EXTEND: Safety and Efficacy of EXercise Training in Men Receiving ENzalutamide in Combination with Conventional Androgen Deprivation Therapy for Hormone Naïve Prostate Cancer

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A Phase II Multicenter Randomized Controlled Trial

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DUKE CANCER INSTITUTE

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1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS

AE	Adverse Event
ADT	Androgen Deprivation Therapy
AJCC	American Joint Committee on Cancer
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AR	Androgen Receptor
ACSM	American College of Sports Medicine
AST	Aspartate Aminotransferase
BRPC	Biospecimen Repository and Processing Core (Duke Biobank)
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
COPD	Chronic Obstructive Pulmonary Disease
CPC	Cancer Protocol Committee
CPET	Cardiopulmonary exercise testing
CR	Complete Response
CRF	Case Report Forms
CRPC	Castration-resistant prostate cancer
CSA	Cross Sectional Area
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCI	Duke Cancer Institute
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology GroupENZ Enzalutamide
FACIT-F	Functional Assessment in Chronic Illness Therapy – Fatigue
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FBM	Fat Body Mass
GCP	Good Clinical Practice
GnRH	Gonadotropin-releasing Hormone
H&P	History & Physical Exam
HgbA1c	Glycosylated Hemoglobin
HNPC	Hormone-naïve prostate cancer
HRPP	Human Research Protections Program
IB	Investigator Brochure
ICH	International Conference on Harmonization
ICS	Investigational Chemotherapy Service
IV (or iv)	Intravenously
LBM	Lean Body Mass
LLN	Lower Limit of institutional Normal
LVEF	Left ventricular ejection fraction
MS	Mass Spectrometry
MSKCC	Memorial Sloan-Kettering Cancer Center
MTD	Maximum Tolerated Dose
MUGA	Multigated acquisition scan
NCI	National Cancer Institute
NPP	Named Subject Program
NSCLC	Non-small cell lung cancer

NYHA	New York Heart Association
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PC	Prostate cancer
PCM	Subject Care Monitor
PD	Progressive Disease
PFS	Progression Free Survival
p.o.	Per os/by mouth/orally
PR	Partial Response
PROs	Patient-reported Outcomes
PSA	Prostate-Specific Antigen
PSADT	PSA Doubling Time
QOL	Quality of life
RDSP	Research Data Security Plans
RIO	Research Integrity Office
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SOP	Standing Operating Procedures
SPGT	Serum Glutamic Pyruvic Transaminase
TEAEs	Treatment-Emergent Adverse Events
TUG	Timed Get Up and Go
WBC	White Blood Cells
6MWD	6 Minute Walk Distance
6MWT	Six-Minute Walk Testing

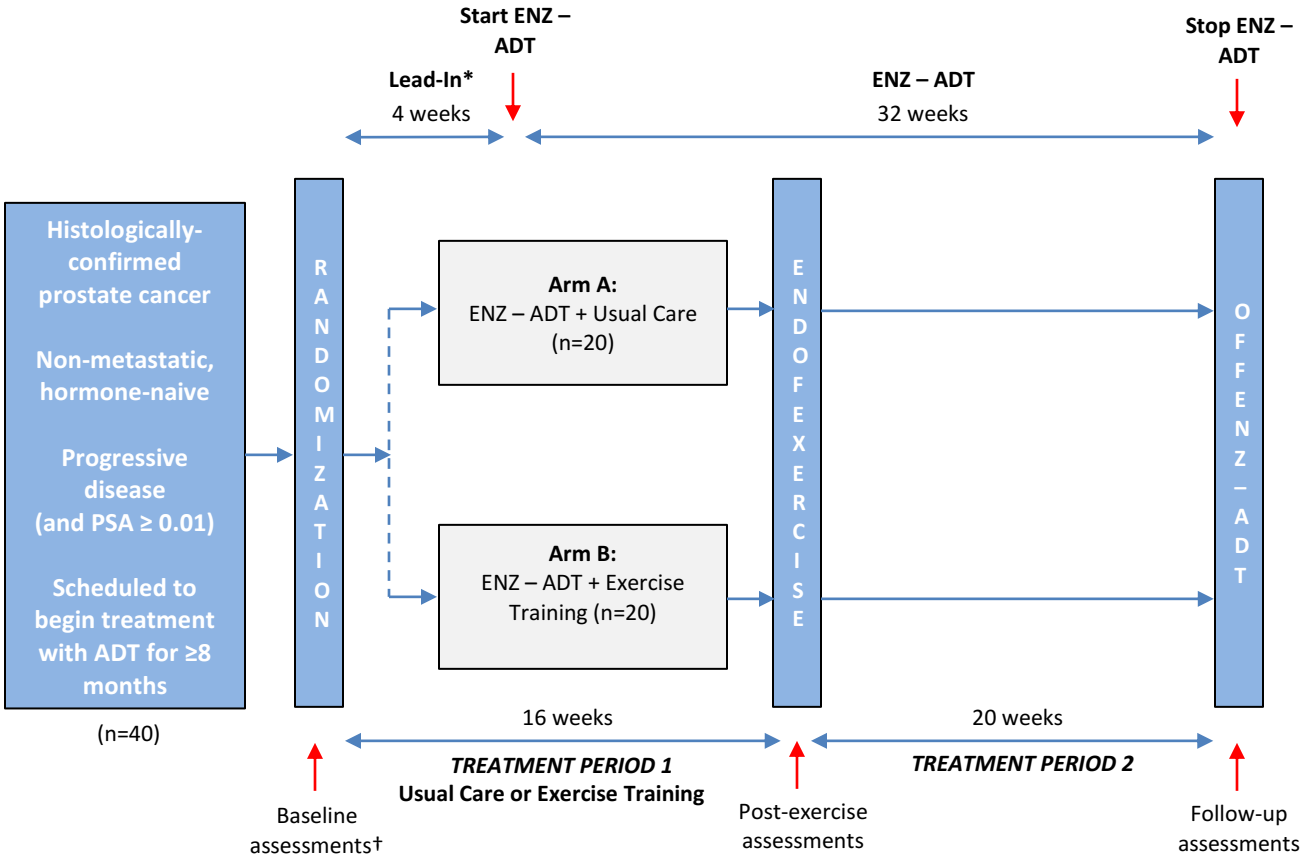
3 STUDY SCHEMA

Primary Objective: To study the effect of supervised exercise training on cardiopulmonary function in men receiving the combination of enzalutamide (ENZ) and androgen deprivation therapy (ADT) for treatment of non-metastatic, hormone-naïve prostate cancer.

Design: Subjects with histologically-confirmed, progressive, non-metastatic, hormone-naive prostate cancer, with a PSA ≥ 0.01 ng/ml, scheduled to be treated with ADT for ≥8 months, will be randomly allocated to one of two following arms:

A. Enzalutamide (ENZ) with androgen deprivation therapy (ADT) (n=20), or

B. Enzalutamide (ENZ) with androgen deprivation therapy (ADT) plus supervised exercise training (n=20)



*The **Lead-In Period** will consist of 4 weeks of either usual care or combined aerobic and resistance exercise training prior to starting ENZ – ADT. Upon initiation of ENZ – ADT, subjects on Arm B will continue the exercise training program for 12 additional weeks. Hence, ***Treatment Period 1*** is 16 weeks in total.
†Baseline exercise testing will be done prior to randomization, but after confirmation of eligibility.

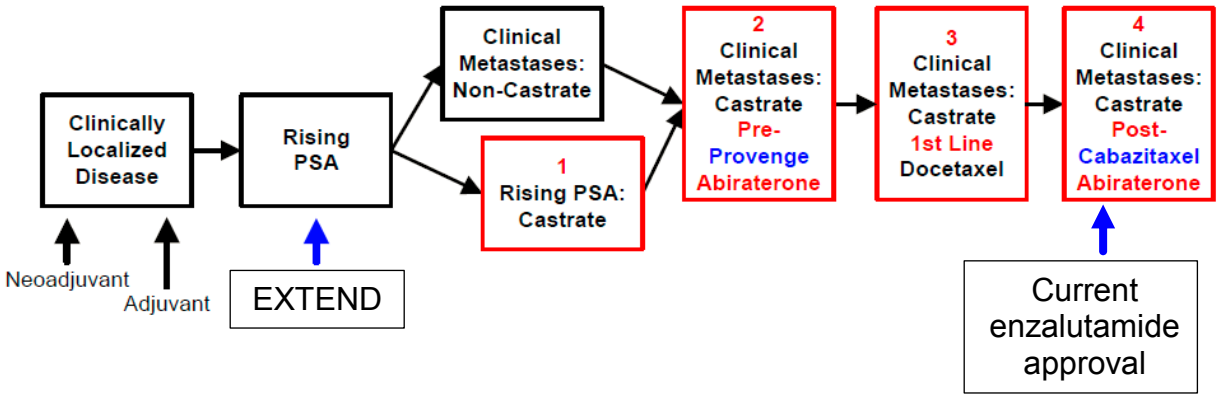
4 BACKGROUND AND SIGNIFICANCE

4.1 Study Disease

Disease Background

In 2013, it is estimated that 238,590 men were diagnosed with prostate cancer and 29,720 died of the disease.[1] The course of prostate cancer from diagnosis to death can be categorized as a series of clinical states (**Figure 1**) based on the status of the primary tumor, presence or absence of visible metastatic disease on an imaging study, and the measured level of testosterone in the blood.[2] The states are localized disease, rising levels of prostate-specific antigen (PSA) after radiation therapy or surgery with no detectable metastases, and clinical metastases in the non-castrate or castrate state. The patient's progression through these clinical states may take a decade or more. Blue arrows in **Figure 1** show the clinical states that will be enrolled on this protocol (*Rising PSA*) and in which enzalutamide is currently approved (*Clinical Metastases: Castrate, Post-Docetaxel*).

Figure 1. Clinical states of prostate cancer



Rising PSA Clinical State

Although surgery, radiation, or a combination of both can be curative for patients with localized disease, a significant proportion of these patients have recurrent disease as evidenced first by a rising level of PSA. For these individuals, the issue is to determine whether the disease is local or systemic, and in the cased of the latter, the risk of developing metastatic disease – a transition to the lethal phenotype of the illness and in what time frame. A number of nomograms based on the characteristics of the primary tumor, time to a detectable PSA following surgery, and rate of rise in PSA or PSA doubling time (PSADT) have been developed to estimate prognosis, which for the group as a whole is heterogeneous.[3-5]

In one series of patients with rising PSA enrolled on clinical protocols (N = 148) PSADT was a statistically significant independent predictor for metastatic progression (P = 0.001).[6] Moreover, a shorter PSADT is significantly associated with prostate cancer-specific and all-cause mortality with virtually all men who ultimately die of the disease having a PSADT of 3 months or less.[7,8] In practice, most men with a PSADT of 12 months or less are treated, but restricting ADT to men with a PSADT of 9 months or less may be optimal based on the recently reported metastases free survival times in a contemporary series (**Table 1**).

Table 1. Metastasis-free survival (MFS) after PSA recurrence according to PSADT

	PSADT < 3 mos (N = 46)	PSADT 3-9 mos (N = 106)	PSADT 9-15 mos (N = 86)	PSADT ≥ 15 mos (N = 212)
Median MFS, years (95% CI)	1 (0,1)	4 (2,4)	13 (6, >15)	15 (15, >17)
Metastasis-free rate at 5 years, % (95% CI)	5 (1, 21)*	27 (16, 39)	77 (63, 86)	91 (85, 95)
Metastasis-free rate at 10 years, % (95% CI)	N/A	7 (1, 22)	51 (34, 66)	72 (59, 83)

*Last subject sensored at 4 years. In each subgroup, the median MFS as well as the 5- and 10-year probabilities of MFS from the time of PSA recurrence are shown. N/A, not applicable.

In this series, 73% of men with a PSADT in the range of 3-9 months, and 95% of men with a PSADT of less than 3 months developed visible metastatic disease at 5 years.

Androgen Deprivation Therapy and/or Blockade for PSA Progression

Androgen deprivation therapy (ADT) and/or blockade as currently practiced with a gonadotropin-releasing hormone (GnRH) agonist/antagonist with or without an antiandrogen produces declines in PSA followed by tumor shrinkage, a period of quiescence during which the disease does not proliferate, followed by a rise in PSA and regrowth as a castration-resistant prostate cancer (CRPC) that for most men is invariably lethal. Overall outcomes are inversely related to disease burden and the results of multiple series show that patients with more advanced disease progress sooner in comparison to those with less advanced disease.[9,10]

ADT Alone Does Not Completely Suppress Androgen Signaling

ADT, or androgen depletion, as traditionally utilized does not completely inhibit androgen responsive gene expression (PSA, etc.),[11] it does not consistently produce serum levels of testosterone below 20 ng/dl,[12-14] and does not completely eradicate disease due to the presence of cells that can resist and/or survive in a low androgen environment when the disease is first manifest clinically.[15] Overall outcomes with ADT are inversely related to disease burden and the results of multiple series show that subjects with more advanced disease progress and die sooner in comparison to those with less advanced disease.[9,10] Even in the neoadjuvant setting where the disease is clinically confined to the gland, prostates removed after 3 months or up to 8 months of treatment are rarely tumor-free.[16] Overall survival appears to be greater with the addition of a non-steroidal antiandrogen (i.e. bicalutamide) to ADT, at the expense of greater toxicity.[17] Given that enzalutamide is much more potent than bicalutamide in nonclinical models of CRPC,[18] there is rationale for the addition of enzalutamide to ADT in an attempt to more completely suppress androgen signaling.

Intermittent Hormone Therapy as a Therapeutic Option

Most of the approvals for the hormonal therapies to treat prostate cancer have been on the basis of an equivalent effect on serum testosterone levels, or an improved safety profile relative to other available agents.[19-21] None have shown superiority in a cancer specific outcome such as an improvement in disease related symptoms, time to progression or overall survival. Recently, a Canadian study comparing intermittent vs. continuous therapy was reported which showed no difference in cancer specific outcomes, but a marked improvement in overall quality of life for men treated on the intermittent approach.[22] Other groups have explored the approach with "on cycles" of varied duration, but in most studies, the maximal response is observed by 8 months, which is the duration of therapy we have selected for the current study.[23]

Deleterious Metabolic and Physical Side Effects of ADT

Androgen deprivation therapy (ADT) is the mainstay of treatment for advanced prostate cancer (PC), with about 600,000 US men currently on ADT.[24,25] However, despite demonstrated efficacy, ADT causes multiple deleterious metabolic and physical adverse events (AEs) including muscle wasting (atrophy), decreased lean body mass (sarcopenia), increased body fat mass (obesity) and increased insulin resistance leading to a 44% increased risk of new onset type II diabetes and 16% risk of new coronary heart disease.[26-29]

Exercise Training in Prostate Cancer

To address these detrimental and previously underappreciated toxicities, in recent years several research groups have started to examine the safety and efficacy of exercise training (i.e., aerobic training alone, resistance training alone, or the combination) in men either initiating ADT or undergoing ADT for localized as well as advanced prostate cancer.[30]

For example, in the first published study, Segal et al.[31] studied the effects of resistance exercise training on muscle strength and quality of life (QOL) in men with prostate cancer. Specifically, 155 men with diagnosed locally advanced prostate cancer scheduled to receive ADT were randomized to a supervised resistance training group or usual care group. Subjects randomized to exercise training participated in supervised upper and lower body resistance training three times per week for 15 weeks. Results indicated that resistance training significantly increased upper and lower body strength, increased QOL measures, and decreased fatigue as compared to usual care.[31]

In a follow-up study, Segal et al.[32] investigated the effects of efficacy of resistance training alone or aerobic training alone on fatigue, QOL, cardiorespiratory fitness (VO_{2peak}), and other related outcomes in 121 men with prostate cancer initiating radiotherapy with or without ADT. Results demonstrated that both aerobic and resistance training mitigated fatigue, although resistance training was associated with greater longer-term improvements in strength, QOL, and body composition. Finally, recent work by Galvao et al.[33] examined the efficacy of a combined 12-week aerobic and resistance training program on body composition, functional capacity, and QOL endpoints in 57 men undergoing ADT. Results indicated that exercise training was well-tolerated and associated with significant improvements in a number of study endpoints relative to usual care.

4.2 Study Agent

The androgen receptor (AR) is a well-known target in prostate cancer, as prostate cancer growth is dependent on androgens. Depleting or blocking androgen action has been a mainstay of treatment for over 6 decades in the setting of metastatic disease or when prostate cancer recurs following resection and/or radiation.

Enzalutamide (MDV3100) is a selective AR signaling inhibitor. Enzalutamide exerts more substantial beneficial effects than bicalutamide in nonclinical models of CRPC.[18] Enzalutamide has a novel mechanism of action that slows tumor growth and induces apoptosis via 3 complementary actions: 1) enzalutamide competitively inhibits binding of androgens to the AR, has higher affinity for the receptor than bicalutamide and is a pure receptor antagonist whereas bicalutamide has partial agonist activity; 2) enzalutamide inhibits nuclear translocation of the AR while bicalutamide enhances this effect and 3) enzalutamide inhibits binding of the AR to DNA better than bicalutamide even in prostate cancer cells resistant to antiandrogens and with AR overexpression. These three properties of enzalutamide impart a more complete blockade of the AR signaling pathway in the setting of AR overexpression.

Astellas Pharma Global Development, Inc. (Astellas) and Medivation, Inc. (Medivation) are developing enzalutamide for the treatment of cancer. Enzalutamide was approved in the United States on 31 August 2012 under the trade name XTANDI® for the treatment of subjects with metastatic castration-resistant prostate cancer who have previously received docetaxel. On 10 September 2014 the FDA approved the expansion of the use of enzalutamide to also include men with mCRPC prior to receiving chemotherapy. Enzalutamide has subsequently been approved in more than 35 countries. Clinical development is ongoing for other indications for enzalutamide in prostate cancer and breast cancer.

Enzalutamide is formulated with Labrasol® (caprylocaproyl macrogolglycerides) and provided as an orally available immediate-release dosage form filled into soft gelatin capsules containing 40 mg of the active pharmaceutical ingredient.

4.2.1 Pre-clinical experience (Enzalutamide IB, edition 7)

Pharmacology

The primary pharmacodynamic effect of enzalutamide is inhibition of the AR signaling pathway. Enzalutamide inhibits androgen binding to the AR, AR nuclear translocation in the presence of androgen and AR:chromatin association. In multiple prostate cancer cell lines that specifically model castration-resistant prostate cancer (CRPC) (LNCaP/AR, VCaP, W741C LNCaP), the consequences of enzalutamide treatment include inhibition of AR-induced gene transcription, reduced cell proliferation, increased cell death by apoptosis and tumor regression. In a mouse xenograft model of CRPC using prostate cancer cells that overexpress the AR (LNCaP/AR), enzalutamide inhibits tumor growth and reduces tumor size. One of the two major human metabolites of enzalutamide, N-desmethyl enzalutamide, demonstrates key primary pharmacodynamics of similar potency to the parent molecule, while the second major human metabolite, a carboxylic acid metabolite has no known pharmacodynamic effect. In humans, *N*-desmethyl enzalutamide circulates at approximately the same steady-state plasma concentrations as enzalutamide and is assumed to contribute to clinical effects.

Nonclinical studies have shown that enzalutamide suppresses the growth of AR-expressing breast cancer cells that also express the estrogen receptor (ER), as well as cells that do not express the ER.

Enzalutamide and N-desmethyl enzalutamide bind to and antagonize the γ-aminobutyric acid (GABA)-gated chloride channel. Enzalutamide given at high doses to mice induced dose-dependent convulsions, an observation that parallels the clinical safety data showing that dose appears to be an important predictor of the risk of seizure in subjects. As some molecules that antagonize the GABA-gated chloride channel are associated with convulsions, enzalutamide and N-desmethyl enzalutamide may both contribute to the convulsions that were observed in nonclinical studies. Safety pharmacology studies evaluating the central nervous, respiratory and cardiovascular systems did not identify any additional acute effects of enzalutamide at exposures relevant to the proposed human clinical dose of 160 mg/day.

Pharmacokinetics

Nonclinical studies with in vitro test systems have contributed to the understanding of enzalutamide pharmacokinetics and the potential for drug-drug interactions (DDIs). Enzalutamide has high permeability across Caco-2 monolayers. Both enzalutamide and *N*-desmethyl enzalutamide are inducers and inhibitors of P-glycoprotein (P-gp).

Data from a study with human cytochrome P450 (CYP) enzymes showed that CYP2C8 and CYP3A4/5 are both responsible for the metabolism of enzalutamide, and a clinical study showed that it is primarily CYP2C8 that is responsible for the metabolism of enzalutamide and the subsequent formation of the active metabolite (N-desmethyl enzalutamide). Inhibition studies with CYP enzymes showed that enzalutamide, N-desmethyl enzalutamide, and the inactive carboxylic acid metabolite caused direct inhibition of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 and time-dependent inhibition of CYP1A2. Induction studies with CYP enzymes showed that enzalutamide caused induction of CYP2B6, CYP3A4, and uridine 5'-diphospho-glucuronosyltransferase (UGT) and that enzalutamide is not expected to induce CYP1A2 at therapeutically relevant concentrations. Subsequent clinical studies showed that enzalutamide is an inducer of CYP2C9, CYP2C19, CYP3A4, and possibly UGTIA1, while enzalutamide has no clinically meaningful effect on CYP2C8.

Enzalutamide is 97% to 98% bound to plasma proteins, primarily albumin, and there is no in vitro protein binding displacement between enzalutamide and other highly bound drugs (warfarin, ibuprofen, and salicylic acid). *N*-desmethyl enzalutamide is 95% bound to plasma proteins.

Toxicology
Macroscopic and microscopic findings, as well as organ weight changes related to enzalutamide administration, were observed in the prostate gland, seminal vesicles, testes and epididymides after repeat dosing in mice, rats and dogs. These changes are consistent with the primary pharmacological properties of enzalutamide and have been previously observed with non-steroidal antiandrogen compounds, such as bicalutamide. Mild and reversible hypertrophy or hyperplasia of Leydig cells in the testes was found in repeat-dose studies of enzalutamide and/or *N*-desmethyl enzalutamide in mice and dogs. Leydig cell hypertrophy/hyperplasia is a common finding in toxicity studies for antiandrogen compounds such as bicalutamide, flutamide and nilutamide and is related to the occurrence of Leydig cell tumors in carcinogenicity studies for these agents. The extensive clinical experience with antiandrogens has shown that Leydig cell tumors in animals do not translate to a risk for humans. Mammary gland changes were not observed in male and female dogs treated with enzalutamide for 39 weeks.

In embryo-fetal toxicity studies in mice, enzalutamide induced premature deliveries in dams and embryo-fetal deaths. Decreased fetal body weights and high incidence of external and skeletal abnormalities, such as decreased anogenital distance and cleft palate associated with absent palatine bone were also observed. Such effects are likely to be attributed to AR inhibition, as similar effects in rodents have also been found for other AR antagonists. No effects on dams or on embryo-fetal development were found in rabbits.

4.2.2 Clinical experience (Enzalutamide IB, edition 7)

Pharmacokinetics
The pharmacokinetics and metabolism of enzalutamide have been evaluated in subjects with CRPC, hormone-naïve prostate cancer patients, healthy male volunteers, and subjects with mild or moderate hepatic impairment. Individual doses have ranged from 30 to 600 mg. Pharmacokinetic studies of enzalutamide in women have not been completed.

After oral administration to subjects with CRPC, the median time to reach maximum enzalutamide plasma concentrations was 1 hour, and the mean terminal half‑life was 5.8 days. Enzalutamide steady state was achieved by day 28, and the accumulation ratio was 8.3-fold. At steady state, enzalutamide showed approximately dose proportional pharmacokinetics over the range of 30 to 360 mg/day.

A mass balance and biotransformation study in healthy male volunteers showed that enzalutamide is primarily eliminated by hepatic metabolism.

A food-effects study showed that food does not have a clinically relevant effect on the area under the plasma concentration-time curve (AUC) of enzalutamide or N-desmethyl enzalutamide; therefore, enzalutamide can be taken with or without food.

A hepatic impairment study showed that the composite AUC of enzalutamide plus N-desmethyl enzalutamide after single-dose enzalutamide was similar in subjects with baseline mild or moderate hepatic impairment (Child-Pugh Class A and B, respectively) relative to subjects with normal hepatic function, and no starting dose adjustment is needed. Enzalutamide is currently being evaluated in subjects with baseline severe hepatic impairment (Child-Pugh Class C).

Based on population pharmacokinetics modeling, age, weight and renal function (creatinine clearance [CLCR] ≥ 30 mL/min) do not have clinically meaningful effects on enzalutamide exposures; therefore, no dose adjustments are indicated for these covariates. Based on pharmacokinetic data from a study in Japanese patients with prostate cancer, there were no clinically relevant differences in exposure

between Japanese and white patients. Clinical data are insufficient to assess the potential effect of severe renal impairment (CLCR < 30 mL/min) and end-stage renal disease on enzalutamide pharmacokinetics.

A drug-drug interaction study in prostate cancer patients showed that enzalutamide can affect exposures to other co-medications. At steady state, enzalutamide reduced the AUC of oral midazolam (CYP3A4 substrate), S-warfarin (CYP2C9 substrate) and omeprazole (CYP2C19 substrate) by 86%, 56% and 70%, respectively. Therefore, enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. Substrates of CYP3A4, CYP2C9 and CYP2C19 with a narrow therapeutic index are to be avoided, as enzalutamide may decrease plasma exposure of these drugs. If enzalutamide is coadministered with warfarin (CYP2C9 substrate), additional international normalized ratio (INR) monitoring is to be conducted. Enzalutamide (160 mg/day) did not have a clinically relevant effect on exposure to intravenous docetaxel (CYP3A4 substrate) or oral pioglitazone (CYP2C8 substrate).

A drug-drug interaction study in healthy subjects showed that concomitant medications can affect exposure to enzalutamide. Coadministration of gemfibrozil (a strong CYP2C8 inhibitor) increased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 2.2 fold; therefore, strong CYP2C8 inhibitors are to be avoided. If coadministration with a strong CYP2C8 inhibitor is necessary, the dose of enzalutamide is to be reduced to 80 mg once daily. Coadministration of itraconazole (strong CYP3A4 inhibitor) increased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 1.3-fold; as this small change is not clinically meaningful, no starting dose adjustment is needed when coadministering enzalutamide with CYP3A4 inhibitors.

Efficacy

The efficacy of enzalutamide in patients with metastatic CRPC was assessed in 5 clinical studies including two phase 3, randomized, placebo-controlled studies, MDV3100-03 (PREVAIL) and CRPC2 (AFFIRM); phase 1 Study S-3100-1-01; phase 2 Study CRPCMDA- 1; and phase 1/2 Study 9785-CL-0111.

In the two pivotal, randomized, placebo-controlled phase 3 studies (MDV3100-03 and CRPC2) in men with metastatic CRPC, enzalutamide treatment showed a statistically significant advantage over placebo across multiple clinically relevant endpoints such as overall survival, radiographic progression-free survival (rPFS), time to first skeletal-related event, time to prostate-specific antigen (PSA) progression, PSA response rate, best overall soft tissue response, and quality of life as measured by the Functional Assessment of Cancer Therapy - Prostate (FACT-P). Notably, in MDV3100-03, a study of enzalutamide versus placebo in men with metastatic CRPC who were chemotherapy-naïve, enzalutamide delayed time to initiation of cytotoxic chemotherapy compared with placebo. In both phase 3 studies of patients with metastatic CRPC, the benefit of enzalutamide treatment on overall survival as measured by the estimated hazard ratio was observed across all prespecified subgroups. A significant benefit on overall survival was observed despite substantially higher and earlier use in the placebo groups of subsequent therapies that are known to have a survival benefit in patients with prostate cancer.

Further data from open-label Studies S-3100-1-01, CRPC-MDA-1, and 9785-CL-0111 in patients with metastatic CRPC provided supportive efficacy information.

Overall Safety Profile

The safety profile of enzalutamide in patients with metastatic CRPC is primarily derived from two randomized, placebo-controlled phase 3 studies (MDV3100-03 and CRPC2), hereafter defined as the combined controlled population. Several other studies in patients with prostate cancer and healthy volunteers provide additional safety data.

In the combined controlled population, the median duration of exposure to enzalutamide was 12.7 months and the median duration of exposure to placebo was 3.8 months. Approximately

52% of patients treated with enzalutamide remained on study drug for at least 1 year compared with 14% of patients treated with placebo; approximately 9% of patients treated with enzalutamide remained on study drug for at least 2 years compared with approximately 2% of patients treated with placebo.

Overall, enzalutamide treatment was generally well tolerated across all studies, and the safety profile in MDV3100-03 was generally consistent with that observed in CRPC2. As expected for this patient population with advanced prostate cancer, nearly all enzalutamide-treated and placebo-treated patients experienced at least 1 adverse event (AE) during each study. In MDV3100-03, a higher proportion of enzalutamide-treated patients experienced grade 3 or higher AEs compared with placebo-treated patients (42.9% vs 37.1%); however, time to event analyses showed that these events occurred much later in the enzalutamide group than the placebo group. The median time to first grade 3 or higher AE in MDV3100-03 was 22.3 months in the enzalutamide group versus 13.3 months in the placebo group. A similar pattern was observed in time to first grade 3 or higher event in the combined controlled population. In MDV3100-03, a higher incidence of serious adverse events (SAEs) was observed for enzalutamide compared with placebo (32.0% vs 26.8%), but with a longer median time to first SAE (not yet reached vs 23.3 months). A similar pattern was observed for the incidence of SAEs and time to first SAE in the combined controlled population.

In the combined controlled population, the proportion of patients who discontinued treatment primarily as a result of an AE and the proportion of patients with fatal AEs were comparable between treatment groups.

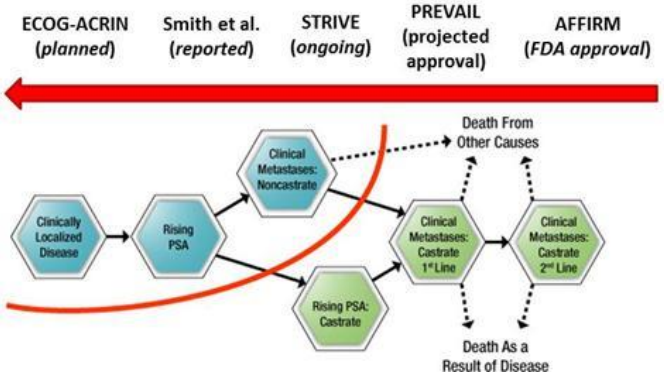
The following adverse drug reactions (ADRs) were identified in patients with metastatic CRPC (either primarily in chemotherapy-naïve patients with earlier stage disease, or patients with more advanced stage disease after docetaxel): seizure, hypertension, fatigue, hot flush, falls/nonpathological fractures, cognitive/memory impairment, neutropenia, headache, anxiety, hallucination, pruritus/dry skin, gynecomastia and restless legs syndrome.

4.3 Study Purpose/Rationale

Enzalutamide Will be Used in Earlier Clinical Disease States of Prostate Cancer

As discussed above, ADT does not completely suppress androgen signaling and the novel anti-androgen *enzalutamide* (Xtandi®, Medivation/Astellas) provides more potent inhibition of the androgen receptor than prior anti-androgens (i.e. bicalutamide). Enzalutamide was initially approved in men with metastatic, castrate-resistant prostate cancer following docetaxel treatment based on a significant improvement in overall survival versus placebo in the *AFFIRM* trial (**Figure 2**).[34] However, a recent press release from Medivation/Astellas announced that the *PREVAIL* trial, which randomized men with metastatic castrate-resistant prostate cancer who had not received chemotherapy to enzalutamide versus placebo, was being stopped due to a favorable risk-benefit ratio including improved survival and radiographic progression free survival in the enzalutamide arm.[35] The ongoing *STRIVE* study randomizes asymptomatic or minimally symptomatic subjects who have failed primary androgen deprivation therapy to either bicalutamide or enzalutamide (NCT01664923). Enzalutamide also has been studied as monotherapy in hormone-naïve prostate cancer by *Smith et al*.[36] In this phase II study, men were asymptomatic at baseline and fatigue was the

Figure 2. Enzalutamide Moves to Earlier Clinical States of Prostate Cancer



second most common adverse event (34.3%). For now, however, combining enzalutamide with ADT remains standard of care. ADT plus enzalutamide is also being studied in even earlier stage prostate cancer: for example, an *ECOG-ACRIN* adjuvant trial in high-risk men post-prostatectomy is being planned. *Therefore, alongside these efficacy studies there is a need to evaluate the functional and metabolic changes that occur in treatment-naïve men with enzalutamide and ADT, as well as possible mitigation strategies (i.e. exercise training)*.

Rationale for Exercise Training with ADT and Enzalutamide

Overall, the extant data provides initial evidence to suggest that the addition of enzalutamide, an androgen receptor antagonist, to conventional castration therapy (GnRH agonists/antagonists or orchiectomy to maintain serum testosterone <50 ng/dL) may be a highly effective approach for the treatment of hormone-naïve prostate cancer but also may exacerbate the well-described adverse toxicities associated with androgen suppression. Against this background, as described, there is strong evidence that relatively short-term supervised exercise training (aerobic alone, resistance alone, or the combination) is well-tolerated and associated with significant improvements in a broad range of physiological and subject-reported outcomes in men either initiating or currently receiving androgen suppression therapy.

No study to date has examined the efficacy, tolerability, and safety of exercise training to prevent and/or mitigate common adverse toxicities in men receiving combination androgen suppression therapy for hormone-naïve prostate cancer.

Rationale for and Clinical Importance of VO_2peak

Over the past decade, there has been increased research and clinical interest in the application of exercise therapy following a cancer diagnosis. Systematic reviews and meta-analyses have extensively evaluated the available literature investigating the role of exercise therapy following a cancer diagnosis.[37-41] For example, Speck et al.[42] identified a total of 66 'high quality' studies that examined the effects of exercise on 60 different physiological, functional, biological, or psycho-social outcomes in adults with cancer. In brief, the majority of studies were conducted in women with early breast cancer with fewer studies in non-small lung cancer (NSCLC), hematologic malignancies, or involving subjects from various types of cancer populations.

Of note, in the vast majority of exercise studies to date, subject-reported outcomes (PROs) such as QOL, fatigue, or physical functioning were the primary endpoint. To this end, in general, the current extant literature base indicates that exercise training is associated with significant improvements in PROs. Few adverse events (AEs) were reported. It was concluded that exercise training is a beneficial adjunct therapy both during and following the completion of adjuvant therapy in adult cancer subjects, with low incidence of AEs.[42]

Although the importance of PROs are undisputed, there is growing sentiment in the scientific community that exercise – oncology trials now need to look beyond PROs particularly when assessing functional or physiological-based end points in oncology populations such as deconditioning, physical functioning, and fatigue.[43] Indeed, PROs are subjective and have poor inter-rater reliability. Moreover, these instruments fail to characterize the degree or potential causes of physiologic limitation, assess symptom responses to exertion or inform therapeutic intervention.[44] In response, our group, as well as others, have started to assess the utility of alternative clinical tools that provide a more sensitive and objective assessment of physical functioning in the oncology setting.

Cardiorespiratory fitness, as measured by an objective exercise tolerance test, reflects the integrative ability of the cardiopulmonary system to deliver adequate oxygen and substrate to metabolically active skeletal muscles for ATP resynthesis.[45] Peak oxygen consumption (VO_{2peak}) provides the gold standard (direct) assessment of cardiorespiratory fitness. Direct or estimated measurement of VO_{2peak} is a well-established independent predictor of mortality in a broad range of non-cancer populations.[46,47] In a series of studies, our group has demonstrated that measurement of VO_{2peak} is safe and well-tolerated in a broad range of cancer subjects both during and following cytotoxic therapy.[44,48-50] In addition, a diagnosis of cancer and associated therapeutic

management is associated with significant impairments in VO_{2peak},[51-53] while low VO_{2peak} is a significant predictor of physical and functional QOL domains, fatigue, and other PROs in cancer populations.[54,55] Finally, we also recently showed that VO_{2peak} was a significant predictor of overall mortality, that provided prognostic information beyond established factors including performance status.[48,56]

5 OBJECTIVES AND ENDPOINTS

All endpoints will be evaluated at the time points specified in the Schedule of Events at the beginning of **Section 9**. See **Section 12** for Statistical Methods and Data Analysis. Key comparisons will be the change from Day 1 (week 1) to Day 113 (week 17), which corresponds to the end of the 16 week exercise training program for Arm B, and from Day 1 (week 1) to Day 252 (week 37), which corresponds to the end of the 32 weeks of treatment with enzalutamide and ADT for both Arms.

	Objective	Endpoint	Analysis
Primary	Compare cardiopulmonary function in usual care vs. exercise training arms	Change in VO_2peak with usual care or exercise training at 16 weeks from baseline	See Section 12.1 to 12.4
Key Secondary	Compare the effects on physical functioning / functional capacity	Objective assessments (i.e., chair-stand test, timed up and go, 6 minute walk distance) of functional capacity	See Section 12.5
Other Secondary	Compare the effects on primary physiological determinants of VO_2peak	Upper and lower extremity maximal muscular strength (voluntary one-repetition maximum [1-RM]) and muscular endurance (repetitions to fatigue at 70% of 1-RM and muscle cross sectional area of the dominant thigh (3.0 T magnetic resonance imaging)	See Section 12.5
Other Secondary	Compare the effects on metabolic outcomes of interest	Metabolic control (fasting glucose, insulin, glycosylated hemoglobin, HOMA-IR) and body composition (lean and fat body mass)	See Section 12.5
Other Secondary	Compare the effects on patient reported outcomes (PROs) of interest	Quality of Life (FACT-P), Fatigue (FACIT-F), and Leisure Time Exercise Habits (Godin Leisure Time Exercise Questionnaire)	See Section 12.5
Other Secondary	Evaluate safety, feasibility, and acceptability of exercise training	Eligibility rate, acceptance rate, adherence rate, attrition rate, and adverse event rate (CTCAE v4.0) in each arm	See Section 12.5
Exploratory	Compare PSA response rates	Maximum decrease in PSA from baseline (waterfall plot)	See Section 12.5
Exploratory	Describe metabolomics changes	Targeted and untargeted metabolic profiling	See Section 12.5
Sensitivity	Assay the robustness of results observed in analyses based on the modified ITT population	Primary and Key secondary endpoints, using Last Observation Carried Forward methods	See Section 12.5

6 INVESTIGATIONAL PLAN

6.1 Study Design

This is a two-arm, non-blinded randomized (1:1) phase II trial to determine the efficacy on aerobic capacity of the combination of enzalutamide (ENZ) with androgen deprivation therapy (ADT) compared to the same regimen plus supervised exercise training (ENZ-ADT plus exercise training) in men with hormone-naïve prostate cancer. This study will be conducted at 2 centers: Duke Cancer Institute (DCI) and Memorial Sloan-Kettering Cancer Center (MSKCC). A total of 40 subjects will be enrolled. Subjects will be treated with enzalutamide plus ADT for 32 weeks. If randomized to the exercise arm, subjects will undergo supervised exercise training for 16 weeks.

6.1.1 Dose Modification

Subjects who experience a Grade 3 or greater toxicity attributed to enzalutamide, which cannot be ameliorated by the use of adequate medical intervention, may have their enzalutamide treatment interrupted for 1 week or until the toxicity grade improves to Grade 2 or lower severity. The enzalutamide may be subsequently restarted at the same or a reduced dose (120 mg or 80 mg) with the written approval of the Duke principal investigator.

6.1.2 Missed Doses

Missed doses of enzalutamide will be skipped. The subject should resume dosing the next day. This should be recorded in the Pill Diary.

6.1.3 Concomitant Medications

All concomitant medications must be recorded on the appropriate CRF. Concomitant medications will be assessed at Screening and all clinic visits. The dosage and regimen of the following medications and any chronic permitted concomitant medications should be stable during the screening period (≥ 4 weeks prior to randomization) and held constant throughout the study:

- Bisphosphonates (if applicable)
- Denosumab (if applicable)
- GnRH analogue.

Subjects must be receiving androgen deprivation therapy (continuing therapy with a GnRH analogue) during the treatment phase starting at visit 3, day 29. If androgen deprivation therapy is discontinued, the subject must permanently discontinue study treatment.

Subjects are encouraged to receive standard of care supplementation such as calcium and vitamin D.

Certain concomitant medications and therapies are excluded during study treatment. For subjects who experience disease progression and are eligible to continue to receive study treatment, certain other medications and therapies are excluded. These excluded concomitant medications and therapies during study treatment are:

- Corticosteroids for prostate cancer[a]
- Cytotoxic chemotherapy
- Investigational agents
- Hormonal agents[b]
- Biologics[c]

a. Use for acute onset (or exacerbation) of illness not related to prostate cancer is allowed.
b. Luteinizing hormone-releasing and GnRH analogues are allowed.

c. Bone targeting agents (i.e. bisphosphonates or denosumab) are allowed if used to increase bone mass in men at high risk of fracture, in the opinion of the treating physician.

The risk of seizure may be increased in subjects with a history of seizures or other predisposing factors. The risk of seizure may also be increased in subjects receiving concomitant medications that may lower the seizure threshold.

Deviation from these guidelines should occur only if absolutely necessary for the well-being of the subject. Any deviation from the medication/treatment guidelines are to be recorded on the concomitant medication CRF. Additionally, the Duke principal investigator is to be notified to determine the subject's continued eligibility in the study.

6.1.3.1 Effects of Enzalutamide on Exposure to Other Drugs

Clinical data indicate that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (e.g., phenytoin, warfarin), and CYP2C19 (e.g., S-mephenytoin) should be avoided as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring.

6.1.3.2 Drugs That May Affect Exposure to Enzalutamide

Drugs That Inhibit or Induce CYP2C8

Co-administration of a strong CYP2C8 inhibitor (e.g., gemfibrozil) increased the composite $AUC_{0-\infty}$ of enzalutamide plus its active metabolite in healthy volunteers; therefore, co-administration of enzalutamide with strong CYP2C8 inhibitors should be avoided if possible. If co-administration of enzalutamide with strong CYP2C8 inhibitors cannot be avoided, reduce the enzalutamide dose to 80 mg once daily. If co-administration of the strong inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.

The effects of CYP2C8 inducers on the PK 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. Selection of a concomitant medication with no or minimal CYP2C8 induction potential is recommended.

Drugs That Induce CYP3A4

The effects of CYP3A4 inducers on the PK of enzalutamide have not been evaluated in vivo. 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. Selection of a concomitant medication with no or minimal CYP3A4 induction potential is recommended. 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.

6.1.3.3 Precautions Regarding Concomitant Medications

Refer to the following links for updated lists of CYP inhibitors, inducers, and substrates.

- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency
- http://medicine.iupui.edu/clinpharm/ddis/table.aspx

6.1.4 Randomization

Once the subject has been registered, completed screening, and found to eligible post-baseline testing, the study coordinator at Duke will request the subject's random assignment to one of the two treatment arms from the Medidata RAVE database.

For this pilot study, subjects will be randomly assigned with equal probability to either usual care or exercise training. A stratified block design will be used with randomization stratified by site only. Specifically, stratification will be: Duke versus MSKCC. This study is open label, meaning that neither subjects nor study personnel will be blinded to treatment assignment.

The site will then be notified by the RAVE database to which arm the subject has been assigned. For subjects who are not eligible and fail the screening process, no further action is necessary and no additional information will be collected. However, the number of screen failures and reason for screen failure will be collected at each site and tallied at the end of the study.

Case report forms will only be completed for those registered and randomized subjects, including those who do not receive treatment. However, subjects who do not receive the assigned treatment will be replaced and not counted toward the overall study sample size. Data limited to demographics will be collected for screen failures.

6.2 Rationale for Selection of Dose, Regimen, and Treatment Duration

Enzalutamide has an indication for the treatment of subjects with metastatic castration-resistant prostate cancer who have previously received docetaxel (Enzalutamide Package Insert, version 08/2012). The FDA approved dose of enzalutamide is 160 mg by mouth daily, which is the dose that will be used in this study.

6.3 Rationale for Correlative Studies

FUNCTIONAL CAPACITY END POINTS

Chair-Stand Test: The Chair-Stand Test provides a reliable and valid indicator of functional performance of lower body strength in generally active, community-dwelling older adults.[57] Jones et al. examined the test-retest reliability and construct validity (in comparison to a two maximum leg press tests) of the 30-sec chair stand as a measure of lower body strength in 70 adults over 60 years of age. There was a high correlation between chair-stand performance and maximum weight-adjusted leg-press performance for both men and women (r = .78 and .71, respectively) supports the criterion-related validity of the chair stand as a measure of lower body strength. Chair-Stand performance decreased significantly across age groups in decades--from the 60s to the 70s to the 80s and was significantly lower for participants reporting low levels of exercise behavior compared participants reporting higher levels of exercise behavior. To date, the Chair-Stand Test has not been assessed in men with prostate cancer. However, our group is currently conducting Chair-Stand Tests in ongoing exercise intervention trials in subjects with non-small lung cancer and metastatic breast cancer. This test, in combination with the Timed Get Up and Go and 6MWT, are widely established as the gold standard assessments of functional performance in older adults and will complement the performance-based primary outcome of cardiopulmonary function (VO_{2peak}).

Timed Up and Go: The Timed Get Up and Go (TUG) is field-based test that assesses a person's mobility. Specifically, the TUG measures the time that a person takes to rise from a chair, walk three meters, turn around, walk back to the chair, and sit down. This test has been found to be feasible in the majority of older adults.[58] Scores of ten seconds or less indicate normal mobility, 11 – 20 seconds are within normal limits for frail elderly and disabled subjects, and greater than 20 seconds suggests that indicates that further examination is required. A recommended practical cut-off value for the TUG to indicate normal versus below normal performance is 12 seconds.[59] TUG performance decreases with the presence of mobility impairments.[59] Again, to our knowledge, the TUG test has not been assessed in men with prostate cancer.

However, our group is currently conducting these tests in ongoing exercise intervention trials in subjects with non-small lung cancer and metastatic breast cancer. This test, in combination with other functional performance measures are widely established as the gold standard assessments of functional performance in older adults and will complement the performance-based primary outcome of cardiopulmonary function (VO_{2peak}).

6 Minute Walk Distance (6MWD) : Six-minute walk testing (6MWT) is a simple, clinically feasible and objective assessment of functional capacity that is practical even in severely deconditioned clinical populations (e.g., chronic heart failure, chronic obstructive pulmonary disease (COPD), and organ transplant recipients). 6MWT is a robust predictor of mortality in non-cancer settings;[60-63] only three studies to date have investigated the prognostic importance of 6MWT in the oncology setting.[64,65]

Specifically, Kasymjanova et al. investigated the association between 6MWD and survival in 64 subjects with inoperable NSCLC.[64] Relative to <400m, a 6MWD ≥400m was associated with a 56% reduction in the risk of death after adjustment for important covariates. Similarly, in recent work among 118 subjects with histologically confirmed metastatic NSCLC, we found that compared with subjects achieving a 6MWD <358.5m, the adjusted hazard ratio (HR) for all-cause mortality was 0.61 (95% CI, 0.34 to 1.07) for a 6MWD of 358.5 – 450m, and 0.48 (95% CI, 0.24 to 0.93) for a 6MWD >450m.[66] Interestingly, in further work by our group we found that 6MWD was not an independent predictor of prognosis in 243 subjects with grade III/IV recurrent malignant glioma,[65] suggesting that 6MWD may not be an appropriate clinical tool for objectively assessing physical functioning in all cancer populations.

QUANTITATIVE SKELETAL MUSCLE FUNCTION END POINTS

It is well-established that ADT causes significant muscle wasting (atrophy), decreased lean body mass, and decreased muscle strength.[67,68] For example, Galvao and colleagues examined the effects of ADT on upper and lower body muscle strength and a range of direct measures of physical performance using a cross-sectional design with 118 men (48 men undertaking ADT for prostate cancer and 70 healthy aged-matched controls) from a single tertiary center.[69] Men on ADT had significantly reduced muscle strength for the upper- and lower-body and impaired functional performance compared to controls. Also, men treated with ADT were consistently impaired across a broad range of physical and functional musculoskeletal performance assessments compared with their age-matched normal controls. Subsequent work by the same group examined the effects of ADT on muscle attenuation, an indirect measure of intramuscular lipid content, as well as the muscle cross-sectional area (CSA) in 39 men with prostate cancer.[67] Muscle attenuation of the rectus femoris muscle was significantly reduced following the initiation of ADT by 18.9%. In addition, there was a significant decrease in the CSA for the sartorius, quadriceps and rectus femoris muscles. These results indicate that not only muscle size but also muscle quality may be adversely affected by the undertaking of ADT in men with prostate cancer. Accordingly, measurement of skeletal muscle function in the present using gold-standard, quantitative assessments is of obvious importance.

In this study, skeletal muscle function will be quantified using three outcomes: **(1) lower extremity skeletal muscle cross-sectional area**, **(2) upper and lower body dynamic strength and (3) upper and lower body muscular endurance**. Our team has extensive experience in assessing components of skeletal muscle function including muscle strength and muscle cross-sectional area. For example, our investigative team recently completed a prospective pilot study investigating, for the first time, changes in skeletal muscle function in terms of muscle strength and muscle cross-sectional area (MRI) among 25 newly diagnosed postsurgical high grade glioma and 10 low grade glioma subjects from surgery to 24 weeks post-surgery. Results also indicated that such skeletal muscle assessments can detect changes in function during chemoradiation. Such changes may predict symptomology and even long-term disease outcome.[70]

Given that the primary endpoint of this protocol is change in VO_2peak, in the context of the data presented above regarding the effects of ADT on skeletal muscle and the known mechanism of action of enzalutamide, an important measure of indicating that the periphery has both adapted to the exercise training and will assist

in the entire cardiopulmonary system improving functionality may be **muscular endurance**. Whereas muscular strength is the ability of a muscle or muscle group to generate maximal force, muscular endurance describes the muscle's ability to exert successive submaximal force for a certain period of time. So, in addition to 1-RM testing for muscular strength, we will evaluate muscular endurance by testing the number of repetitions to fatigue at 70% of 1-RM. These methods have been demonstrated by Franks & Howley (1989) and others (Nieman, 1995); in particular, there may be discordance between muscular strength and endurance.

METABOLIC AND RELATED END POINTS

Metabolic Control (fasting glucose, fasting insulin, HgbA1c): Prospective clinical trials have documented that ADT leads to decreased insulin sensitivity, or insulin resistance (IR).[71-73] Although metabolic changes such as IR may continue for three years or more, they begin within the first 12 weeks of therapy.[74] Furthermore, ADT is associated with an increased risk of new onset diabetes. In one large population-based study men receiving a GnRH agonist had a dramatically increased incidence of diabetes (HR 1.44, $p<0.001$).[29] Exercise is known to improve glycemic control and reverse IR, and may prevent the development of diabetes in general populations.[75]

The metabolic changes with enzalutamide in combination with ADT are not known. However, enzalutamide also has been studied as monotherapy in hormone-naïve prostate cancer by Smith et al.[36] In this phase II study, IR developed as measured by ΔHOMA-IR (+45.1% ± 192.5% at 25 weeks), although there was no significant change in fasting blood glucose (-0.1% ± 14%). The change from baseline to week 25 in HgbA1c was -2.0 ± 6.0% and fasting insulin was +39.4 ± 170.7%. These data suggest that the addition of enzalutamide to ADT could cause worse insulin resistance and provide rationale for evaluating the metabolic changes in this setting.

Body Composition: ADT causes a decrease in lean body mass (LBM) and increase in fat body mass (FBM), termed sarcopenic obesity.[74] Randomized trials have demonstrated that a combination of aerobic and resistance exercise training can help maintain LBM during ADT.[76] In the study by Smith et al. discussed above, the mean change from baseline to week 25 in LBM and FBM were -4.2 ± 3.4% and +6.9 ± 12.1%, respectively. These data suggest that the addition of enzalutamide to ADT could cause worse sarcopenic obesity and provide rationale for evaluating body composition changes in this setting.

Food Frequency Questionnaire: Diet and exercise are inter-related; as such, beneficial changes may tend to rise and fall together. The Food Frequency Questionnaire (FFQ) is the most common dietary assessment tool used in large epidemiologic studies of diet and health. The self-administered FFQ booklet asks participants to report the frequency of consumption and portion size of approximately 125 line items over a defined period of time (e.g. the last month; the last three months).[77] Each line item is defined by a series of foods or beverages. The Nutrition Assessment Shared Resource (NASR) at the Fred Hutchinson Cancer Research Center (FHCRC) periodically updates its standard FFQ to reflect U.S. food consumption patterns and major changes in the market place. The GSEL and MSEL FFQs were designed in 2001 under the direction of FHCRC nutritional scientists and epidemiologists and are based on the questionnaires used in two large NIH funded studies, the Selenium and Vitamin E Cancer Prevention Trial (SELECT)[78] and the VITamins and Lifestyle study (VITAL).[79] The GSEL FFQ was updated in late 2010. It is now called the GNA (General Nutrition Assessment) and has a male counterpart called the MNA (Men's Nutritional Assessment). A MNA FFQ will be administered at the Week 1 and Week 17 time points to explore the collinearity of diet/exercise and to potentially correct for imbalances in the dietary intake between arms.

PATIENT REPORTED OUTCOMES END POINTS (FACT-P, FACIT-F, Godin Leisure Time)

ADT causes fatigue and worse quality of life; these changes can be mitigated with exercise training.[31,80] For example Segal et al. randomized 155 men with prostate cancer treated with ADT[76] to an intervention group that participated in a resistance exercise program three times per week for 12 weeks (82 men) or to a waiting list control group (73 men). The primary outcomes were fatigue and disease-specific quality of life as assessed by self-reported questionnaires after 12 weeks. Men assigned to resistance exercise had less interference

from fatigue on activities of daily living (P =.002) and higher quality of life (P =.001) than men in the control group. In the phase II study of enzalutamide monotherapy in HNPC , fatigue was the second most common adverse event (34.3%) and quality of life data has not been reported.[36] The changes that occur with ENZ – ADT +/- exercise training have not been described. Therefore, we propose to describe the changes that occur in this setting.

The Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire is a commonly used, validated tool for assessing health-related quality of life in men with prostate cancer. FACT-P was used by both phase III trials of enzalutamide in mCRPC.[34,81] Because fatigue is a PRO of interest, we will also evaluate it using the Functional Assessment of Chronic Illness Therapy – Fatigue (**FACIT-F**) questionnaire,[82] which has been validated in subjects with prostate cancer. Finally, because it will be important for interpretation of our data to understand baseline activity levels in both arms, as well as activity levels on the control arm (to assess for contamination), we will evaluate leisure time exercise habits with the simple, Godin Leisure Time Exercise Questionnaire.

PROSTATE SPECIFIC ANTIGEN (PSA) END POINTS

Prostate specific antigen (PSA), a glycoprotein produced by both normal and cancerous prostate tissue, is useful for monitoring response to therapy. As there is no radiographic evidence of disease to follow, PSA is commonly used to monitor response to therapy in the *Rising PSA* clinical state of prostate cancer.[22] A phase II study of enzalutamide monotherapy in men with both metastatic (38.8%) and non-metastatic hormone-naïve prostate cancer documented a 92.5% PSA response rate (≥80%) and 99.6% median PSA decrease.[36] PSA declines were generally consistent between subjects with and without metastases. Because the declines with ADT plus enzalutamide have not been well-described in the hormone-naïve population, we propose to evaluate the maximum PSA decrease from baseline in each subject (waterfall plot) and report the PSA response rate (proportion with ≥80% decline) and median PSA decrease in this population.

METABOLOMICS END POINTS

Metabolomics**,** the measurement of multiple small molecule metabolites in biological specimens, is a promising biomarker platform based on ease-of-use, cost, and close proximity to phenotype. Metabolomics approaches have been used to both detect and predict drug toxicity.[83,84] Saylor et al recently published the first study exploring untargeted metabolomic profiling changes in 36 prostate cancer subjects treated with ADT, measuring changes in plasma metabolomics profiles from baseline to after 3 months treatment.[85] In this exploratory analysis, multiple steroids decreased; most bile acids and metabolites increased; markers of lipid beta-oxidation and omega-oxidation decreased; and two previously identified biomarkers of insulin resistance were stable to decreased. The metabolomics changes induced by adding a potent anti-androgen (e.g. enzalutamide) to ADT are unknown. This provides rationale for more detailed targeted metabolomics analyses in men with PC treated with potent combined androgen blockade with enzalutamide.

6.4 Definition of Evaluable Subjects

For the primary analysis of ΔVO_2peak, patients with measurements at baseline are evaluable.

6.5 Early Study Termination

This study can be terminated at any time for any reason by the Duke PI-sponsor. If this occurs, all subjects on study should be notified as soon as possible. Additional procedures and/or follow up should occur in accordance with Section 9.11, which describes procedures and process for prematurely withdrawn subjects.

7 STUDY DRUG

7.1 Names, Classification, and Mechanism of Action

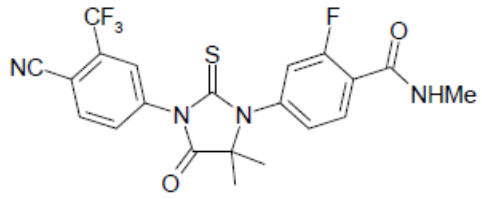
Enzalutamide (Xtandi®, formerly MDV3100) is an androgen receptor signaling inhibitor.

7.2 Packaging and Labeling

Drug Substance

Compound Number:	MDV3100
International Nonproprietary Name:	enzalutamide
Molecular Formula:	$C_{21}H_{16}F_4N_4O_2S$
Chemical Name:	4-{3-[4-Cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-N-methylbenzamide

Chemical Structure of Enzalutamide



Molecular Weight:	464.44
Appearance:	White crystals
Solubility:	Practically insoluble in water
Hygroscopicity:	Not hygroscopic

Drug Product

Ingredients:	Enzalutamide is provided as liquid filled soft gelatin capsules for administration. Each capsule contains 40 mg of enzalutamide. The inactive ingredients are caprylocaproyl polyoxyglycerides (Caprylocaproyl macrogolglycerides [European Pharmacopoeia]), butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide and iron oxide black
Appearance:	Opaque white to off-white oblong liquid filled soft gelatin capsule
Packaging:	Capsules are packaged in bottles with child-resistant caps or 4- to 5- week supply in blister packs.
Storage and Handling:	Store at room temperature (≤ 25°C). For more information please follow the storage instructions provided on the drug product label.

7.3 Supply, Receipt, and Storage

Enzalutamide 40 mg capsules are supplied as white to off-white oblong soft gelatin capsules imprinted in black ink with MDV (this may be updated to ENZ depending on when the trial begins). Enzalutamide capsules are available in the following package sizes:

- Bottles of 120 capsules (NDC 0469-0125-99)

Recommended storage: Store enzalutamide capsules at 20°C to 25°C (68°F to 77°F) in a dry place and keep the container tightly closed. Excursions permitted from 15°C to 30°C (59°F to 86°F).

Medivation will manage the packaging and distribution activities for this protocol for the product enzalutamide (Xtandi®) to Duke and sub-site(s).

7.4 Dispensing

At Duke, enzalutamide with be dispensed by the Duke Investigational Chemotherapy Service (ICS) in accordance with usual ICS policy and practice. Dispensing at subsite(s) will be by the ICS-equivalent, in accordance with usual ICS-equivalent policy and practice. Subjects will be provided with a diary in which to record their intake of study drug. However, the actual number of tablets taken by the subject must be calculated from the number of tablets dispensed and returned (see below).

7.5 Compliance, Accountability, Reconciliation, and Return

Regulatory agencies require accounting for the disposition of all investigational drugs received by each clinical site. Information on drug disposition required by law consists of the date received, date administered, quantity administered, and the subject to whom the drug was administered. The site investigator is responsible for the accounting for all unused test articles and all used test article containers. The investigator uses this information to maintain an accurate and complete dispensing and inventory record.

The study drug, enzalutamide, will be provided by Medivation/Astellas, Inc. and distributed by them to all sites. The DCI monitoring team will perform drug accounting during monitoring visits. At the completion or termination of the study, a final drug accountability review and reconciliation must be completed. Any discrepancies must be investigated and their resolution documented. Instructions for this are provided as a separate attachment.

The site may destroy partially used or empty enzalutamide containers once the monitor completes the accountability of the test article. Test article destruction must be documented on the drug inventory records.

The test article accountability, reconciliation, and return procedures also apply to all test articles that are required by the protocol and supplied by the sponsor.

8 SUBJECT ELIGIBILITY

8.1 Inclusion Criteria

1. Male age ≥ 18 years.
2. Histologically-confirmed adenocarcinoma of the prostate.
3. Completion of appropriate prior treatment with local therapy (i.e., prostatectomy, radiation therapy or equivalent), per NCCN Guidelines.[86]
4. Detectable PSA, defined as PSA ≥0.01 ng/ml
5. Appropriate for treatment with ADT in the opinion of the treating physician.
6. Serum total testosterone ≥150 ng/dL (5.2 nmol/L).
7. ECOG performance status of ≤ 1 (Appendix A)
8. Planned treatment with castration therapy (GnRH agonist/antagonist) for ≥8 months.
9. Must not have any of the following absolute contraindications to cardiopulmonary exercise testing and/or aerobic training as determined by the attending oncologist:
   Absolute Contraindications
   - Acute myocardial Infarction (within 3-5 days of any planned study procedures)
   - Unstable angina
   - Uncontrolled arrhythmia causing symptoms or hemodynamic compromise
   - Recurrent syncope
   - Active endocarditis
   - Acute myocarditis or pericarditis
   - Symptomatic severe aortic stenosis
   - Uncontrolled heart failure
   - Acute (within 3 months) pulmonary embolus or pulmonary infarction
   - Thrombosis of lower extremities
   - Suspected dissecting aneurysm
   - Uncontrolled asthma
   - Pulmonary edema
   - Room air desaturation at rest ≤85%
   - Respiratory failure
   - Acute non-cardiopulmonary disorders that may affect exercise performance or be aggravated by exercise (i.e. infection, renal failure, thyrotoxicosis)
   - Mental impairment leading to inability to cooperate.
10. Able to swallow enzalutamide and comply with study requirements.
11. Must be able to complete an acceptable cardiopulmonary exercise test (CPET) at baseline (see Section 9), defined as at least one of the following:
    1. Achieving a plateau in oxygen consumption concurrent with an increase in power output;
    2. Respiratory exchange ratio ≥ 1.1 (RER);
    3. Volitional exhaustion with a rating of perceived exertion ≥ 17 (RPE)
12. Must be able to complete an acceptable muscular strength test (assessed using calculated one-repetition maximum (1-RM)) at baseline (see Section 9), in the opinion of the fitness specialist, exercise physiologist, or trained designee administering the test.
13. Life expectancy of ≥ 12 months.
14. Must use a condom if having sex with a pregnant woman.
15. Male subject 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. Two acceptable methods of birth control thus include the following:
    - Condom (barrier method of contraception);

    AND

    One of the following is required:

- Established use of oral, or injected or implanted hormonal method of contraception by the female partner;
- Placement of an intrauterine device (IUD) or intrauterine system (IUS) by the female partner;
- Additional barrier method: Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository by the female partner;
- Tubal ligation in the female partner;
- Vasectomy or other procedure resulting in infertility (e.g., bilateral orchiectomy), for more than 6 months

16. Subjects must have normal organ and marrow function as defined below:
    - absolute neutrophil count >1,500/µL
    - platelets >100,000/µL
    - total bilirubin <2.5 X institutional upper limit of normal
    - AST(SGOT)/ALT(SGPT) <2.5 X institutional upper limit of normal
    - Creatinine ≤ 2.0 OR creatinine clearance >30 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal.

8.2 Exclusion Criteria

1. Definite evidence of metastatic prostate cancer, in the opinion of the treating physician. Pelvic and retroperitoneal lymph nodes < 2.0 cm in short axis are allowed.
2. Subjects who have had treatments with GnRH agonists/antagonists and/or anti-androgens within 1 year of randomization.
3. Use of herbal products that may have hormonal anti-prostate cancer activity and/or are known to decrease PSA values (e.g., saw palmetto) or systemic corticosteroids for prostate cancer within 4 weeks of day 29 visit (start of Enzalutamide and ADT).
4. Subjects who have had radiotherapy within 12 weeks prior to entering the study or those who have not recovered from adverse events due to agents or therapies administered for treatment of prostate cancer more than 4 weeks earlier (except urinary, rectal, and sexual side effects related to prostatectomy or radiotherapy are permitted)
5. Subjects who have had any surgical procedure (i.e. TURP, etc.) within 4 weeks prior to entering the study.
6. Subjects who are receiving any other investigational agents.
7. Significant cardiovascular disease, including:
    - Symptomatic left ventricular dysfunction or known baseline left ventricular ejection fraction (LVEF) by multigated acquisition scan (MUGA) or echocardiogram (ECHO) of < lower limit of institutional normal (LLN). "Symptomatic" is defined as New York Heart Association (NYHA) Class II or greater. Note: MUGA and ECHCO do NOT need to be measured to establish eligibility for this study.
    - Uncontrolled hypertension (in the opinion of the treating provider).
    - Myocardial infarction, severe angina, or unstable angina within 6 months prior to administration of first dose of study drug.
    - History of serious ventricular arrhythmia (i.e., ventricular tachycardia or ventricular fibrillation) within 12 months of first dose of study drug.
    - Uncontrolled cardiac arrhythmias.
    - Coronary or peripheral artery bypass graft within 6 months of first dose of study drug.
    - History of CVA, TIA, or rest claudication within 6 months of first dose of study drug.
8. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements (in the opinion of the treating provider).
9. Subjects with any condition (e.g., gastrointestinal tract disease resulting in an inability to take oral medication or a requirement for IV alimentation, prior surgical procedures affecting absorption, or active peptic ulcer disease) that impairs the ability to swallow and retain enzalutamide are excluded.
10. History of another invasive cancer within 5 years of randomization with the exceptions of (a) non-melanoma skin cancers and (b) American Joint Committee on Cancer (AJCC) Stage 0 or 1 cancers that have

a remote probability of recurrence, in the opinion of the treating physician, in consultation with the principal investigator.

11. Known or suspected brain metastasis or leptomeningeal disease.
12. 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 the Day 1 visit.

9 SCREENING, REGISTRATION, AND ON-STUDY TESTS AND PROCEDURES

In addition to assessment for the **primary** endpoint (VO_2peak) by cardiopulmonary exercise testing (CPET), **secondary** and **exploratory** assessments for functional capacity, quantitative skeletal muscle function, metabolic, patient-reported outcomes, PSA, and metabolomics endpoints will occur throughout the study as specified below in the Schedule of Events.

The important time periods during the study include:

- **Screening** on Day -42 to randomization
- **Exercise Testing on Day -30 to randomization**
- **Randomization on Day -14 to Day 1, but after exercise testing (specifically, CPET) is complete**
- **Lead-In** of Usual Care (UC) or Exercise Training starting on Day 1
- **Treatment Period 1:** Enzalutamide + ADT with either UC or Exercise Training from Day 29 to 113
- **Treatment Period 2:** Enzalutamide + ADT from Day 114 to 252
- **End of treatment/Safety Follow-Up** within 30 days after the last dose of enzalutamide or prior to initiation of cytotoxic or investigation therapy, whichever occurs first

All subjects will receive treatment with ADT + enzalutamide for 32 weeks.

In addition, subjects randomized to Exercise Training (Arm B) will undergo a 16 week combined aerobic and resistance exercise training program, including a 4 week Lead-In before starting therapy with ADT + enzalutamide and during the first 12 weeks of therapy with ADT + enzalutamide.

SCHEDULE OF EVENTS

Phase		Screen	Baseline Exercise Testing[c,p]	4 Week Lead-In[p]		Treatment Period 1: Enzalutamide + ADT +/- Exercise Training				Treatment Period 2: Enzalutamide + ADT and Safety Follow-up	Unscheduled Visit[a]
Clinic Visit Number		1				2	3		4	5 (EOT) SEE NOTE	
Day		-42 to randomization	-30 to randomization	1[q]	22	29	57	64	113	252	
Week		-6 to -1		1	4	5	9	10	17[a]	37[a]	
Window (Days)		NA		NA	+6	±3	±7	±3	±7	-7, +30	NA
General Evaluations	**See Section**										
Informed Consent[b]	9.2.1	X									
Eligibility Criteria	8	X									
Medical History	9.12.1	X									
Randomization[c]	6.1.4			X[c]							
Physical Exam[d]	9.12.2	X				X	X		X	X	X
Height, Weight, BMI	9.12.2	X				X	X		X	X	X
Vital Signs[e]	9.12.2	X				X	X		X	X	X
Performance Status (ECOG)[f]	App. A	X				X	X		X	X	X
Concomitant Medications	6.1.3	X				X	X		X	X	X
Adverse Events[g]	10	X				X	X		X	X	X
Laboratory Evaluations											
CBC with platelets[i]	9.1-9.7	X[i]				X	X		X	X	X[h]
Serum Chemistry[i]	9.1-9.7	X[i]				X	X		X	X	X[h]
Disease Evaluations											
PSA[i,j,]	j, k	X[k]	X[i]			X	X		X	X	X[j]
Testosterone		X					X		X	X	
CT and bone scans[k,l]	k,l	X[k,l]									
Correlative Evaluations											
CPET	9.12.3		X			X			X		
Chair Stand	9.12.3		X						X		
Timed Up and Go	9.12.3		X						X		
6 min walk distance (Duke patients only)	9.12.3		X						X		
Musc. Strength[n]	9.12.3		X		X[q]			X[q]	X		
Muscle CSA[s] (protocol v1-v15 only)	9.12.3		X						X		
Musc. Endur. [n]	9.12.3		X		X[q]			X[q]	X		
FACT-P	9.12.3		X						X	X	
FACIT-Fatigue	9.12.3		X						X	X	
Godin Leisure Time Exercise	9.12.3		X						X	X	
Food Frequency Questionnaire	9.12.3		X						X		

Fasting glucose, insulin, HgbA1C[s] (protocol v1-v15 only)	9.12.3		X						X		
Body Composition[r]	9.12.3		X						X		
Metabolomics	9.12.3		X				X		X		
Treatment											
Exercise Training (***ARM B ONLY***)[p]	9.5-9.6			X	X	X	X	X	X		
Enzalutamide	9.6					X	X	X	X		
ADT[m]	9.6					X	X		X		

NOTE: The Safety Follow-Up visit will occur in conjunction with the End of Treatment visit 30 days after the last dose of enzalutamide or prior to initiation of cytotoxic or investigational therapy, whichever occurs first.

a. Unscheduled visits may be performed at any time during the study as clinically indicated to assess for or follow-up on adverse events. Unscheduled visits may also occur due to holidays or other scheduling difficulties and in between week 17 and week 37 as clinically indicated.
b. Informed consent may be performed within 42 days prior to enrollment (Day 1), but must be obtained prior to the performance of any study-specific procedures.
c. Randomization should be performed within 30 days after baseline testing (specifically, CPET) is completed, but only after eligibility is confirmed and up to 14 days prior to Day 1. **See also footnote p. below.**
d. A complete physical examination is required at the Screening, Day 113, and Day 252 visits. A brief symptom-directed physical examination should be performed at all other clinic visits.
e. Vital signs (temperature, blood pressure, heart rate) are to be obtained at each visit.
f. Performance status by Eastern Cooperative Oncology Group (ECOG) scoring (**Appendix A**).
g. Exercise-related adverse events will be collected from baseline/screening through the End of Study visit for all subjects. All other adverse events will be collected from the start of study drug. Serious adverse events are recorded from the time the informed consent form is signed until the Safety Follow-Up visit (or screen failure). In the event of no Safety Follow-Up visit, adverse event information will be collected through 30 days after the last dose of study drug. Subjects should be contacted by phone for adverse event follow-up if they do not come to the clinic for the Safety Follow-Up visit.
h. Clinical laboratory tests may be performed at unscheduled visits if clinically indicated.
i. Labs performed as part of screening are good for 30 days before randomization and do not need to be repeated.
j. PSA may be performed at Unscheduled Visits as indicated to confirm PSA progression. No subject should discontinue study drug due to PSA rise during the first 12 weeks of therapy. Subjects with PSA progression on or after Week 17 must have progression confirmed by a second consecutive assessment conducted at least 3 weeks later before study drug discontinuation.
k. CT of the abdomen and pelvis and bone scans should be performed to document that there is no definite evidence of metastatic disease at the time of screening. MRI of the abdomen and pelvis may be used in place of the CT.
l. Baseline imaging performed per NCCN Guidelines[86] prior to informed consent as standard of care may be used so long as it is performed within 84 days prior to randomization.
m. ADT (GnRH analogue) will be administered as per standard of care to maintain a castrate level of serum testosterone (<50 ng/dL) from Day 29 to Day 252.
n. Muscular Strength and Muscular Endurance must be done at least 24 hours before or after CPET to allow adequate recovery time.
o. Both the usual care group and the exercise training group will have a 4 week lead-in before starting ADT plus enzalutamide; only the exercise training group will undergo exercise training during this time.
p. Day 1 is defined as the randomization day for Arm A (non-exercise) and the start of exercise for Arm B.
q. Randomization may be done on Day 1 prior to the patient's exercise training session(s) for that week.
r. DEXA scan for body composition should be fasting, if possible.
s. Muscle CSA and Fasting glucose, insulin, and HgbA1C will no longer be collected starting from Protocol v16 approval (5/25/17 moving forward). This applies to subjects currently enrolled and future enrollments.

UC, usual care; ADT, androgen deprivation therapy; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; CBC, complete blood count; PSA, prostate-specific antigen; CT, computed tomography; CPET, cardiopulmonary exercise test;1-RM, 1-repetition maximum (voluntary); CSA, cross-sectional area; Musc. Endur., muscular endurance; FACIT, Functional Assessment of Chronic Illness Therapy; FACT-P, Functional Assessment of Cancer Therapy-Prostate; HgbA1c, glycosylated hemoglobin.

9.1 Screening Examination

The screening examination will take place between Day -42 and randomization. An informed consent must be signed by the subject before any screening procedure takes place. Subject data to be collected at the Screening Examination includes:

- Informed Consent
- Eligibility Criteria
- Medical History
- Physical Exam
- Height, Weight, BMI
- Vital Signs
- Performance Status (ECOG)
- Concomitant Medications
- Adverse Events
- CBC with Platelets (hemoglobin, hematocrit, platelet count, white blood cell count, total [absolute] neutrophils)
- Serum Chemistry (sodium, potassium, chloride, total CO2 [bicarbonate], calcium, BUN, creatinine, glucose, albumin, total bilirubin, total protein, alkaline phosphatase, AST, ALT)
- Testosterone
- PSA
- CT or MRI of the abdomen and pelvis and bone scans should be performed to document that there is no definite evidence of metastatic disease at the time of screening.
    - These scans must occur within 84 days prior to enrollment (Day 1).

9.2 Subject Registration

After signing informed consent and completing eligibility screening, subjects who are selected to participate will be registered with the lead site (Duke) and with their study site/institution. A record of subjects who fail to meet entry criteria (i.e., screen failures) will be maintained. Subject registration must be complete before beginning any treatment.

9.2.1 Informed Consent

Authorized study personnel should fully explain the scope of the study to each subject before obtaining informed consent. Subjects should be advised of any known risks inherent in the planned procedures, of any alternative treatment options, of their right to withdraw from the study at any time for any reason, and of their right to privacy.

When obtaining informed consent, study personnel should:
First: Confirm that the subject is a potential candidate for study participation.
Next: Obtain dated and signed informed consent.
Finally: Confirm that the subject is eligible as defined in **Section 8** (Inclusion/Exclusion Criteria). A record of subjects who fail to meet entry criteria (i.e., screening failures) will be maintained.

For subjects consented at the lead site ONLY, registration in the Duke clinical trial subject registry must be completed within 1 business day of the subject providing informed consent.

9.2.2 Lead Site Registration

Subject registration for all subjects signing informed consent will be completed by Duke University Medical Center Genitourinary Oncology Group. Following consent and completion of the Eligibility Checklist, documents will be submitted for review and registration of subject. Enrolled subjects will be assigned a unique study ID.

Refer to Subject Registration Instructions for details.

Subjects will be enrolled only after all pre-treatment screening evaluations are completed and all eligibility criteria are met. Once the subject has signed consent and been found to meet all eligibility criteria, the subject will be enrolled, and a unique patient study identification number will be assigned. Treatment must not commence until the subject has received his identification number from the lead site.

9.2.3 Institutional Registration

Subject registration at each study site/institution will be conducted according to the institution's established policies. Prior to registration, subjects will be asked to sign and date an Institutional Review Board (IRB)-approved consent form. Subjects must be registered with their local site/institution and with the lead site before beginning any treatment or study activities.

9.3 Baseline Exercise Testing

Baseline exercise testing will take place up to 30 days prior to randomization, over approximately 2 days. An informed consent must be signed by the subject before any screening procedure takes place. Subject data to be collected at Baseline Exercise Testing includes:

- CPET
- Chair Stand
- Timed Up and Go
- 6 Minute Walk Distance **(Duke patients only)**
- Muscular Strength (*must be at least 24 hours before or after CPET to allow for adequate recovery*)
- Muscle CSA (MRI, **protocol v1-v15 only)**
- Muscular Endurance (*must be at least 24 hours before or after CPET to allow for adequate recovery*)
- Body Composition
- FACT-P
- FACIT-Fatigue
- Godin Leisure Time Exercise Questionnaire
- Food Frequency Questionnaire
- Fasting glucose, insulin, HgbA1c (fasting, pre-exercise, **protocol v1-v15 only)**
- PSA
- Metabolomics (fasting, pre-exercise)

Of note, CPET and Muscular Strength/1-RM results will be used to formulate the exercise training prescription for Arm B.

9.4 Randomization

Subjects will be randomized after inclusion/exclusion criteria are met and after exercise testing (specifically, CPET) is complete. Randomization can be on Day 1 for Arm A and up to 14 days prior to start of exercise program (Day 1) for Arm B.

9.5 Lead-In Period

Subjects will be randomized to usual care or exercise training up to 14 days prior to Day 1, but only after eligibility is confirmed and baseline exercise testing (specifically, CPET) has been performed. See **Sections 6.1.4** and **9.4** for randomization details. See also **Schedule of Events**, above.

Arm A, ENZ – ADT plus Usual Care: Subjects randomized to usual care will be asked not to make any changes in their physical activity beginning on Day 1. These subjects will start ENZ – ADT on Day 29 (week 5) after the 4 week lead-in period. This delay is felt to be insignificant from a clinical perspective. While two Phase III studies are currently examining this question (NCT00439751; NCT00110162), the delay in initiation of ADT in these studies is much longer than 4 weeks. There is currently no evidence that a delay, especially one as short as 4 weeks, in starting ADT in men with non-metastatic prostate cancer, affects outcomes.[88]

Arm B, ENZ – ADT plus Exercise Training: Subjects randomized to exercise training will begin the exercise training program detailed below beginning on Day 1. The goal for the ENZ-ADT plus exercise training will be 3 supervised exercise sessions per week at an intensity between 50 and 100% of the individually determined exercise capacity (at baseline) for aerobic training and an intensity between 60% and 80% of one-repetition maximum (1-RM) for resistance training for 30-90 minutes/session. The exercise training intervention is designed such that participants begin exercising at a low intensity (~50%-60% VO_2peak) that is subsequently increased to more moderate to vigorous intensity (~70%-80% VO_2peak) when appropriate. All interventions will be individually tailored to each subject following the principles of aerobic or resistance training prescription guidelines for adults as recommended by the American College of Sports Medicine (ACSM).[89] All exercise sessions will also be performed in a supervised setting with one-on-one supervision by certified exercise physiologists, physical therapists, exercise physiology students under the supervision of an ACSM-certified exercise physiologist, or trained designee. The exercise prescription for each subject will be created centrally by either Dr. Lee Jones' group at MSKCC or the CPX Lab at Duke based on both the interpretation of the CPET plus Muscular Strength/1-RM data and a standardized template, within 24-48 hours of these tests.

The major reason for early training during this Lead-In Period is to 'buffer' the expected rapid deleterious impact of hormonal therapy on cardiovascular and skeletal muscle function. This 'pre-treatment' exercise training is hypothesized to attenuate this impact that, in turn, will facilitate higher intensity exercise training during hormonal therapy.

9.6 Treatment Period 1: ENZ-ADT plus either Usual Care or Exercise Training

Arm A, ENZ – ADT plus Usual Care: Beginning on Day 29 (week 5), subjects will be treated with androgen deprivation therapy (ADT) per standard of care (orchiectomy, GnRH agonist, or GnRH antagonist to maintain total testosterone <50 ng/dl for the remaining 32 weeks of the study). In addition, subjects will take enzalutamide (ENZ) 160 mg by mouth daily for the remaining 32 weeks of the study. The dosing of both the GnRH agonist and enzalutamide (160 mg daily) is the standard-of-care dosing. The treatment duration of approximately 8 months was selected to achieve maximal efficacy while minimizing toxicity and is based on intermittent hormonal therapy regimens studied in Phase III clinical trials.[22,23] Concomitant medication will be evaluated at every clinic visit during enzalutamide therapy. Concomitant medications include all vitamins, herbal remedies, over the counter, and prescription medications.

Arm B, ENZ – ADT plus Exercise Training: Beginning on Day 29 (week 5), Subjects randomly allocated to this group will receive the same ADT-ENZ regimen as described above. In addition, subjects will continue the defined exercise training initiated during the Lead-In Period for a total of 16 weeks (through Day 113, week 17).

The window is ±7 days for this period, EXCEPT Day 29 (week 5) which has a window of ±3 days. See **Schedule of Events**, above.

Subject data to be collected during Treatment Period 1 includes:

- Physical Exam
- Height, Weight, BMI
- Vital Signs
- Performance Status (ECOG)
- Concomitant Medications
- Adverse Events
- CBC with Platelets (hemoglobin, hematocrit, platelet count, white blood cell count, total [absolute] neutrophils)
- Serum Chemistry (sodium, potassium, chloride, total CO2 [bicarbonate], calcium, BUN, creatinine, glucose, albumin, total bilirubin, total protein, alkaline phosphatase, AST, ALT)
- Testosterone (Day 57 and 113)
- PSA
- CPET (Day 29 and Day 113)
- Chair Stand (Day 113)
- Timed Up and Go (Day 113)
- 6 Minute Walk Distance (Day 113; **Duke patients only)**
- Muscular Strength (*at least 24 hours before or after CPET on Week 4, Week 10(not in conjunction with CPET) and week 17 in treatment period 2)*
- Muscle CSA (MRI; Day 113; **protocol v1-v15 only**)
- Muscular Endurance *(must be at least 24 hours before or after CPET to allow for adequate recovery on week 4, week 10 (not in conjunction with CPET) and week 17 in treatment period 2)*
- FACT-P (Day 113)
- FACIT-Fatigue (Day 113)
- Godin Leisure Time Exercise Questionnaire (Day 113)
- Food Frequency Questionnaire (Day 113)
    - Fasting glucose, insulin, HgbA1c (Day 113; pre-exercise; **protocol v1-v15 only**)
    - Note that the glucose from the serum chemistry, if drawn in a fasted state, may be used.
- Body Composition (Day 113)
- Metabolomics (Day 57 and 113; fasting, pre-exercise)
- Collect Pill Diary for Enzalutamide

9.7 Treatment Period 2: ENZ-ADT

Subjects on both arms will continue ADT per standard of care and enzalutamide through Week 37 (Day 252).

The window is -7/+30 days for this period. See **Schedule of Events**, above.

Subject data to be collected during Treatment Period 2 includes:

- Physical Exam
- Height, Weight, BMI
- Vital Signs
- Performance Status (ECOG)
- Concomitant Medications
- Adverse Events
- CBC with Platelets (hemoglobin, hematocrit, platelet count, white blood cell count, total [absolute] neutrophils)
- Serum Chemistry (sodium, potassium, chloride, total CO2 [bicarbonate], calcium, BUN, creatinine, glucose, albumin, total bilirubin, total protein, alkaline phosphatase, AST, ALT)
- Testosterone (Day 169 and 252)

- PSA
- FACT-P (Day 252)
- FACIT-Fatigue (Day 252)
- Godin Leisure Time Exercise Questionnaire (Day 252)
- Collect Pill Diary for Enzalutamide

9.8 End of Treatment and Safety Follow-Up

The End of Treatment/Safety Follow-Up visit will be on Day 252 (-7/+30 days). See Section **9.7** and the **Schedule of Events**, above.

9.9 Safety Follow-up Period

The Safety Follow-Up visit will be within 30 days after the last dose of enzalutamide or prior to initiation of cytotoxic or investigational therapy, whichever occurs first. See **Schedule of Events**, above.

9.10 Off Study and End of Study

A subject is considered *off study* when he has completed the Safety Follow-Up visit. All subjects discontinuing study drug for any reason will have a Safety Follow-Up visit approximately 30 days after their last dose of study drug or prior to initiation of cytotoxic or investigational therapy, whichever occurs first.

Reasonable effort should be made to contact any subject 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 subject by mail using a method that provides proof of receipt should be attempted. Such efforts should be documented in the source documents.

The *end of the study* will occur when the last subject enrolled has completed his Safety Follow-Up visit. A database lock will occur once the data has been cleaned to the specifications in the data quality plan. The database will then be frozen, and no further changes will be permitted.

9.11 Early Withdrawal of Subject(s)

9.11.1 Criteria for Early Withdrawal

Subjects may voluntarily withdraw from the study at any time. The PI may also withdraw a subject from the study at any time based on his/her discretion. Reasons for PI-initiated withdrawal may include, but is not limited to the following:

- Adverse events
- Abnormal laboratory values
- Abnormal test procedure results
- Protocol deviation
- Administrative issues
- Disease progression, defined as follows:
    - PSA progression. PSA is evaluated per the Schedule of Events in Section 9. If a measured PSA is higher than the preceding value, then the rising PSA will be confirmed in 4 weeks (± 1 week) in the same laboratory as the first two values. If that third PSA value is higher still and the range of values is 50% above the baseline, then the patient is off study treatment. If not, the patient will remain on study, and the PSA will once again be checked when the patient presents for his regularly scheduled clinic visit.
    - Radiographic progression (in the opinion of the investigator)

9.11.2 Follow-up Requirements for Early Withdrawal

The Premature Withdrawal visit will be the same as the Safety Follow-Up visit. As mentioned above, all subjects discontinuing study drug for any reason will have a Safety Follow-Up visit approximately 30 days after their last dose of study drug or prior to initiation of cytotoxic or investigational therapy, whichever occurs first.

9.11.3 Replacement of Early Withdrawal(s)

Subjects who withdraw prior to completing the baseline assessment for the primary endpoint will be replaced. See also Sections **9.1** and **9.2** for eligibility criteria, as well as **12.1** and **12.4.3** for analysis related to withdrawals.

9.12 Study Assessments

9.12.1 Medical History

Medical history, such as previous treatments, procedures, and conditions will be collected during the screening period.

9.12.2 Physical Exam

Evaluations should be performed by the same evaluator throughout the study whenever possible. Weight will be recorded at every visit. Height will be recorded at screening visit only. Body mass index (BMI) will be calculated at every visit. Vital signs include upright blood pressure, heart rate, respiratory rate, and oral or aural body temperature. A complete physical examination is required at the Screening, Day 113, and Day 252 visits. A brief symptom-directed physical examination should be performed at all other clinic visits.

9.12.3 Correlative Assessments

All Correlative Assessments will be performed at Day 1 and Day 113 (see Schedule of Events at the beginning of this Section for details). Patient reported outcomes will also be performed at Day 252. In addition, a CPET will be performed at Day 29 to assess VO_2peak changes during the Lead-In Period and Metabolomics samples will be drawn at Day 57 to assess for early changes that may predict later changes in metabolic parameters. All samples will be collected in the fasting, pre-exercise state unless otherwise noted below.

Cardiopulmonary Exercise Testing (CPET)

Exercise Capacity will be assessed using a symptom-limited CPET on a motorized treadmill with expired gas analysis to determine $VO_{2peak,}$ according to guidelines for clinical populations.[90] All CPET data will be recorded as the highest 30s value elicited during the CPET. During exercise, heart rate and rhythm will be monitored continuously using a 12-lead ECG. Equipment with similar technical specifications will be used across the two study sites to ensure reasonably accurate and precise results.

Physical Functioning / Functional Capacity

Physical Functioning / Functional Capacity will be assessed using the following assessments: chair-stand test, timed up and go, and 6 min walk distance outcomes as described previously.[91] [57,92,93]These measures will complement the exercise capacity measure.

> **Chair-Stand Test:** The 5-repetition chair-stand test measured the time taken to complete 5 repetitions of the sit-to-stand maneuver. All sit-to-stand maneuvers will be performed from a chair without an arm rest at 43cm in height and 47.5cm in depth. Standardized instructions will be provided as follows: “By the count of 3, please stand up and sit down as quickly as possible for

5 times. Place your hands on your lap and do not use them throughout the procedure. Lean your back against the chair's backrest at the end of every repetition." Timing will start when the subject's back left the backrest and will be stopped once the back touched the backrest.

Timed Get Up and Go: Subjects will be required to stand up from a chair with armrests, walk 3m, turn around, return to the chair, and sit down. The time taken to complete this task will be measured in seconds with a stopwatch.[93]

6-minute Walk Distance (Duke patients only): The six minute walk test will be conducted according to the guidelines of the ATS.[94] Subjects will be instructed to cover the longest distance possible in six minutes under the supervision of an exercise physiologist or trained designee. The distance walked will be determined in a measured corridor, between 2 cones that were placed 30 meters apart. The test will be performed twice at each study timepoint with the average recorded. Age and sex-predicted 6MWD will be calculated from the equation of Gibbons et al.[95]

Quantitative Skeletal Muscle Function

Quantitative Skeletal Muscle Function will be assessed by two outcomes:

Muscle Cross Sectional Area (CSA; **protocol v1-v15 only**) of the dominant thigh will be assessed using magnetic resonance imaging (MRI) with a 3.0T-scanner (Siemens Tim Trio 3 Tesla MRI, Erlangen, Germany). Imaging will be performed using sequence turbo spin echo (T1-weighted sequence) recall scans at the mid-femur level. Seventeen serial slices will be obtained with one at the juncture of the middle third of the femur (this point will be landmarked to ensure within subject reproducibility) as previously described.[96] The CSA of the quadriceps, hamstrings, and total mid-thigh muscle will be assessed using semiautomatic generation of the region of interest using a combination of console software and/or third party commercially available independent workstation in conjunction, as needed. If the patients MRI screening form is positive, the muscle CSA will not be performed but the subject will continue on the study.

Muscular Strength of the upper and lower body will be assessed as a *one-repetition maximum* (1-RM). This dynamic strength assessment will be conducted using the following exercises: leg press, chest press, and row. The heaviest weight lifted while adhering to the strict technique and form will be used to score the assessment. A certified exercise physiologist or trained designee will conduct this assessment in a controlled environment. A 1-RM is defined as the greatest resistance that can be moved through the full range of motion in a controlled manner. Mean percentage of age and sex-predicted muscle strength will be obtained from available normative data.

Muscular Endurance of the upper and lower body will be assessed as the *number of repetitions to fatigue at 70% of the 1-RM*. The same exercises and methods will be used as in the 1-RM determination, detailed above. Subjects will continue until technique, tempo, volition or inability to complete two consecutive repetitions causes finality (per discretion of the exercise physiologist or trained designee).

Metabolic Control (protocol v1-v15 only)

Subjects will undergo sampling of fasting, pre-exercise, **plasma insulin** and **glucose** concentrations for calculation of **HOMA-IR**, as previously described.[97] **Glycosylated hemoglobin** (HgbA1c) will also be measured. These will be measured in a CLIA-certified clinical laboratory.

Body Composition

Body composition will be assessed by dual energy x-ray absorptiometry scan in the morning (after an overnight fast, if possible). Transverse scans from head to toe measured absorption of x-ray beams at two different energy levels allowing for a valid determination of lean body mass, fat mass and fat percentage.

Patient Reported Outcomes

Data on health related quality of life will be collected using the Functional Assessment of Cancer Therapy-Prostate (**FACT-P**) scale, which can be found in **Appendix C**.[98,99] Data on subject-reported changes in fatigue will be collected using the Functional Assessment in Chronic Illness Therapy – Fatigue questionnaire (**FACIT-F**), which can be found in **Appendix B**. Data on leisure time exercise habits will be collected using the 4-item **Godin Leisure Time Exercise Questionnaire**, which can be found in **Appendix D**.[100]

Food Frequency Questionnaire (FFQ)

A food frequency questionnaire (FFQ) developed by the Nutrition Assessment Shared Resource (NASR) of Fred Hutchinson Cancer Research Center (FHCRC) will be administered at the Week 1 and Week 17 time points to explore the collinearity of diet/exercise and to potentially correct for imbalances in the dietary intake between arms. Participants will be queried regarding their dietary intake over the last 1 month prior to completing the questionnaire.

Specifically, nutrient data will be collected using the Men's Nutritional Assessment (MNA). Nutrition Assessment uses the University of Minnesota Nutrition Data Systems for Research (NDSR) software for data entry and nutrient analysis via the FFQ. A sample booklet is provided at: http://sharedresources.fhcrc.org/sites/default/files/FFQ-MNA-Sample.pdf

Questionnaires will be batched (approximately 30-40 questionnaires/batch) and sent via UPS/FedEx to NASR for scanning. FFQs are optically scanned at FHCRC. Each batch of scanned FFQs yields files containing food consumption data, nutrient intake data, and an error report that specifies questionnaire completion errors (e.g. incomplete erasures, missed questions).

Following is the contact information for the NASR:

Location: Arnold Building, 4th floor
Mailing Address: 1100 Fairview Ave N., P.O. Box 19024, M4-B402 Seattle, WA 98109-1024
Phone: [redacted]
Fax: [redacted]
Email: [redacted]
Contact: Carolyn Ehret, M.S.,R.D.,C.D., Director

Prostate-Specific Antigen (PSA)

Prostate-Specific Antigen (PSA) will be measured in a CLIA-certified clinical laboratory.

Metabolomics

Fasting EDTA plasma will be collected from each participant at each time point and stored at -80°C for metabolic profiling. Refer to lab manual for blood collection volumes. Metabolic intermediates will be measured using a targeted, mass spectrometry (MS)–based platform as described previously.[101] Profiling will include ~96 serum metabolic intermediates, hormones of energy regulation, and serum cytokines known to be associated with insulin sensitivity, exercise/diet induced changes, or treatment with ADT (**Table 2**). Our collaborators at the Stedman Center at Duke have reported sample preparation methodology and coefficients of variation for each assay.[102,103] Cytokines and inflammatory markers will be measured using a Luminex panel. Conventional metabolites will be measured in a CLIA-certified clinical laboratory.

Table 2. Targeted Metabolomics Analysis – Metabolic Factors to be Assessed	
Conventional Metabolites	C-reactive protein (CRP), glucose, total cholesterol, HDL, LDH, triglycerides, total free fatty acids, ketones, 2-OH butyrate, 3-OH butyrate, succinate, steroids (multiple[85])
Energy Regulation Hormones	Insulin, ghrelin, adiponectin, leptin, glucagon, C-peptide, IGF-1, IGFBP-1, -2, -3, resistin

Cytokines	TNF-α, IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12p40, IL-12p70, IFN-γ
Amino Acids[102,104,105]	Glycine, alanine, serine, proline, valine, leucine/isoleucine, methionine, histadine, phenylalanine, tyrosine, Asx (asparagine, aspartate, aspartic acid), Glx (glutamate/glutamine/glutamic acid), ornithine, citrulline, arginine
Acylcarnitines (AC)/Other[106]	~30 selected AC, including C3, C5; medium and long chains; cholate; dicarboxylic acids

All metabolomics samples will be prepared as specified in the SOP document, "Preparing samples for submission to the Metabolomics Laboratory, Sarah W. Stedman Nutrition & Metabolism Center, Duke University Medical Center." Samples will be batched and sent to the Duke Biospecimen Repository and Processing Core (BRPC) for storage for future analysis via courier or FedEx/UPS at the following address:

Duke Biospecimen Repository and Processing Core
253M Davison Building, 201 Trent Drive
Durham, NC 27710
[redacted]

Prior to shipping, the BRPC must be contacted either by phone or email to confirm that someone will be available to receive the shipment on the desired delivery date. Written or verbal confirmation must be obtained from the BRPC staff prior to the shipment.

10 SAFETY MONITORING AND REPORTING

The PI is responsible for the identification and documentation of adverse events and serious adverse events, as defined below. At each study visit, the PI or designee must assess, through non-suggestive inquiries of the subject or evaluation of study assessments, whether an AE or SAE has occurred.

10.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject undergoing a study procedure/intervention and/or receiving study drug; which may or may not have a causal relationship with study procedures, interventions or treatments. For this protocol, the definition of AE also includes worsening of any pre-existing medical condition. An AE can therefore be any unfavorable, unintended or worsening sign or symptom (including an abnormal laboratory finding, or disease temporally associated with exercise testing for both arm A and arm B; exercise training for arm B; and/ or related to the use of enzalutamide. Abnormal laboratory findings without clinical significance (based on the PI's judgment) should not be recorded as AEs. But laboratory value changes that require therapy or adjustment in prior therapy are considered adverse events.

Research exercise-related adverse events will be collected from the baseline exercise testing to the End of Study visit (as defined in **Section 9.8**) for all subjects (Except anticipated AEs-see section 10.1.2). All subjects will have enzalutamide related adverse events collected from the start of study drug on week 5, day 29 through the Safety Follow-up visit.

Serious adverse events that are related to study exercise procedures (CPET, 1RM, Chair testing, etc) are recorded from the time the informed consent form is signed until the Safety Follow-Up visit (withdrawal or screen failure). All SAEs will be collected regardless of attribution starting once the patient takes his first dose of study drug through the Safety Follow-Up visit. All AEs and SAEs must be recorded in the subject medical record and adverse events case report form.

AEs will be assessed according to the CTCAE version 4.0. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the study drug and/or exercise training and/or exercise testing
- Probably: The AE is likely related to the study drug and/or exercise training and/or exercise testing
- Possible: The AE may be related to the study drug and/or exercise training and/or exercise testing
- Unlikely: The AE is doubtfully related to the study drug and/or exercise training and/or exercise testing
- Unrelated: The AE is clearly NOT related to the study drug and/or exercise training and/or exercise testing

10.1.1 AEs of Special Interest

"Fatigue" and "generalized muscle weakness" (regardless of site) are AEs of special interest. Care should be taken to appropriately identify, grade, and note the attribution of these AES throughout the study. However, there is no special reporting requirement for these AEs.

10.1.2 Expected AEs with Exercise Training and Testing (CPET)

Anticipated (expected) side-effects associated with a symptom-limited cardiopulmonary exercise test or exercise training include:

- Muscle soreness
- Joint pain
- Lower back pain
- Leg cramps

These anticipated side-effects associated with CPET will not be recorded as AEs as long as they are transient in nature.

Unanticipated but possible side-effects that are *rare, but serious* include:

- Cardiovascular: angina, AV blocks, bradycardia, edema, hypotension, palpitations, rebound hypertension, shock, syncope.
- Arrhythmias
- Myocardial ischemia
- Sudden cardiac death
- Cerebrovascular accident

These rare but serious AEs that may be related to CPET will be recorded as AEs or SAEs. The CPET may uncover previously unknown arrhythmias or other abnormal cardiac findings. These will be assessed for clinical significance by the cardiologist and/or Principal Investigator and will be recorded and graded as AEs if deemed to be clinically significant.

10.2 Serious Adverse Events

An AE is considered "serious" if in the opinion of the investigator it is one of the following outcomes:

- Fatal
- Life-threatening

- Constitutes a congenital anomaly or birth defect
- A medically significant condition (defined as an event that compromises subject safety or may require medical or surgical intervention to prevent one of the three outcomes above).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption to conduct normal life functions.

10.2.1 Reporting of SAEs

Serious adverse events, whether or not considered drug related, should be reported to the lead site/sponsor (Duke) within 24 hours of becoming aware of the event, using the provided DCI SAE Report Form and the SAE Report Review Form (Site Assessment). These documents should be sent to:

The DCI Safety Desk – fax: [redacted]

If the safety desk cannot be reached within 24 hours, the Principal Investigator should be contacted: Dr. Michael Harrison, [redacted]; email: michael.harrison@dm.duke.edu

The initial report for each SAE or death should include at minimum the following information:

- Protocol # and title
- Patient initials, study identification number, sex, age
- Date the event occurred
- Description of the SAE
- Dose level and cycle number at the time the SAE occurred
- Description of the patient's condition
- Indication whether the patient remains on study
- Causality

Follow-up information including severity, action taken, concomitant medications, and outcome should be communicated to Duke as soon as possible.

Upon receipt of the Serious Adverse Event Reporting form by the DCI Safety Desk, the PI will be notified and be required to complete the PI assessment of the DCI Safety SAE Report Review Form. The DCI safety desk will, in turn, report the event to Astellas if felt to be at least possibly related to enzalutamide using the DCI SAE Report Form.

The SAE documentation, including the DCI SAE Report Form and available source records should be emailed or faxed to:

Astellas Pharma Global Development – United States
Email: [redacted]
Fax number: [redacted]

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.

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

10.3 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. With the permission of the pregnant partner, the Investigator should report the pregnancy to Medivation/Astellas 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.

With the permission of the pregnant partner, the Investigator should report the outcome of the pregnancy (independent of outcome, e.g. 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. Informed consent will need to be obtained from the pregnant partner to document her permission to disclose this information with Medivation/Astellas.

10.4 Safety Oversight Committee (SOC)

The Duke Cancer Institute SOC is responsible for annual data and safety monitoring of DUHS sponsor-investigator phase I and II, therapeutic interventional studies that do not have an independent Data Safety Monitoring Board (DSMB). The primary focus of the SOC is review of safety data, toxicities and new information that may affect subject safety or efficacy. Annual safety reviews includes but may not be limited to review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. The SOC in concert with the DCI Monitoring Team (see **Section 11.1** for Monitoring Team description) oversees the conduct of DUHS cancer-related, sponsor-investigator therapeutic intervention and prevention intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standard operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Monitoring

The Duke Cancer Institute (DCI) Monitoring Team will conduct monitoring visits to ensure subject safety and to ensure that the protocol is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, good clinical practice, and applicable regulatory requirements. As specified in the DCI Data and Safety Monitoring Plan, the DCI Monitoring Team will conduct routine monitoring after the third subject is enrolled, followed by annual monitoring of 1 – 3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of DUHS and DCI leadership, the DCI Cancer Protocol Committee, Duke Clinical Trials Quality Assurance (CTQA), the Safety Oversight Committee (SOC), the Sponsor-Investigator, the site Principal Investigator, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

11.2 Data Management and Processing

11.2.1 Study Documentation

Study documentation includes but is not limited to source documents, case report forms, monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

11.2.2 Case Report Forms (CRFs)

The electronic CRF will be the primary data collection document for the study. The CRFs will be updated in a timely manner following acquisition of new source data. Only the research staff members listed on the delegation of authority log are permitted to make entries, changes, or corrections in the CRF.

An audit trail will be maintained automatically by the electronic CRF management system. All users of this system will complete user training, as required or appropriate per regulations.

11.2.3 Data Management Procedures and Data Verification

Completeness of entered data will be checked automatically by the eCRF system, and users will be alerted to the presence of data inconsistencies. Additionally, queries may be issued by the study data manager or project leader. Missing or implausible data will be queried for completion or correction (i.e. confirmation of data, correction of data, completion or confirmation that data is not available, etc.).

The database will be reviewed and discussed prior to database closure, and will be closed only after resolution of all remaining queries. An audit trail will be kept of all subsequent changes to the data.

11.2.4 Study Closure

Following completion of the studies, the PI will be responsible for ensuring the following activities:

- Data clarification and/or resolution
- Accounting, reconciliation, and destruction/return of used and unused study drugs
- Review of site study records for completeness
- Shipment of all remaining laboratory samples to the designated laboratories (i.e. BRPC at Duke)

12 STATISTICAL METHODS AND DATA ANALYSIS

All statistical analysis will be performed under the direction of the statistician designated in key personnel. Any data analysis carried out independently by the investigator must be approved by the statistician before publication or presentation.

12.1 Analysis Sets

The intent-to-treat (ITT) population will consist of all randomized patients. The modified intent-to-treat (ITT) population will consist of all randomized patients who have both a baseline and week 17 evaluation. In the ITT analyses and the modified ITT analyses patients will be analyzed according to the study arm to which they were randomized. The modified ITT population will be the primary analysis population.

The per-protocol population will consist of all randomized patients with both baseline and week 17 measurements for the primary endpoint and prior to any analysis: have been deemed compliant and properly evaluated for efficacy per investigator, satisfied all inclusion and exclusion criteria, and correctly assigned treatment.

The safety population will be all patients with at least one safety evaluation.

12.2 Subject Demographics and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized for the ITT population. Mean, median, standard deviation, minimum, and maximum will be displayed by treatment arm for continuous variables. Categorical variables will be summarized by counts and percentages for each treatment arm.

12.3 Treatments

Compliance with supervised exercise training will be summarized as number and percent of exercise sessions attended.

Compliance with ENZ and ADT will be described, for each treatment arm, by the number and percent of intended doses taken. In addition, the number and percent of patients having delays or dose reductions will be displayed by treatment arm.

Numbers of patients discontinuing treatment and reasons for discontinuation will be displayed for each treatment arm. Numbers of patients failing to complete full follow-up (through week 36) and reasons for loss to follow-up will be displayed for each treatment arm.

12.4 Primary Objective

Refer to **Section 5** for the primary objective and endpoint. Briefly, the primary objective is to study the effect of supervised exercise training on cardiopulmonary function in men receiving the combination of enzalutamide (ENZ) and androgen deprivation therapy (ADT) for treatment of hormone-naïve prostate cancer.

12.4.1 Variable

The primary endpoint is the change in peak oxygen uptake (ΔVO_2peak) from week 1 to week 17 in each group.

12.4.2 Statistical Hypothesis, Model, and Method of Analysis

The primary analysis will be comparison of the change in peak oxygen uptake (ΔVO_2peak) from week 1 to week 17 between the usual care and exercise training groups, using a t-test. The primary analysis will be done for complete cases, (i.e. patients with VO_2peak measured at baseline and at week 17) in the ITT population.

Descriptive comparisons of ΔVO_2peak will be done:

- between baseline and end of week 4 to assess the effect of exercise (or usual care) alone,
- between end of week 4 and start of week 17 to assess the effect of exercise during ENZ + ADT treatment, and
- between the start of week 17 and the end of week 36 to assess whether there is a lasting effect of the supervised exercise regimen after it is discontinued.

12.4.3 Handling of missing values, censoring, and discontinuations

The primary analysis from baseline to week 17 will include only complete cases.

Patients without VO_2peak measured at week 17 who have one or more measurements during the period from week 17 to the end of week 36 will have their week 17 measurement estimated by interpolation from the end of week 4 to the closest measurement following week 17. A sensitivity analysis will be done including these patients with complete cases.

12.5 Secondary and Exploratory Objectives

Refer to **Section 5** for the secondary objectives and endpoints. Secondary objectives are to compare effects on physical functioning / functional capacity, primary physiological determinants of VO_2peak, metabolic outcomes of interest, and subject-reported outcomes (PROs) of interest. The safety, feasibility, and acceptability of exercise training will also be evaluated.

Refer to **Section 5** for the exploratory objectives and endpoints. Exploratory objectives are to compare PSA response rates and describe metabolomics changes.

Secondary and exploratory endpoints are generally assessed at baseline, week 17, and at the end of week 36.

Descriptive comparisons of changes in secondary and exploratory endpoints will be done both:

- between baseline and the start of week 17 to assess the effect of exercise on changes due to ENZ + ADT, and
- between the start of week 17 and the end of week 36 to assess whether there is a lasting effect of the supervised exercise regimen after it is discontinued.

Continuous measures will generally be analyzed using a repeated measures model with the measure as the dependent variate and treatment arm and week of assessment as independent variates. Appropriate transformations will be used in cases where the measures the assumption of normally distributed errors would be violated.

Categorical measures will be analyzed using categorical data modeling techniques.

Whenever possible, transformation or categorization of secondary and exploratory measures will done as reported in previously published studies in the field.

Eligibility rate is defined as the number of subjects found to be eligible for the study divided by the number approached for the study (i.e. screen fail rate). (Note: ineligible patients will not be randomized.) *Acceptance rate* is defined as the number of patients agreeing to participate divided by total number randomized.

Adherence rate is defined as the proportion of patients adhering to the exercise intervention (obtained from weekly exercise training attendance logs). *Attrition rate* is defined as the proportion of subjects who complete the 16 week exercise training program.

For analysis of metabolomics, PCA analysis will be used to reduce the large number of correlated factors into a smaller number of dimensions. Unless otherwise noted, all analyses will be done separately for the usual care and exercise groups. Of primary interest is the association of metabolomic biomarkers with changes in both VO_2peak and HOMA-IR. Changes in metabolite concentrations and VO_2peak or HOMA-IR will be compared between the usual care and exercise groups using ANOVA. Correlation analysis and linear regression will be used to describe the relationship between metabolomics biomarker changes and VO_2peak or and HOMA-IR. Nominal statistical significance will be defined as $p<0.05$.

In addition, the maximum PSA change from baseline in each patient will be described using waterfall plots. The PSA response rate, defined as the proportion of men with a ≥80% decline in PSA from baseline, will be reported for each arm. The median decrease in PSA will also be reported for each arm.

Sensitivity analyses will be performed repeating primary endpoint and key secondary endpoint analyses using Last Value Carried Forward (LOCF) methods. The intent of this sensitivity analysis is to assay the robustness of results observed in the modified ITT population.

Adjustment for multiple comparisons is not planned for secondary or exploratory measures.

Rates of adverse events, classified by CTCAE v4.0, will be displayed by body system and preferred term for each arm.

12.6 Sample Size Calculation

The primary purpose of this study is to investigate to study the effect of supervised exercise training on cardiopulmonary function in men receiving the combination of enzalutamide (ENZ) and androgen deprivation therapy (ADT) for treatment of hormone-naïve prostate cancer.

The initial sample size calculations was based on the expected change in VO_2peak based on relevant prior reports or unpublished observations by the study team. Regarding the ENZ + ADT group, Segal et al.[80] reported that VO_2peak showed a mean decrease of 1.4 $mL.kg.^{-1}min^{-1}$ in 41 men initiating radiation with or without ADT for prostate cancer. During the same period, structured supervised resistance training completely abrogated the decline in VO_2peak observed in the usual care group. In unpublished data from our group among 50 men following prostatectomy for localized prostate cancer, mean VO_2peak was 29.5 mL.kg.-1min-1 (± 5.0 $mL.kg.^{-1}min^{-1}$). Following baseline assessments, subjects were randomly allocated to supervised aerobic training (n=25) or usual care (n=25) for 6 months. VO_2peak increased by 2.71 ± 3.5 $mL.kg^{-1}.min^{-1}$ in the exercise group and 0.6 ± 2.2 $mL.kg^{-1}.min^{-1}$ in the usual care group, resulting in a between group difference of +1.95 $mL.kg^{-1}.min^{-1}$ that favored the exercise training group (p=0.024).

Against this background, this protocol adopted the following assumptions: (1) a decline of 2.0 $mL.kg^{-1}.min^{-1}$ ENZ-ADT group from baseline to 16 weeks, and (2) an increase of 1.0 $mL.kg^{-1}.min^{-1}$ ENZ-ADT plus exercise training group from baseline to 16 weeks, for a between group delta of 3.0 $mL.kg^{-1}.min^{-1}$, favoring the ENZ-ADT plus exercise training group. A total of 56 subjects (n=28 / per group) provides 80% power to detect a mean 3.0 $mL.kg^{-1}.min^{-1}$ between group difference in VO_2peak from baseline to post-intervention, assuming a SD of 3.5 $mL.kg^{-1}.min^{-1}$ and a two-sided alpha of 0.05. These calculations assume a lost-to-follow-up rate of 15%, thus approximately 23 per group will provide evaluable data at 16 weeks post-randomization.

In November 2016, an interim analysis was performed due to the slow accrual and subjective feedback from subjects and exercise physiologists. That is, subjects in the exercise training group (Arm B) seemed to feel and perform better after the 16-week exercise training program compared with the usual care (Arm A) group at

the same time point. A difference in the point estimates of ΔVO_2peak (week 1 to week 17) between groups was seen in the first 8 subjects who had completed testing for the primary endpoint of ΔVO_2peak at week 17 (N=4 each in the usual care and exercise training groups), suggesting less decline of VO2peak in Arm B. Based on the interim analysis data, the study statisticians revised the sample size calculation.

We expect to use a one-sided t-test to check whether Arm B has a significant increase in VO_2peak from the baseline compared to Arm A. When each group has 20 evaluable subjects for significance level 0.10, we have 80% power to reject the null hypothesis that the two groups have the same change of VO_2peak given the effect size is 0.68 (the ratio of mean difference over common standard deviation). In case the test result is not significant, we will report the mean reduction descriptively with 95% confidence interval for this pilot study. **In summary, the revised sample size estimate is 40 total evaluable subjects, or 20 subjects in each arm.**

13 ADMINISTRATIVE AND ETHICAL CONSIDERATIONS

13.1 Regulatory and Ethical Compliance

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable federal, state, and local regulations.

13.2 DUHS Institutional Review Board and DCI Cancer Protocol Committee

The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the DUHS Institutional Review Board (IRB) and DCI Cancer Protocol Committee (CPC) for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the CPC and IRB.

The Principal Investigator must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. The CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, statistical analysis, etc.).

The Principal Investigator must obtain protocol re-approval from the IRB within 1 year of the most recent IRB approval. The Principal Investigator must also obtain protocol re-approval from the CPC within 1 year of the most recent IRB approval, for as long as the protocol remains open to subject enrollment.

13.3 Informed Consent

The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The Principal Investigator or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Appropriate accommodations will be made available for potential subjects who cannot read or understand English or are visually impaired. Potential subjects will have the opportunity to contact the Principal investigator or authorized key personnel with questions, and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the Principal Investigator must obtain written informed consent from the subject or a legally acceptable representative. The original informed consent form will be stored with the subject's study records, and a copy of the informed consent form will be provided to the subject.

13.4 Privacy, Confidentiality, and Data Storage

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained. Research Data Security Plans (RDSPs) will be approved by the appropriate Duke clinical research unit for the Duke site.

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. Prospective participants will be consented in an exam room where it is just the research staff, the patient and his family, if desired. For all future visits, interactions with research staff (study doctor and study coordinators) regarding research activities will take place in a private exam room. All research related

interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Electronic records of subject data will be maintained using a dedicated database which is housed in an encrypted and password-protected DCI file server. Access to electronic databases will be limited to delegated personnel. The security and viability of the IT infrastructure will be managed by the DCI and/or Duke Medicine.

Upon completion of the study, research records will be archived and handled per DUHS HRPP policy. Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

13.5 Data and Safety Monitoring

Data and Safety Monitoring will be performed in accordance with the DCI Data and Safety Monitoring Plan. For a more detailed description of the DSMP for this protocol, refer to Section 11 (Sections 11.6 and 11.7 in particular) and Section 12.

13.6 Protocol Amendments

All protocol amendments must be initiated by the Principal Investigator and approved by the IRB prior to implementation. IRB approval is not required for protocol changes that occur to protect the safety of a subject from an immediate hazard. However, the Principal Investigator must inform the IRB and all other applicable regulatory agencies of such action immediately.

Though not yet required, the CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, etc.).

13.7 Records Retention

The Principal Investigator at each site will maintain study-related records at least six years after study completion.

13.8 Conflict of Interest

The Principal Investigator and Sub-Investigators must comply with applicable federal, state, and local regulations regarding reporting and disclosure of conflict of interest. Conflicts of interest may arise from situations in which financial or other personal considerations have the potential to compromise or bias professional judgment and objectivity. Conflicts of interest include but are not limited to royalty or consulting fees, speaking honoraria, advisory board appointments, publicly-traded or privately-held equities, stock options, intellectual property, and gifts.

The Duke University School of Medicine's Research Integrity Office (RIO) reviews and manages research-related conflicts of interest. The Principal Investigator and Sub-Investigators must report conflicts of interest annually and within 10 days of a change in status, and when applicable, must have a documented management plan that is developed in conjunction with the Duke RIO and approved by the IRB/IEC.

14 APPENDICES

Appendix A PERFORMANCE STATUS CRITERIA

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

Appendix B and C FACT-P and FACIT FATIGUE SCALE (VERSION 4)

Below is a list of statements that other people with your illness have said are important**.** **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	GENERAL ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	FATIGUE ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix D GODIN LEISURE TIME EXERCISE QUESTIONNAIRE

1. During a typical **7-Day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your free time (write on each line the appropriate number).

	Times Per Week
a) STRENUOUS EXERCISE **(HEART BEATS RAPIDLY)** (e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)	_____
MODERATE EXERCISE **(NOT EXHAUSTING)** (e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)	_____
b) MILD EXERCISE **(MINIMAL EFFORT)** (e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking)	_____

2. During a typical **7-Day period** (a week), in your leisure time, how often do you engage in any regular activity **long enough to work up a sweat** (heart beats rapidly)?

OFTEN	SOMETIMES	NEVER/RARELY
1. ☐	2. ☐	3. ☐

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