- CT scan and assessment of tumor burden +/- 5 days
- Bone scan +/- 5 days
- Short Physical Performance Battery
- Collection of concomitant medications
- Collection of adverse events
- Dosing of medication, or documentation of continued dosing
- Verification of calcium/vitamin D administration

Month 10 Day 1+/- 5 days

- Physical examination
- Vital signs, including weight and waist circumference
- ECOG performance status
- Blood samples for CBC, Comprehensive metabolic panel (fasting), testosterone, PSA, N-telopeptide, bone specific alkaline phosphatase, lipid profile, estradiol, hs-CRP
- Optional tube of blood for future biomarker testing
- FACT-P, SHIM completed
- Short Physical Performance Battery
- Collection of concomitant medications
- Collection of adverse events
- Dosing of medication, or documentation of continued dosing
- Verification of calcium/vitamin D administration

Month 13 Day 1 or End of Treatment (+/- 5 days)

- Physical examination
- Vital signs, including weight and waist circumference
- ECOG performance status
- Blood samples for CBC, Comprehensive metabolic panel (fasting), testosterone, PSA, N-telopeptide, bone specific alkaline phosphatase, lipid profile, estradiol, hs-CRP, 25-OH Vitamin D
- Optional tubes of blood for future biomarker testing
- FACT-P, SHIM completed
- DXA scan (+/-14 Days of Day 1 Dosing); note that there must be a 14 day separation of bone scan and a DXA scan
- CT scan and assessment of tumor burden +/- 5 days
- Bone scan +/- 5 days
- Short Physical Performance Battery
- Collection of concomitant medications
- Collection of adverse events

End of Study (EOS) safety visit

- Physical examination
- Vital signs, including weight and waist circumference

- ECOG performance status
- Blood samples for CBC, Comprehensive metabolic panel
- Collection of concomitant medications
- Collection of adverse events

7. STUDY ASSESSMENTS

7.1 Assessment of metabolic syndrome

The primary endpoint is the determination of the incidence of metabolic syndrome in patients with advanced prostate cancer treated with either enzalutamide or standard ADT. Metabolic syndrome will be assessed every 3 months and defined by the presence of 3 of the following five traits [36]:

- Abdominal obesity, defined as a waist circumference >102 cm (>40 in)
- Serum triglycerides ≥150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides
- Serum HDL cholesterol <40 mg/dL (1 mmol/L) or drug treatment for low HDL
- Blood pressure ≥130/≥85 mmHg or drug treatment for elevated blood pressure
- Fasting plasma glucose (FPG) ≥100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose

Patients may continue on treatment even upon development of metabolic syndrome at the discretion of the PI.

7.2 Efficacy Evaluations

7.2.1 PSA

Patients will be monitored for clinical efficacy while on study. Serum PSA will be obtained every 3 months. PSA rise is allowable at the discretion of the investigator. However, patients must discontinue treatment if there is evidence of PSA progression as defined by an increase in ≥50% from nadir and an absolute increase of at least 2 ng/mL above the nadir, occurring at least 12 weeks after start of therapy that is confirmed by two consecutive increases taken at least 2 weeks apart. The date of first recorded increase will serve as the date of progression.

7.2.2 Radiographic evaluation

Patients will be removed from study if they have evidence of radiographic disease progression as defined below. Radiographic analysis via CT scan (and/or MRI), and bone scan will occur at baseline, 6 months, and 12 months. For the purposes of this study, investigators should utilize the protocol-specified tumor assessment criteria, defined as assessment of evaluable soft tissue disease sites according to RECIST v1.1, and/or assessment of bone disease according to the PCWG2 criteria. Soft tissue disease will be assessed on CT (or MRI) and defined by RECIST v1.1. Bone disease will be assessed on bone scan and progression will be defined as the development of two or more new bone lesions from baseline confirmed with an additional lesion on bone scan 6 weeks later. New bone lesions noted after the 6-month radiographic assessment do not require a confirmatory bone scan. Increase in intensity of known bone lesions will not constitute progression. The date of progression will be recorded as the date the first scan shows change.

7.3 Body composition evaluation

The change in bone health will be assessed via urine N-telopeptide and serum bone specific alkaline phosphatase measurements. Bone density will be assessed via a DXA scan. The density of the posterior-anterior lumbar spine, total hip, femoral neck, and total body bone mineral density will be analyzed. Additional body composition analysis of lean body mass and total body mass will be analyzed via cross sectional CT image analysis. Changes in body composition can be seen as early as 3 months in studies of testosterone supplementation [39] or ADT [40] causing an increase in adipose tissue and decrease in lean muscle.

7.4 Quality of life assessment

The Functional Assessment of Cancer Therapy – Prostate (FACT-P) questionnaire will provide data on how patients perceive their QOL while on enzalutamide or ADT. The FACT-P tests five subscales: physical, social, emotional, functional wellbeing and additional concerns specific to men with prostate cancer [41]. The FACT-P scales have been widely used to evaluate quality of life in clinical trials for prostate cancer treatments. Internal consistency of the FACT-P (version 4) subscales ranges from 0.85 to 0.89. Concurrent, construct and discriminant validity has been documented (41). The FACT-P will be used descriptively. The questionnaire must be administered at each study visit unless the patient refuses. It is permissible to assist the patient with the completion of the questionnaire. The study staff must review the questionnaire at each visit in order to ensure that all items were answered. Patients should be given the option to complete any unmarked questions, but it is not required.

The Sexual Health Inventory for Men (SHIM) will also be used to evaluate alterations in sexual health as a result of treatment with enzalutamide or ADT. The SHIM is a scale used widely to assess the presence and severity of erectile dysfunction. The scale is used regularly in clinical practice as well as in the research setting. The SHIM will be used descriptively. The questionnaire must be administered at each study visit unless the patient refuses. It is permissible to assist the patient with the completion of the questionnaire. The study staff must review the questionnaire at each visit in order to ensure that all items were answered. Patients should be given the option to complete any unmarked questions, but it is not required.

7.5 Physical function evaluation

The Short Physical Performance Battery (SPPB) will be used for physical function evaluation. This battery of tests evaluates physical function and mobility. The test includes assessment of a patient's ability to perform a chair rise, standing balance, and a 8 foot walk. This battery has a clear scoring system and a validated score above which patients are identified as at-risk of physical decline. Change in score of 1 is clinically significant. The SPPB will be modified to include a 10-time chair rise. The coordinator will record the time it takes the subject to perform both 5 and 10 rises from the chair. This modification has been made to increase the sensitivity of the exam in identifying small changes in function given the generally fit population seen in the clinic.

7.6 Safety evaluations

The principal investigator will oversee the care and safety of all subjects enrolled in the trial. Study visits will include monitoring and recording all adverse events and serious adverse events; regular monitoring of hematology, blood chemistry, hepatic function; regular measurement of vital signs, physical examination including weight and performance status. Safety and tolerability will be assessed using the CTCAE v4.1 guidelines.

7.6.1 Adverse Events

Monitoring of AEs will be conducted throughout the study. AEs will be reported from the date written informed consent is obtained and through 30 days post-last dose of study drug. Serious pretreatment events and serious adverse events (SAE) will be reported to the Astellas, Inc. designee. All SAEs will be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness (es).

7.6.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Chemistry and hematology results must be drawn and reviewed within 24 hours prior to each cycle of dosing.

7.7 Concomitant Medication and Therapies

Concomitant Strong CYP2C8 Inhibitors

The concomitant use of strong CYP2C8 inhibitors (i.e. gemfibrozil) should be avoided if possible as this increases the plasma AUC of enzalutamide and its active metabolite. If patients must be co-administered a strong CYP2C8 inhibitor, reduce the enzalutamide dose to 80 mg once daily. The enzalutamide dose should be readjusted if the inhibitor is discontinued.

The effects of CYP2C8 inducers on the pharmacokinetics of enzalutamide have not been evaluated *in vivo*. Co-administration of enzalutamide with strong or moderate CYP2C8 inducers (e.g., rifampin) may alter the plasma exposure of enzalutamide and should be avoided if possible.

Drugs that Inhibit or Induce CYP3A4
Co-administration of a strong CYP3A4 inhibitor increased the AUC of enzalutamide and its active metabolite by 1.3 times.

Co-administration of enzalutamide with strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) may decrease the plasma exposure of enzalutamide and should be avoided if possible. Moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) and St. John's Wort may also reduce the plasma exposure of enzalutamide and should be avoided if possible.

The following medications and procedures are PROHIBITED during the study:

- Any anti-cancer therapies other than enzalutamide or single agent ADT. Anti-androgens used during the initiation of ADT to avoid a flare phenomenon are acceptable for up to 4 weeks.
- Patients not on osteoclast inhibitors at study enrollment may not begin this treatment while on trial.

The following medications and procedures are ALLOWED during the study:

- Any supportive medications to treat the symptoms of enzalutamide or ADT are allowed such as agents to manage hot flashes, nausea, diarrhea, or depression

- Palliative radiotherapy, for treatment of the patient's malignancy. Patients with a fracture in an area of pre-existing metastasis without clear progression, the patient may remain on trial if approved by the PI.
- Anti-androgens used during the initiation of ADT to avoid a flare phenomenon are acceptable for up to 4 weeks.

7.8 Completion of Study

Patients will be considered to have completed the study if they (1) have received at least 1 cycle of treatment, AND (2) experienced progressive disease OR (3) experienced unacceptable toxicity. In the absence of progressive disease or unacceptable toxicity, and in the setting of continued clinical benefit, patients may be permitted to remain on therapy upon discussion with the PI. Patients wishing to continue therapy beyond cycle 12 may continue on their current therapy at the discretion of their treating provider.Patients receiving enzalutamide will no longer receive this as a study medication beyond the 12-month timepoint but may be able to obtain the medication through standard prescribing methods.

Withdrawal of Patients from Study

Patients will be informed that they have the right to withdraw from study treatment at any time for any reason, without prejudice to their medical care. A patient may be withdrawn from study treatment for any of the following reasons:

- Adverse Event
- Protocol Violation
- Radiographic Progressive Disease as defined in section 7.2
- Serologic progressive disease as defined in section 7.2
- Symptomatic Deterioration
- Study Terminated by the University of Colorado Cancer Center
- Withdrawal by Subject
- Lost to Follow-up
- Other

At the time of study drug discontinuation, all study procedures outlined for the EOS visit should be completed within 30 days after the last dose of study drug. The primary reason for a patient's withdrawal from the study is to be recorded.

The consequence of withdrawal of consent by a patient will be that no new information will be collected from that patient and added to the existing data or any database. However, every effort will be made to follow all patients for safety.

7.9 Study Compliance

Study drug will be dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing, including the following: applicable lot numbers and total drug administered in milligrams. Any discrepancy regarding the dose administered and the reason for the discrepancy will be noted.

Patients will receive a sufficient quantity of enzalutamide for each treatment cycle. The study center staff will check the returned pill bottles at each study visit to ensure proper compliance with dosing. Patients who are not compliant with the dosing schedule may be withdrawn from the study.

8. INVESTIGATIONAL AGENTS

8.1 Precautions and Restrictions

Patients should be instructed to consult with the investigator before taking any new medications, including over-the-counter and herbal products. Patients should be instructed to limit the use of alcohol while enrolled in this study.

8.2 Description of Investigational Agents

8.2.1 Enzalutamide

Enzalutamide 40 mg capsules are white to off-white oblong soft gelatin capsules imprinted in black ink with MDV. Enzalutamide is provided as liquid-filled soft gelatin capsules for oral administration. Each capsule contains 40 mg of enzalutamide as a solution in caprylocaproyl polyoxylglycerides. The inactive ingredients are caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, and black iron oxide. Enzalutamide is an androgen receptor inhibitor. The chemical name is 4-{3-4-cyano-3-(trifluoromethyl) phenyl-5, 5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl-2-fluoro-*N*-methylbenzamide. Enzalutamide is a white crystalline non-hygroscopic solid. It is practically insoluble in water.

8.2.2 Androgen deprivation therapy

ADT includes agents such as degarelix, goserelin, leuprolide, triptorelin, and histerelin. These agents are long-acting analogues of the GnRH peptide and alter the feedback loop of FSH and LH production to subsequently reduce circulating testosterone levels. These agents are FDA approved and may be used for the purposes of ADT in this study. These agents are generally administered as a subcutaneous or intramuscular injection and should be administered according to manufacturer instruction. Please refer to the FDA package insert for information.

8.3 Preparation, Reconstitution, and Dispensation

The University of Colorado Cancer Center clinical trials team and the PI will assign each patient who signs a consent form a patient number. Patients will be dispensed bottles of study drug containing an appropriate number of capsules in order to achieve the assigned doses. Patients may be dispensed a maximum of 3 complete cycle's capsules.
Patients will be asked to bring back all remaining study drug at each visit. All unused study drug and the amount of study drug returned will be recorded on the drug accountability form. Patients will be instructed to store the enzalutamide capsules only in the bottles dispensed.

8.4 Storage, Handling, Accountability

8.4.1 Enzalutamide

Enzalutamide capsules are available in bottles of 120 capsules. These should be stored at 20°Celsius (C) to 25°C in a dry place with the container tightly closed.

8.4.2 Handling and Accountability

All clinical drug supplies must be kept in an appropriate, limited-access, secure place until used or destroyed. The investigator must maintain 100% accountability for all study medication received and dispensed. Proper drug accountability includes, but is not limited to:

- Frequently verifying that actual inventory matches documented inventory
- Verifying that the log is completed for the drug lot used to prepare each dose
- Verifying that all containers used are documented accurately on the log
- Verifying that required fields are completed accurately and legibly

If any dispensing errors or discrepancies are discovered, the PI must be notified immediately.

The investigator must maintain a current inventory of all study medication delivered to the site, inventory at the site, and records of patient use. This log must accurately reflect the drug accountability of the study medication at all times. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of study medication, expiration date, date and amount dispensed, and the date and amount returned to the site by the patient, including the initials of the person dispensing and receiving the study medication. The log should include all required information as a separate entry for each patient to whom study medication is dispensed.

Before site closure, or at appropriate intervals, a representative from the PI or its designee will perform clinical study material accountability and reconciliation before clinical study materials are destroyed. The investigator will retain the original documentation regarding clinical study material accountability and destruction.

The investigator will monitor any expiration date and subsequently segregate and destroy expired clinical study drug.

9. STUDY CONDUCT

This trial will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

9.1 Oversight of multiple participating sites

Study will be conducted at multiple sites with the University of Colorado Anschutz Campus as the coordinating site. Dr. Kessler, as the Lead PI, will work with the Site PI(s) to insure proper training and conduct.

A PI oversight plan has been drafted to outline the procedures for maintaining oversight, data monitoring and study auditing. All study sites involved will follow the process outlined in the document in order to ensure safe and accurate conduct.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/independent ethics committee

(IEC). It is not envisioned that prisoners (or other populations that might be subject to coercion or exploitation) will be enrolled into this study.

The study will aim to enroll at least 1 patient per month to the trial.

9.3 Treatment Group Assignments

Patients will be assigned through the randomization process with a 1:1 ratio of patients in each treatment group. Randomization will occur centrally through a non-clinical project manager at the coordinating site. Participating sites will contact this central manager for randomization assignment during regular business hours (M-F 8-5pm).

10. STATISTICAL AND QUANTITATIVE ANALYSES

10.1 Statistical Methods

We estimate a 7% (2 patients) and 32% (9 patients) incidence of metabolic syndrome for enzalutamide and ADT treated patients based on historic data [7]. Historical cross-sectional data would suggest that almost 50% of patients on ADT will develop metabolic syndrome, however, the trial population proposed will be pre-selected. Twenty-eight (28) patients in each of the two groups will provide 80% power to detect the 25% difference using a one-sided chi-square test with a significance level of 0.05 (actual alpha=0.054).

10.1.1 Endpoint Analysis

Primary endpoint

Metabolic syndrome incidence will be summarized by the proportion of patients with at least 3 of the 5 pre-specified criteria within the first 12 months of therapy.

Secondary endpoint

The secondary endpoints will be presented as follows:

Metabolic syndrome incidence will be summarized by the proportion of patients acquiring with at least 3 of the 5 pre-specified criteria within the first 6 months of therapy.

The change in bone turnover markers from baseline will be assessed for each treatment group. Measurements will be taken at day 1 of each cycle and reported as a continuous variable. A paired t-test will test within an arm as to whether the change from baseline to each time point is significantly different from zero.

The change in bone density, free fat mass, and fat mass will be measured at baseline, 3 months and 12 months and assessed for each treatment group. A paired t-test will test within an arm as to whether the change from baseline to each time point is significantly different from zero.

The change in QOL scores as measured by the FACT-P and SHIM at each visit, will be assessed in each treatment group.

Median time to PSA progression as defined in section 7.2. Time to PSA progression is defined as the time from randomization to the earliest objective evidence of PSA progression as defined per

protocol. If a patient has had a decline in PSA while on study, the PSA progression date is defined as the time from documented PSA nadir to an increase in PSA with confirmation as defined by protocol. Time to radiographic progression is defined as the time from randomization to the earliest objective evidence of radiographic progression as defined per protocol. Patients will be monitored at regular intervals for PSA change and radiographic change. Log rank test will be used to compare the distributions of above variables between the group treated with enzalutamide to the group on standard ADT.

The change in markers of inflammation as measured by circulating hs-CRPwill be obtained at the beginning of each cycle.

Adverse events data will be summarized using tables and descriptive statistics.

The change in SPPB from baseline to 12 months will be measured as a continuous outcome. A clinically relevant change is a change in total score of 1, with a standard deviation at baseline of 1.5 [42].

Mean, standard deviation, median, and range will be reported for each outcome at each time point, and the mean and standard deviation of the changes, will be calculated. One-group t-test will be used to estimate effect size of each outcome measure and test if the change is significant at 0.05 significance level. Pearson or Spearman correlation coefficients will be used to assess the association between continuous variables.

10.1.2 Accrual

The study center treats approximately 6-7 patients monthly who would be eligible for enrollment in the trial. We estimate that 3-4 patients will enroll a month.

10.2 Safety population

The safety population is defined as all patients who receive at least 1 dose of either enzalutamide or ADT. This population will be used for all safety analyses as well as efficacy analyses.

10.3 Metabolic syndrome population

The metabolic syndrome population is defined as patients who have received at least 1 dose of either drug, have baseline values and at least 1 post-baseline assessment.

10.4 Secondary endpoint population

Defined as patients who have received at least 1 dose of either drug, have baseline values and at least 1 post-baseline assessment.

11. SAFETY ANALYSIS

The safety population will be used for the analysis of the toxicities and AEs. Individual toxicities will be summarized by their frequency and intensity for each treatment group. Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital

signs, weight, and clinical laboratory results using the safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

Treatment related AEs that occur after administration of the first dose of study drug and through 30 days after the last dose of study drug will be tabulated. AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) and will include the following categories:

- Drug-related AEs
- Grade 3 or higher AEs
- Grade 3 or higher drug-related AEs
- The most commonly reported treatment-emergent AEs (i.e., those events reported by ≥ 10% of all patients)
- SAEs

A listing of AEs resulting in study discontinuation will be provided.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time.

All concomitant medications collected from screening through the study period will be classified to preferred terms according to the World Health Organization (WHO) drug dictionary.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of enzalutamide and ADT.

11.1 Oversight and Monitoring

The Lead Principal Investigator (PI) will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial, executing the DSM plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and patient safety for all clinical studies at the CU Cancer Center. A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all serious adverse events (SAEs), unanticipated problems (UAPs) and reportable adverse events (AEs)
- Has the authority to close and/or suspend trials for safety or trial conduct issues
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs, UAPs and reportable AEs are reported to the DSMC, IRB and the sponsor per study protocol. All SAEs, UAPs and reportable AEs are to be reported to the DSMC within 5 business days of receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the Site PI(s) and appropriate staff at regularly scheduled disease-oriented working group meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The Lead PI in this multi-site trial is responsible for organizing and conducting monthly teleconferences with all participating sites. The Lead PI will also be responsible for including data from all of the participating sites to include the minutes from these regularly scheduled teleconferences between the Lead PI and the sites within the overall trial's six-month DSM report.

The Lead PI will provide a DSM report to the CU Cancer Center DSMC on a six-month basis. The DSM report will include a protocol summary; current enrollment numbers; summary of toxicity data to include specific SAEs, UAPs and AEs; any dose modifications; all protocol deviations; and protocol amendments. The DSM report to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted, as well as any internal DSMB reports. Results and recommendations from the review of this six-month report by the DSMC will then need to be submitted by the site to the IRB of record at the time of continuing review.

12. ADVERSE EVENTS

12.1 Definitions

Definition of Adverse Events (AEs)

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a study drug and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

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.

Definition of Serious Adverse Events (SAEs)

An AE is considered "serious" if, in the view of either the investigator or sponsor, is unexpected and is potentially related to study participation and it results in any of the following outcomes:

- Results in death,
- Is life threatening (an AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.),
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- Results in congenital anomaly, or birth defect,

- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious),
- Other medically important events.

Serious Adverse Event Reporting

For patients on enzalutamide therapy, within 48 hours of awareness of a serious adverse event, whether or not related to enzalutamide, the Investigator will complete and submit a Medwatch 3500A Form, containing all required information (reference 21 CFR 312.32). The Investigator will submit a copy of this MedWatch 3500A form to FDA and Astellas by either e-mail or fax, within the same timeframe if subject is on enzalutamide. If submission of this SAE to FDA or Astellas or is not possible within 48 hours, the Investigator's local drug safety contact (IRB, etc.) should be informed by phone.

The SAE 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:

- Study number/IIT regulatory identifier
- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

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

All SAEs , regardless of treatment arm, will be reported to the University of Colorado DSMC within 48 hours of awareness of the event.

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.

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.

12.2 Maintenance of Safety Information

Safety information will be maintained in a clinical database/repository in a retrievable format. At a minimum, at the end of the treatment phase (=”last patient off treatment”) as well as the end of the follow-up phase (=”last patient out”) of the Study, the Principal Investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent review of the safety data may be necessary, e/g/ to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Astellas, Inc.’s request.

12.2.1 Product Quality Complaints

Any product quality complaint, with or without an AE, (including reports of suspicion of counterfeiting, diversion, or tampering, and suspected transmission of pathogens) will be transmitted by the Principal Investigator within **24 hours** of becoming aware of the event(s).

12.3 Monitoring of Adverse Events and Period of Observation

AEs, both non-serious and serious (which include all deaths), will be monitored throughout the study as follows:

- AEs will be reported from the time of consent through 30 days after administration of the last dose of study drug and recorded.
- Serious pretreatment events will be reported to Astellas, Inc. from the time of the signing of the informed consent form (ICF) up to first dose of study drug.
- SAEs will be reported to Astellas, Inc. from the time of consent through 30 days after administration of the last dose of study drug and recorded. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient’s stable or chronic

condition or intercurrent illness (es). If an SAE occurs in the follow-up period and is thought to be possibly related to study drug, it must be reported.

13. ADMINISTRATIVE REQUIREMENTS

This is an investigator-initiated trial and thus major trial decisions and document design will occur with the PI and supporting institution, the University of Colorado Cancer Center. Astellas Inc. is providing study support and thus will have access to trial data and patient safety information.

13.1 Data Quality Assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Study monitors will discuss instances of missing or uninterpretable data with the investigator for resolution. Any changes to study data will be monitored via an audit trail.

13.2 Study Monitoring

Monitoring for this study will be performed by CU Cancer Center Clinical Monitor in accordance with the clinical monitoring plan (CMP), incorporated herein by reference. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports.

The CMP will be approved by the PI and will be followed to comply with GCP guidelines. All study records must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify study record against source documentation, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner that ensures that patient confidentiality is maintained.

Independent audits will be conducted by the CU Cancer Center DSMC to ensure monitoring practices are performed consistently across all participating sites, if applicable, and that monitors are following the CMP.

13.3 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the patients. The protocol, Investigator Brochure (IB), ICF, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator, as allowed by local regulations.

13.4 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

13.5 Patient Confidentiality

To maintain patient privacy, study drug accountability records, study reports, and communications will identify the patient by initials where permitted and/or by the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

13.6 Investigator Compliance

Changes to the protocol will require written IRB/IEC approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard or hazards to patients. When immediate deviation from the protocol is required to eliminate an immediate hazard or hazards to patients, the investigator will contact Astellas, Inc., or a designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

13.7 On-site Audits

Regulatory authorities, the IRB, and/or Astellas, Inc. may request access to all source documents, and any study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

13.8 Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at the trial site is the responsibility of the investigator. Please see section 8.4.2 for details.

All material containing study drug will be treated and disposed of in accordance with governing regulations.

13.9 Closure of the Study

Study participation may be prematurely terminated if, in the opinion of the investigator or Astellas, Inc., there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete, and/or unevaluable data

13.10 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 3 years after the last patient is removed from trial or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility.

14. USE OF INFORMATION

Upon completion of the clinical study and evaluation of results by the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

15. REFERENCES

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9-29.

2. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. Jama 1999;281:1591-7.

3. Bianco F, Dotan ZA, Kattan MW, et al. Duration of response to androgen deprivation therapy and survival after subsequent biochemical relapse in men initially treated with radical prostatectomy. J Clin Oncol 2004;22:4552, abstr

4. Strum SB, McDermed JE, Scholz MC, Johnson H, Tisman G. Anaemia associated with androgen deprivation in patients with prostate cancer receiving combined hormone blockade. Br J Urol 1997;79:933-41.

5. van Andel G, Kurth KH. The impact of androgen deprivation therapy on health related quality of life in asymptomatic men with lymph node positive prostate cancer. Eur Urol 2003;44:209-14.

6. Potosky AL, Knopf K, Clegg LX, et al. Quality-of-life outcomes after primary androgen deprivation therapy: results from the Prostate Cancer Outcomes Study. J Clin Oncol 2001;19:3750-7.

7. Braga-Basaria M, Dobs AS, Muller DC, et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. J Clin Oncol 2006;24:3979-83.

8. Smith DS, Carvalhal GF, Schneider K, Krygiel J, Yan Y, Catalona WJ. Quality-of-life outcomes for men with prostate carcinoma detected by screening. Cancer 2000;88:1454-63.

9. Saad F, Olsson C, Schulman CC. Skeletal morbidity in men with prostate cancer: quality-of-life considerations throughout the continuum of care. Eur Urol 2004;46:731-39; discussion 9-40.

10. Fossa SD, Woehre H, Kurth KH, et al. Influence of urological morbidity on quality of life in patients with prostate cancer. Eur Urol 1997;31 Suppl 3:3-8.

11. Wei JT, Dunn RL, Sandler HM, et al. Comprehensive comparison of health-related quality of life after contemporary therapies for localized prostate cancer. J Clin Oncol 2002;20:557-66.

12. Kiratli BJ, Srinivas S, Perkash I, Terris MK. Progressive decrease in bone density over 10 years of androgen deprivation therapy in patients with prostate cancer. Urology 2001;57:127-32.

13. Daniell HW, Dunn SR, Ferguson DW, Lomas G, Niazi Z, Stratte PT. Progressive osteoporosis during androgen deprivation therapy for prostate cancer. J Urol 2000;163:181-6.

14. Clay CA, Perera S, Wagner JM, Miller ME, Nelson JB, Greenspan SL. Physical function in men with prostate cancer on androgen deprivation therapy. Phys Ther 2007;87:1325-33.

15. Joly F, Alibhai SM, Galica J, et al. Impact of androgen deprivation therapy on physical and cognitive function, as well as quality of life of patients with nonmetastatic prostate cancer. J Urol 2006;176:2443-7.

16. Sadetsky N, Greene K, Cooperberg MR, Hubbard A, Carroll PR, Satariano W. Impact of androgen deprivation on physical well-being in patients with prostate cancer: analysis from the CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor) registry. Cancer 2011;117:4406-13.

17. Bylow K, Hemmerich J, Mohile SG, Stadler WM, Sajid S, Dale W. Obese frailty, physical performance deficits, and falls in older men with biochemical recurrence of prostate cancer on androgen deprivation therapy: a case-control study. Urology 2011;77:934-40.

18. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. Jama 2002;288:2709-16.

19. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. Jama 2002;287:356-9.

20. Smith MR, Goode M, Zietman AL, McGovern FJ, Lee H, Finkelstein JS. Bicalutamide monotherapy versus leuprolide monotherapy for prostate cancer: effects on bone mineral density and body composition. J Clin Oncol 2004;22:2546-53.

21. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA : the journal of the American Medical Association 2002;288:2709-16.

22. Phillips GB, Jing TY, Resnick LM, Barbagallo M, Laragh JH, Sealey JE. Sex hormones and hemostatic risk factors for coronary heart disease in men with hypertension. Journal of hypertension 1993;11:699-702.

23. Smith JC, Bennett S, Evans LM, et al. The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. The Journal of clinical endocrinology and metabolism 2001;86:4261-7.

24. Dockery F, Bulpitt CJ, Agarwal S, Donaldson M, Rajkumar C. Testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and hyperinsulinaemia. Clinical science 2003;104:195-201.

25. Laaksonen DE, Niskanen L, Punnonen K, et al. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. Diabetes care 2004;27:1036-41.

26. Alibhai SM, Duong-Hua M, Sutradhar R, et al. Impact of androgen deprivation therapy on cardiovascular disease and diabetes. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2009;27:3452-8.

27. Keating NL, O'Malley AJ, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. Journal of the National Cancer Institute 2010;102:39-46.

28. Tombal B, Borre M, Rathenborg P, et al. Enzalutamide monotherapy in hormone-naive prostate cancer: primary analysis of an open-label, single-arm, phase 2 study. Lancet Oncol 2014;15:592-600.

29. Cella D, Hackshaw M, Diaz J, et al. Quality of life (QoL) among patients with renal cell carcinoma (RCC) treated with pazopanib versus sunitinib in the COMPARZ study. J Clin Oncol 2013;31:suppl 6; abstr 346.

30. Scher HI, Fizazi K, Saad F, et al. Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy. N Engl J Med 2012.

31. Medivation and Astellas Announce the Phase 3 PREVAIL Trial of Enzalutamide Meets Both Co-Primary Endpoints of Overall Survival and Radiographic Progression-Free Survival in Chemotherapy-Naive Patients With Advanced Prostate Cancer. Medivation, 2013. (Accessed January 4, 2014, at

32. Smith M, Borre M, Rathenborg P, al e. Efficacy and safety of enzalutamide monotherapy in hormone-naive prostate cancer. In: 2013 ASCO Annual Meeting; 2013; Chicago, IL; 2013. p. abstract 5001.

33. www.astellas.us/docs/us/12A005-ENZ-WPI.pdf AHopiX.

34. Scher HI, Beer TM, Higano CS, et al. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. Lancet 2010;375:1437-46.

35. Common Terminology Criteria for Adverse Events (CTCAE). In; 2010.

36. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Executive summary. Cardiol Rev 2005;13:322-7.

37. Visser M, Fuerst T, Lang T, Salamone L, Harris TB. Validity of fan-beam dual-energy X-ray absorptiometry for measuring fat-free mass and leg muscle mass. Health, Aging, and Body Composition Study--Dual-Energy X-ray Absorptiometry and Body Composition Working Group. J Appl Physiol 1999;87:1513-20.

38. Chen Z, Wang Z, Lohman T, et al. Dual-energy X-ray absorptiometry is a valid tool for assessing skeletal muscle mass in older women. J Nutr 2007;137:2775-80.

39. Haseen F, Murray LJ, Cardwell CR, O'Sullivan JM, Cantwell MM. The effect of androgen deprivation therapy on body composition in men with prostate cancer: systematic review and meta-analysis. J Cancer Surviv 2010;4:128-39.

40. Segal RJ, Reid RD, Courneya KS, et al. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. J Clin Oncol 2003;21:1653-9.

41. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1993;11:570-9.

42. Pahor M, Blair SN, Espeland M, et al. Effects of a physical activity intervention on measures of physical performance: Results of the lifestyle interventions and independence for Elders Pilot (LIFE-P) study. The journals of gerontology Series A, Biological sciences and medical sciences 2006;61:1157-65.

43. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.