ACADEMIC: A Randomized Phase II Clinical Trial of ADT Combined with Abiraterone or Docetaxel in Metastatic Hormone Sensitive Prostate Cancer

HCI-18-GU-11/Trial ID: HCI115099

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Commercial agents	Abiraterone Acetate (Zytiga, Yonsa, or generic), Docetaxel (Taxotere)
IND Number	N/A
NCT Number *(CT.gov)*	NCT03827473

Historical Protocol Version Dates

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LIST OF ABBREVIATION

Abbreviation or Term[1]	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AV	Atrioventricular
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
Cl-	Chloride
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
D/C	Discontinue
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
Eg	Exempli gratia (for example)
FACS	Fluorescence Activated Cell Sorting
FDA	Food and Drug Administration

Abbreviation or Term[1]	Definition/Explanation
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography (PET)
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCO_3^-	Bicarbonate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
hr	Hour or hours
IC_{50}	Half maximal inhibitory concentration
i.e.	Id est (that is)
IEC	Independent ethics committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional review board
IU	International unit
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase
LHRH	Luteinizing hormone releasing hormone
LLQ	Lower limit of quantitation
MedRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic resonance imaging
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect-level
PD	Pharmacodynamic(s)
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QC	Quality control
RBC	Red blood cell

Abbreviation or Term[1]	Definition/Explanation
QD	Once daily
QTc	QT interval corrected
QTcF	QT interval corrected using Frederichia equation
SAE	Serious adverse event
SD	Standard deviation or stable disease
$T_{1/2}$	Terminal elimination half-life
T_3	Triiodothyronine
T_4	Thyroxine
T_{max}	Time of maximum observed concentration
TID	Three times daily
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
ULQ	Upper limit of quantitation
UV	Ultraviolet
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of nonchildbearing potential

[1] All of these abbreviations may or may not be used in protocol.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

This document is signed electronically through submission and approval by the Principal Investigator at Huntsman Cancer Institute in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system. For this reason, the Principal Investigator at Huntsman Cancer Institute will not have a hand-written signature on this signature page.

Instructions to multi-site Principal Investigators at locations other than Huntsman Cancer Institute: SIGN and DATE this signature page and PRINT your name. Return the original, completed and signed, to the HCI Research Compliance Office. Retain a copy in the regulatory binder.

_____ _____

Signature of Principal Investigator **Date**

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Principal Investigator Name (Print)

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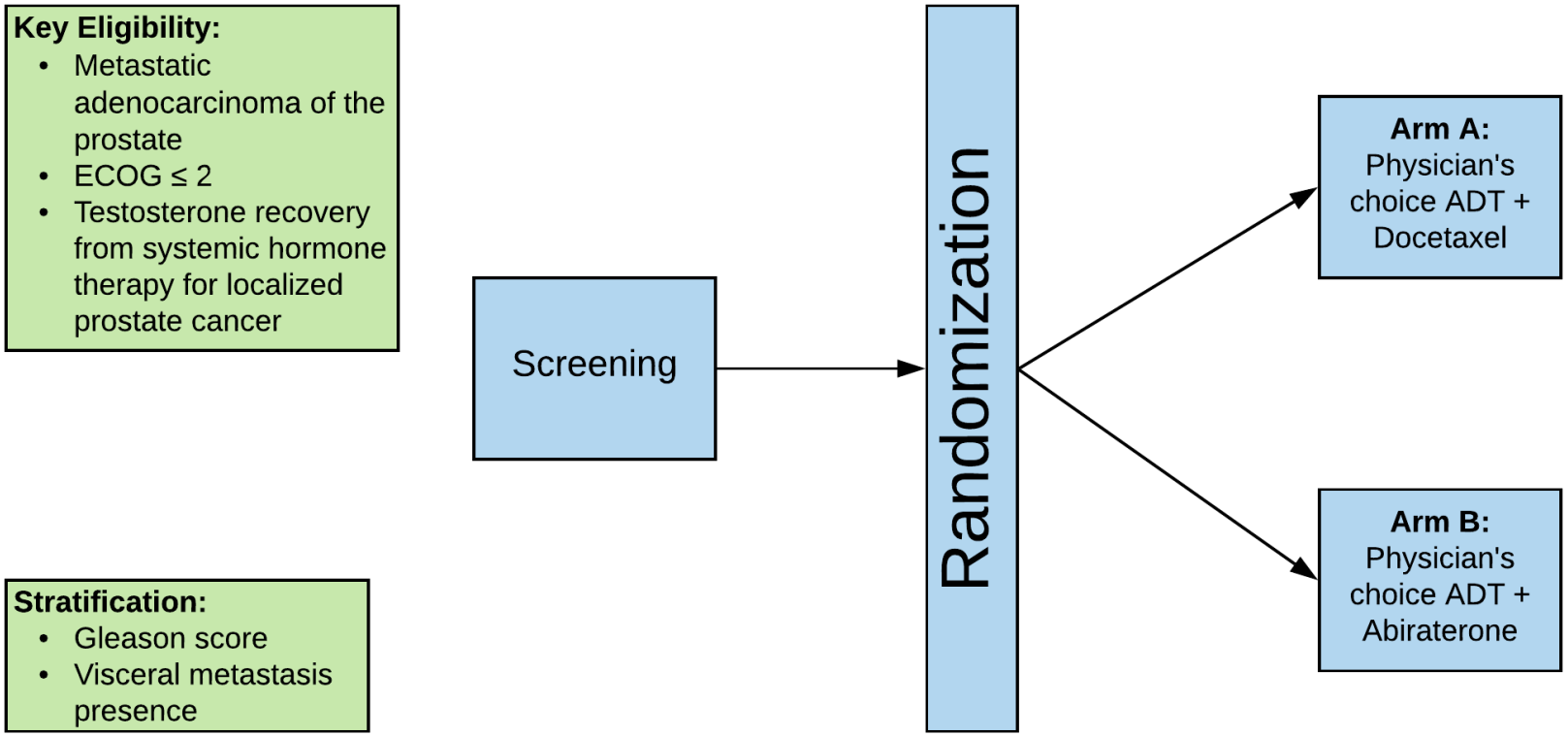
Name of Institution

STUDY SUMMARY

Title	A Randomized Phase II Clinical Trial of **A**DT **C**ombined with **A**biraterone or **D**oc**e**taxel in **M**etastat**ic** Hormone Sensitive Prostate Cancer.
Short Title	***ACADEMIC***
Protocol Identifiers (IRB – internal)	IRB 115099 - HCI-18-GU-11
IND number	Exempt
Phase	Phase II
Design	This is an open label, randomized prospective study of ADT + Abiraterone vs. ADT + Docetaxel in men with metastatic hormone sensitive prostate cancer.
Study Duration	This study is expected to enroll for 24 months. Patients will be followed for 18 months or until disease progression, whichever occurs first. It will take approximately 3.5 years to complete the study.
Study Center(s)	This will be a multi-institution trial conducted at the Huntsman Cancer Institute, at the University of Utah. Up to 7 additional centers may be opened.
Objectives	The primary objective of this study is to assess the difference in QOL from baseline to month 12 between ADT + Docetaxel vs ADT + Abiraterone.
Number of Subjects	89 patients will be enrolled. Patients will be randomized 1:1 to each treatment arm.
Diagnosis and Main Eligibility Criteria	- Male subject aged ≥ 18 years. - Histologically diagnosed adenocarcinoma of the prostate by WHO. - Radiographically confirmed metastatic disease prior to patient enrollment. Metastatic disease can be confirmed based on conventional imaging (CT, MRI, nuclear medicine bone scan) or molecular imaging (fluciclovine-PET/CT, PSMA-PET/CT, Choline-PET/CT etc). - ECOG ≤ 2. - Prior therapy with ADT or first generation anti-androgen receptor therapy (example: bicalutamide) is allowed. - Prior abiraterone or docetaxel use for metastatic hormone sensitive prostate cancer is not allowed.

	- Completed any hormone therapy for localized prostate cancer and testosterone has recovered. - Patients must not have a histologic diagnosis of small cell prostate cancer or pure squamous cell prostate cancer.
Study Product, Dose, Route, Regimen, Duration of administration	All patients will be treated with ongoing standard of care ADT (surgical or medical castration, documented testosterone should be < 50 ng/dL while on study.) Arm A: ADT + 75mg/m2 Docetaxel IV Q3weeks x 6 cycles. Arm B: ADT + Abiraterone PO continuous until disease progression.
Statistical Methodology	Statistical analysis will be performed in collaboration with HCI biostatistical support and use descriptive statistics as well as the Kaplan-Meier estimates and the log-rank test.

SCHEMA


Key Eligibility:
• Metastatic adenocarcinoma of the prostate
• ECOG ≤ 2
• Testosterone recovery from systemic hormone therapy for localized prostate cancer
Stratification:
• Gleason score
• Visceral metastasis presence
Screening
Randomization
Arm A: Physician's choice ADT + Docetaxel
Arm B: Physician's choice ADT + Abiraterone

1 OBJECTIVES

1.1 Primary Objective

To assess the impact of abiraterone and docetaxel on total quality of life between screening and month 12 of the study.

Primary Endpoint: The FACT-P questionnaire will be administered at baseline and month 12. Total Scores will be quantified and compared between treatment arms.

1.2 Secondary Objectives

1. To assess PSA response rates across the entire population and compared between groups.

   Secondary Endpoint: PSA evaluations will occur every 3 months while on study. The Prostate Cancer Working Group 3 criteria (PCWG3) will be used to define PSA response rates of 50% and 90% reductions.

2. To assess impact of abiraterone and docetaxel on additional quality of life measurements and quality of life trends throughout the duration of the study.

   Secondary Endpoint: Patient reported questionnaires—including FACT-P, FACT/GOG-NTX, and PROMIS Fatigue—will be administered at baseline and months 3, 6, 9, 12, and 18. Total scores, subscale scores, and trends will be analyzed.

3. To assess the potential clinical efficacy between treatment groups.

   Secondary Endpoint: To assess the PSA progression free survival (PSA-PFS) between treatment arms. PSA-PFS is defined based on PCWG3 criteria.

1.3 Exploratory Objectives

1. To assess biomarkers that may predict treatment response to hormonal therapy versus chemotherapy. Changes to tumor suppressors and the androgen receptor as well as other mechanisms will be analyzed from urine, blood and tumor tissue molecular analysis.

   Exploratory Endpoint: Patients will have tissue collected during this study for correlative analysis. Blood will be collected at baseline, and months 3, 6, and 18. Also, archival tissue will be collected (if available) as well as an optional soft-tissue biopsy at the time of disease progression.

2. To assess additional measures of overall quality of life between groups.

   Exploratory Endpoint: The Overall Treatment Utility (OTU) form, Was It Worth It (WIWI) questionnaire, and End of Study Evaluation Form will be administered to patients for exploratory purposes. The OTU form should be completed by the treating physician at the patient's 3 month visit and the WIWI questionnaire and End of Study Evaluation Form administered to the patient at the end of treatment (month 18 or progression visit, whichever comes first).

2 BACKGROUND

2.1 Hypothesis

Currently there are two competing standards of care for first-line treatment of patients with metastatic hormone sensitive prostate cancer (mHSPC), with docetaxel plus ADT and abiraterone plus ADT both demonstrating improved disease control over ADT alone. No direct comparisons have been done between these therapies, so the optimal treatment for these patients is currently not clear.

The first studies published to demonstrate improved overall survival over monotherapy of androgen deprivation therapy (ADT) alone were the CHAARTED[1] and STAMPEDE[2] (arms A, B, C and E) prospective clinical trials. In the CHAARTED study, 790 patients were randomized to ADT alone versus ADT plus 6 cycles of docetaxel. The median overall survival (OS) with the addition of docetaxel was significantly longer 57.6 months vs. 44.0 months (hazard ratio {HR} 0.61; 95% confidence interval {CI}, 0.47—0.80; P<0.001). These finding were verified in the STAMPEDE trial where six cycles of docetaxel plus ADT also improved clinical outcomes over ADT alone. The two docetaxel arms resulted in significant improvement to OS compared to the two ADT alone arms with hazard ratios of 0.78 (95% CI, 0.66—093; p=0.006) and 0.82 (95% CI, 0.69—0.97; p=0.022) respectively.

Two studies have shown superior outcomes with the addition of abiraterone to ADT in mHSPC, the LATITUDE[3] and STAMPEDE[4] (arms A and G) clinical trials. The LATITUDE trial randomized 1199 patients and the STAMPEDE randomized 1917 patients to ADT versus ADT plus abiraterone. The combination improved the median OS in the LATITUDE trial (not reached vs. 34.7 months; HR 0.62; 95% CI, 0.51—0.76; P<0.001) and improved 3 year survival in the STAMPEDE trial at 83% vs 76% (HR 0.63; 95% CI 0.52—0.76; P<0.001).

These two approaches of combination therapy have not been directly compared so no high-level evidence is available to make optimal treatment choices based on clinical outcomes. Treatment decision is instead based on other clinical factors such as drug availability, fitness for chemotherapy, toxicity or cost.[5]

There is likely a difference in these treatments regarding toxicities and cost. For instance, docetaxel is known to cause alopecia, febrile neutropenia fatigue and neuropathy. Abiraterone is known to cause fatigue, drug induced hepatitis and hypertension. There are differences in the treatment duration as well with docetaxel given for 6 cycles (approximately 4 months) whereas abiraterone is given until disease progression which may result in differences in quality of life and does result in difference in financial expense.[6] The patient reported outcomes in the LATITUDE study favored the combination group[7]. The reported quality of life was initially worse with docetaxel than ADT alone at three months, but better than ADT alone at 12 months in the CHAARTED study.[8]

Finally, there might be molecularly identified subgroups that will preferentially respond to a hormonal based treatment (i.e. ADT + abiraterone) or a chemotherapy based treatment (i.e. ADT + docetaxel). For instance, previous studies have demonstrated some subgroups of patients in the castration-resistant setting that are more sensitive to docetaxel over abiraterone.[9-11]

We hypothesize that treatment efficacy will be similar across the entire population studied in this clinical trial between ADT + docetaxel versus ADT + abiraterone. However, we

hypothesize that quality of life will be superior throughout the study for the abiraterone treated patients. Doing this clinical trial directly comparing these two treatment options will also allow for exploratory analysis of biomarkers of treatment response between hormonal versus chemotherapy treatment in this population of patients which may identify additional factors that may be important in the treatment selection between docetaxel and abiraterone for this patient population.

3 DRUG INFORMATION

3.1 Androgen Deprivation Therapy

All subjects must receive ADT of Investigator's choice (LHRH agonist or antagonist, or orchiectomy) per FDA approved dosing regulations as standard therapy for the duration of the clinical trial. Patients should maintain a castrate level testosterone concentration (i.e. total testosterone ≤ 50 ng/dL) as validation of therapeutic efficacy for the chosen ADT therapy.

3.2 Docetaxel (Taxotere)

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions.

Refer to Sanofi Package Insert for detail regarding clinical administration of TAXOTERE. The following information is taken from the Package Insert

3.2.1 Pharmacology

Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells.

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20 mg/m2 to 115 mg/m2 in phase 1 studies. The area under the curve (AUC) was dose proportional following doses of 70 mg/m2 to 115 mg/m2 with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α, β, and γ phases of 4 min, 36 min, and 11.1 hr, respectively. Mean total body clearance was 21 L/h/m2.

Distribution: The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean steady state volume of distribution was 113 L. In vitro studies showed that docetaxel is about 94% protein bound, mainly to α1-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the in vitro binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel.

Metabolism: In vitro drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4.

Elimination: A study of 14C-docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the tert-butyl ester

group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug

3.2.2 Pharmaceutical Properties and Formulation

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,N-tert-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate. Docetaxel is a white to almost-white powder with an empirical formula of C43H53NO14• 3H2O, and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water

3.2.3 Clinical Safety

The following data are based on the experience of 332 prostate cancer patients, who were treated with TAXOTERE 75 mg/m² every 3 weeks in combination with prednisone 5 mg orally twice daily:

	TAXOTERE 75 mg/m² every 3 weeks + prednisone 5 mg twice daily n=332 %		**Mitoxantrone 12 mg/m² every 3 weeks + prednisone 5 mg twice daily n=335 %**	
Adverse Reaction	**Any**	**Grade 3/4**	**Any**	**Grade 3/4**
Anemia	67	5	58	2
Neutropenia	41	32	48	22
Thrombocytopenia	3	1	8	1
Febrile neutropenia	3	N/A	2	N/A
Infection	32	6	20	4
Epistaxis	6	0	2	0
Allergic Reactions	8	1	1	0
Fluid Retention*	24	1	5	0
Weight Gain*	8	0	3	0
Peripheral Edema*	18	0	2	0
Neuropathy Sensory	30	2	7	0
Neuropathy Motor	7	2	3	1
Rash/Desquamation	6	0	3	1
Alopecia	65	N/A	13	N/A
Nail Changes	30	0	8	0

	TAXOTERE 75 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n=332 %		Mitoxantrone 12 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n=335 %	
Adverse Reaction	**Any**	**Grade 3/4**	**Any**	**Grade 3/4**
Nausea	41	3	36	2
Diarrhea	32	2	10	1
Stomatitis/Pharyngitis	20	1	8	0
Taste Disturbance	18	0	7	0
Vomiting	17	2	14	2
Anorexia	17	1	14	0
Cough	12	0	8	0
Dyspnea	15	3	9	1
Cardiac left ventricular function	10	0	22	1
Fatigue	53	5	35	5
Myalgia	15	0	13	1
Tearing	10	1	2	0
Arthralgia	8	1	5	1

*Related to treatment

3.3 Abiraterone Acetate (Abiraterone)

Abiraterone is an inhibitor of CYP17 (17α-hydroxylase/C17,20-lyase).

Abiraterone for this trial will be dispensed as part of the patient's standard of care therapy. Depending on insurance and/or physician preference, Zytiga, Yonsa, or a generic abiraterone acetate will be allowed. Dosing for each regimen should be consistent with FDA prescribing information.

Refer to Package Insert for detail regarding clinical administration of Zytiga, Yonsa, or generic abiraterone acetate. The following information is taken from these documents:

3.3.1 Pharmacology

Abiraterone acetate (abiraterone) is converted in vivo to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17 α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis. CYP17 catalyzes two sequential reactions: 1) the conversion of pregnenolone and progesterone to their 17α-hydroxy derivatives by 17α-hydroxylase activity and 2) the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively, by C17, 20 lyase activity. DHEA and androstenedione are androgens and are precursors of testosterone.

Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals. Androgen sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with GnRH agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumor. Abiraterone decreased serum testosterone and other androgens in patients in the placebo-controlled clinical trial. It is not necessary to monitor the effect of Abiraterone on serum testosterone levels. Changes in serum prostate specific antigen (PSA) levels may be observed but have not been shown to correlate with clinical benefit in individual patients.

3.3.2 Physical and Chemical Properties

Abiraterone acetate is a white to off-white, non-hygroscopic, crystalline powder. Its molecular formula is C26H33NO2 and it has a molecular weight of 391.55. Abiraterone acetate is a lipophilic compound with an octanol-water partition coefficient of 5.12 (Log P) and is practically insoluble in water. The pKa of the aromatic nitrogen is 5.19.

3.3.3 Pharmaceutical Properties and Formulation

Zytiga

Each Zytiga tablet contains either 250 mg or 500 mg of abiraterone acetate. Abiraterone acetate is designated chemically as (3β)-17-(3-pyridinyl) androsta5,16-dien-3-yl acetate.

Zytiga tablets are available in 500 mg film-coated tablets, 250 mg film-coated tablets and 250 mg uncoated tablets with the following inactive ingredients:

• 500 mg film-coated tablets: colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, silicified microcrystalline cellulose, and sodium lauryl sulfate. The coating, Opadry® II Purple, contains iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

• 250 mg film-coated tablets: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate. The coating, Opadry® II Beige, contains iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

• 250 mg uncoated tablets: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate

Yonsa

Yonsa (abiraterone acetate) tablets, 125 mg, are white to off-white, oval-shaped tablets debossed with “125 FP” on one side.

3.3.4 Clinical Safety

Zytiga

In a placebo-controlled, multicenter phase 3 clinical trial of patients with metastatic castration-resistant prostate cancer who were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchiectomy, abiraterone was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arm (N =

791). Placebo plus prednisone 5 mg twice daily was given to control patients (N = 394). The median duration of treatment with Abiraterone was 8 months. The most common adverse drug reactions (≥5%) reported in clinical studies were joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection. The most common adverse drug reactions that resulted in drug discontinuation were aspartate aminotransferase increased, alanine aminotransferase increased, urosepsis and cardiac failure (each in <1% of patients taking abiraterone).

Adverse reactions and laboratory abnormalities related to mineralocorticoid effects were reported more commonly in patients treated with abiraterone than in patients treated with placebo: hypokalemia 28% versus 20%, hypertension 9% versus 7% and fluid retention (edema) 27% versus 18%, respectively. In patients treated with abiraterone, grades 3 to 4 hypokalemia occurred in 5% of patients and grades 3 to 4 hypertension was reported in 1% of patients.

Cardiovascular Adverse Reactions:

The majority of arrhythmias were grade 1 or 2. Grade 3-4 arrhythmias occurred at similar rates in the two arms. There was one death associated with arrhythmia and one patient with sudden death in the abiraterone arm. No patients had sudden death or arrhythmia associated with death in the placebo arm. Cardiac ischemia or myocardial infarction led to death in 2 patients in the placebo arm and 1 death in the abiraterone arm. Cardiac failure resulting in death occurred in 1 patient on both arms.

Hepatotoxicity:

Drug-associated hepatotoxicity with elevated ALT, AST, and total bilirubin has been reported in patients treated with abiraterone. Across all clinical trials, liver function test elevations (ALT or AST increases of > 5X ULN) were reported in 2.3% of patients who received abiraterone, typically during the first 3 months after starting treatment. In the phase 3 trial, patients whose baseline ALT or AST were elevated were more likely to experience liver function test elevations than those beginning with normal values. When elevations of either ALT or AST > 5X ULN, or elevations in bilirubin > 3X ULN were observed, abiraterone was withheld or discontinued. In two instances marked increases in liver function tests occurred. These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40X ULN and bilirubin elevations 2 to 6 X ULN. Upon discontinuation of abiraterone, both patients had normalization of their liver function tests and one patient was re-treated with ABIRATERONE without recurrence of the elevations. In clinical trials, the following patients were excluded: patients with active hepatitis, patients with baseline ALT and/or AST ≥ 2.5X ULN in the absence of liver metastases, and patients with ALT and/or AST > 5X ULN in the presence of liver metastases. Abnormal liver function tests developing in patients participating in clinical trials were managed by treatment interruption, dose modification and/or discontinuation [see Dosage and Administration (2.2) and Warnings and Precautions (5.3)]. Patients with elevations of ALT or AST > 20X ULN were not re-treated.

Yonsa

Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess:

Yonsa may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with Yonsa.

In the two randomized clinical trials, grade 3 to 4 hypertension occurred in 2% of patients, grade 3 to 4 hypokalemia in 4% of patients, and grade 3 to 4 edema in 1% of patients treated with abiraterone acetate.

Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Closely monitor patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, such as those with heart failure, recent myocardial infarction, cardiovascular disease, or ventricular arrhythmia. The safety of Yonsa in patients with left ventricular ejection fraction < 50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) was not established because these patients were excluded from these randomized clinical trials.

Adrenocortical Insufficiency:

Adrenal insufficiency occurred in the two randomized clinical studies in 0.5% of patients taking abiraterone acetate and in 0.2% of patients taking placebo. Adrenocortical insufficiency was reported in patients receiving abiraterone acetate in combination with corticosteroid, following interruption of daily steroids and/or with concurrent infection or stress.

Monitor patients for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from corticosteroids, have corticosteroid dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with Yonsa. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

Hepatotoxicity:

In postmarketing experience, there have been abiraterone acetate-associated severe hepatic toxicity, including fulminant hepatitis, acute liver failure and deaths.

In the two randomized clinical trials, grade 3 or 4 ALT or AST increases (at least 5X ULN) were reported in 4% of patients who received abiraterone acetate, typically during the first 3 months after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those beginning with normal values. Treatment discontinuation due to liver enzyme increases occurred in 1% of patients taking abiraterone acetate. No deaths clearly related to abiraterone acetate were reported due to hepatotoxicity events.

Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with Yonsa, every two weeks for the first three months of treatment and monthly thereafter. In

patients with baseline moderate hepatic impairment receiving a reduced Yonsa dose of 125 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt Yonsa treatment and closely monitor liver function.

Re-treatment with Yonsa at a reduced dose level may take place only after return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN. Permanently discontinue treatment with abiraterone acetate for patients who develop a concurrent elevation of ALT greater than 3 x ULN and total bilirubin greater than 2 x ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation. The safety of YONSA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

4 STUDY DESIGN

4.1 Description

This is an open label, randomized prospective clinical trial. All patients will be treated with ongoing standard of care ADT (surgical or medical castration, documented testosterone < 50 ng/dL while on study) plus either docetaxel intravenously (75mg/m2) once every 3 weeks for 6 cycles or abiraterone orally until disease progression. Treatment will occur per standard of care at the discretion of the treating physician. Radiographic disease assessment will be performed per clinical indication. Study visits time points will be based on day 1 of treatment and follow a consistent schedule, regardless of treatment delays. Patients will be followed until disease progression or for 18 months, whichever occurs first.

4.2 Number of Patients

A total of 89 subjects will be enrolled.

4.3 Number of Study Centers

This will be a multi-institution trial conducted at the Huntsman Cancer Institute, at the University of Utah. Up to an additional 7 other centers may be opened.

4.4 Study Duration

This trial is expected complete enrollment within 24 months. Treatment is expected to continue for an additional 18 months. The study will be completed after approximately 42 months.

5 ELIGIBILITY CRITERIA

This eligibility checklist is used to determine patient eligibility and filed with the enrolling investigator's signature in the patient research chart.

Patient No. _____
Patient's Initials: (L,F,M) _____

5.1 Inclusion Criteria
Yes/No (Response of "no" = patient ineligible)

5.1.1 _____ Male subject aged ≥ 18 years.

5.1.2 _____ Histologically diagnosed adenocarcinoma of the prostate.

5.1.3 _____ Radiographically confirmed metastatic disease prior to patient enrollment. Metastatic disease can be confirmed based on conventional imaging (CT, MRI, nuclear medicine bone scan) or molecular imaging (fluciclovine-PET/CT, PSMA-PET/CT, Choline-PET/CT etc).

5.1.4 _____ ECOG Performance Status ≤ 2.

5.1.5 _____ Adequate organ function as defined as:

- **Hematologic:**
  - Absolute neutrophil count (ANC) ≥ 1.5 k/µL.
  - Platelets ≥ 100 k/µL.
  - Hemoglobin ≥ 9 g/dL.
- **Hepatic:**
  - Serum total bilirubin ≤ 1.5 times upper limit of normal (ULN) OR direct bilirubin ≤ ULN for subjects with total bilirubin ≥ 1.5 × ULN.
  - AST or ALT ≤ 2.5 × ULN OR ≤ 4 × ULN for subjects with liver metastases.
- **Renal:**
  - Creatinine < 1.5 × ULN OR
  - Creatinine clearance > 50 mL/min for subject with creatinine levels > 1.5 × ULN by Cockcroft-Gault fomula or standard institutional practice:
    - Males: $\frac{(140-age)\times weight[kg]}{serum\ creatinine\left[\frac{mg}{dL}\right]\times 72}$
    - Females: $\left(\frac{(140-age)\times weight[kg]}{serum\ creatinine\left[\frac{mg}{dL}\right]\times 72}\right)\times 0.85$

5.1.6 ____ Highly effective method of contraception for both male and female partners of subjects throughout the study and for at least 3 months after last study treatment administration if the risk of conception exists.

5.1.7 _____ Recovery to baseline or ≤ Grade 1 CTCAE v5.0 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy as defined by the treating physician.

5.1.8 _____ Able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

5.2 Exclusion Criteria
Yes/No (Response of "yes" = patient ineligible)

5.2.1 _____ No prior abiraterone or docetaxel therapy for metastatic hormone sensitive prostate cancer. Prior therapy with ADT or first generation anti-androgen receptor therapy (example: bicalutamide) is allowed.

5.2.2 _____ Completed any hormone therapy for localized prostate cancer and have recovery of testosterone (i.e. testosterone level is >50ng/dL).

5.2.3 _____ Patients have a histologic diagnosis of small cell prostate cancer or pure squamous cell prostate cancer.

5.2.4 _____ Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before first dose of study treatment. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of first dose of study treatment.

5.2.5 _____ The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

- Cardiovascular disorders:
  - Congestive heart failure New York Heart Association Class 3 or 4, unstable angina pectoris, serious cardiac arrhythmias within 3 months of study enrollment.
  - Uncontrolled hypertension defined as sustained blood pressure (BP) > 170 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment.
  - Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic event, or arterial thromboembolic event within 3 months before first dose.
- Other clinically significant disorders that would preclude safe study participation. As defined by the treating physician

5.2.6 _____ Known history of testing positive for HIV and CD4 count is below 200 or known acquired immunodeficiency syndrome diagnosis.

5.2.7 _____ Known history of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or detectable HCV RNA if anti-HCV antibody screening test positive) and a detectable viral count at screening.

5.2.8 _____ Use of live virus vaccine within 4 weeks of the first dose of treatment or planned use while on trial for the duration of potential docetaxel treatment. Live vaccine use is acceptable after chemotherapy or for patients randomized to the abiraterone arm. There are no restrictions on inactive viruses.

5.2.9 _____ Known prior severe hypersensitivity to investigational product or any component in its formulations (NCI CTCAE v5.0 Grade ≥ 3).

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

Investigator Signature	**Date**	**Time**

5.3 Recruitment Strategies

Potential patients will be identified by Investigators in the setting of their outpatient clinics.

6 RANDOMIZATION

Patients will be randomized in a 1:1 manner. Patients will be stratified based on Gleason score (< 8 versus ≥ 8) and the presence of visceral metastasis (yes versus no). Visceral metastasis is defined as liver, lung, or central nervous system (CNS) involvement.

7 TREATMENT PLAN

7.1 Administration Schedule

Treatment will occur per standard of care at the discretion of the treating physician. All study drugs will be provided by commercial supply. Study visits will be anchored to day 1 of treatment, without regard for changes to treatment schedule.

Patients who are unable to initiate docetaxel or abiraterone therapy within 42 days of randomization will be replaced.

7.2 Docetaxel

7.2.1 How Supplied, Stored, Packaged and Labeled

Docetaxel Injection Concentrate is a clear yellow to brownish-yellow viscous solution. Docetaxel is sterile, non-pyrogenic, and is available in single-dose vials containing 20 mg (0.5 mL) or 80 mg (2 mL) docetaxel (anhydrous). Each mL contains 40 mg docetaxel (anhydrous) and 1040 mg polysorbate 80.

TAXOTERE Injection Concentrate requires dilution with Diluent prior to addition to the infusion bag. A sterile, non-pyrogenic, single-dose diluent is supplied for that purpose. The diluent for TAXOTERE contains 13% ethanol in water for injection, and is supplied in vials.

7.2.2 Preparation and Administration

The docetaxel should be dosed and administered per institutional standards in accordance with FDA approved usage. Cycles should be repeated approximately every 3 weeks for 6 cycles. Treatment delays and potential dose modifications will occur per standard of care at the discretion of the treating physician, to reflect the clinical setting as much as possible.

The recommended pre–medication regimen is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the docetaxel infusion. However, other schedules or use of a different corticosteroid is also acceptable consistent with local practice. Anti-emetic regimens are recommended as per local clinical practice.

Preparation procedures are detailed in the package insert.

7.3 Zytiga (Abiraterone)

7.3.1 How Supplied, Stored, Packaged and Labeled

Zytiga

250 mg tablets are white to off-white, oval tablets debossed with AA250 on one side. Zytiga 250 mg tablets are available in high-density polyethylene bottles of 120 tablets.

Store at 20º C to 25º C (68º F to 77º F); excursions permitted to 15º C to 30º C (59º F to 86°F). Based on its mechanism of action, Zytiga may harm a developing fetus. Therefore, women who are pregnant or women who may be pregnant should not handle Zytiga without protection (e.g., gloves).

Yonsa

Tablets, 125 mg, are white to off-white, oval-shaped tablets debossed with "125 FP" on one side.

Store at 20º C to 25º C (68º F to 77º F); excursions permitted to 15º C to 30º C (59º F to 86°F). Women who are pregnant or women who may be pregnant should not handle Yonsa without protection, e.g., gloves.

7.3.2 Preparation and Administration

Zytiga

The Zytiga should be dosed and administered per institutional standards and in accordance with FDA approved use. The package insert recommends 1,000 mg administered orally once daily in combination with prednisone 5 mg administered orally twice daily. No food should be consumed for at least two hours before the dose of Zytiga is taken and for at least one hour after the dose of Zytiga is taken.

Yonsa

The Yonsa should be dosed and administered per institutional standards and in accordance with FDA approved use. The recommended dose of YONSA is 500 mg (four 125 mg tablets) administered orally once daily in combination with methylprednisolone 4 mg administered orally twice daily with or without food.

7.3.3 Accountability and Compliance

Abiraterone tablets will be supplied per standard practice of the treating physician and pharmacy.

7.4 Concomitant Medications and Therapies

7.4.1 Prohibited Therapy

7.4.1.1 Docetaxel

Docetaxel is a CYP3A4 substrate. In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4. In vivo studies showed

that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of docetaxel and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with docetaxel, close monitoring for toxicity and a docetaxel dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided

7.4.1.2 Abiraterone

Abiraterone is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the Cmax and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid coadministration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug.

Abiraterone is also a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, in vivo. Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during abiraterone treatment.

7.5 Duration of Therapy

Arm A: Patients will receive 6 cycles of docetaxel, given approximately every 3 weeks, in addition to physician's choice ADT.

Arm B: Patients will receive abiraterone continuously, in addition to physician's choice ADT, until disease progression.

7.5.1 Criteria for discontinuation of treatment ("off treatment")

The following will result in treatment discontinuation:

- Subject withdraws consent from the study treatment and/or study procedures.
- Diagnosis of progression, per the discretion of the treating physician. The protocol suggests defining progression based on radiographic or clinical progression and not PSA only progression.
- AEs or intercurrent illness that in the opinion of the investigator warrants the subject's withdrawal from study treatment.
- Significant noncompliance with the protocol schedule or treatment administration in the opinion of the investigator.

7.5.2 Criteria for discontinuation of study ("off study")

Subjects will be taken off study for the following:

- Completed study follow-up period
- Participant requests to be withdrawn from study
- Death
- Subject is lost to follow-up

8 TOXICITIES AND DOSEAGE MODIFICATION

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for adverse event and serious adverse event reporting.

8.1 Dose Modifications and Guidelines for Adverse Event Management

8.1.1 Dose Modifications

Dose adjustments for ADT, docetaxel, and abiraterone will be left to the discretion of treating investigator. Toxicities should be monitored and managed per institutional practice.

8.2 Supportive Care

All supportive measures consistent with optimal patient care may be given throughout the study.

8.3 Contraception

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Male subjects of reproductive potential must agree to avoid impregnating a partner while receiving study drug and for 3 months after the last dose of study drug by complying with one of the following:

(1) practice abstinence from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are[‡]:

- Single method (one of the following is acceptable):
  - intrauterine device (IUD)
  - contraceptive rod implanted into the skin
- Combination method (requires use of two of the following):
  - diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
  - cervical cap with spermicide (nulliparous women only)
  - contraceptive sponge (nulliparous women only)
  - male condom or female condom (cannot be used together)

- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 3 months for males after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

9 STUDY CALENDAR

Protocol Procedures	Screening[1]	Months (+/- 4 days)						Progression[11]
		M0 (Day 1)	M3	M6	M9	M12	M18	
Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Vital Signs	X[2]							
Physical Exam with ECOG	X							
Complete Blood Count (CBC) with Platelet Count, Differential	X							
Comprehensive Metabolic Panel (CMP)	X							
Urinalysis	X							
Testosterone	X	X[9]						
PSA		X[8]	X	X	X	X	X	X
CT – Chest/Abdomen/Pelvis[10]	X	X[3]						X
Whole Body Bone Scan	X	X[3]						X
Archival Tissue Submission (if available)		X[4]						
Fresh Tissue Collection	X[5]							
Correlative Blood Collection[6]		X[8]	X	X			X	X
ADT + Docetaxel or ADT + Abiraterone		X[7]						
Questionnaires – FACT P, FACT/GOG-NTX, PROMIS Fatigue		X[8]	X	X	X	X	X	
Adverse Event Collection[13]		X	X	X	X	X	X	X
Medical History	X							
Exploratory Questionnaires[12]			X				X	X
Extent of Metastases Form (Appendix I)	X							

Note: All visits will be based on treatment start date and will be performed independent of treatment cycles and/or delays. 1 month will be defined as 28 days.

1) Screening procedures should be performed within 28 days of Day 1 (Treatment initiation). There is no window designated for the screening diagnostic CT and/or bone scan prior to study enrollment.
2) Vitals include height, weight, blood pressure, pulse, and temperature.
3) To be repeated per clinical indication.
4) To be performed prior M3 visit.
5) If the patient has consented to optional tissue collection, tissue may be collected from any SOC biopsy performed while on trial or at the end of treatment (month 18 or progression visit, whichever comes first).
6) If the patient consents to optional blood collection, blood will be collected at month 0 (prior to treatment), month 3, month 6 and the end of treatment (month 18 or progression visit, whichever comes first).
7) Treatment length will depend on randomization assignment. Arm A will receive ADT + Docetaxel IV approximately Q3weeks x 6 cycles. Arm B will receive ADT + Abiraterone PO (per drug-specific dosing guidelines), unless there is disease progression.
8) To be performed prior to treatment initiation on Day 1. If treatment initiation is delayed by >4 days after completion of baseline questionnaires, these should be repeated.
9) Testosterone should be monitored monthly, or per institutional standard of care, to confirm castrate level testosterone concentration (i.e. total testosterone $\leq$ 50 ng/dL).
10) Imaging techniques and sequences should be performed per institutional standard of care. Axumin PET CT Skull Base to Mid-Thigh will be allowed at screening.
11) Procedures required at the time of progression will be performed within +/- 30 days of diagnosis of progression. Diagnosis of progression is per the discretion of the treating physician. The protocol suggests defining progression based on radiographic or clinical progression and not PSA only progression.
12) The Overall Treatment Utility (OTU) form, Was It Worth It (WIWI) questionnaire, and End of Study Evaluation Form will be administered to patients for exploratory purposes. The OTU for should be completed by the treating physician at the patient's 3 month visit and the WIWI questionnaire and End of Study Evaluation Form administered to the patient at the end of treatment (month 18 or progression visit, whichever comes first).
13) Due to extensive characterization of study treatment regimens through previous clinical trials and in the standard clinical context, adverse event collection will be limited in scope and occur in accordance with recording and reporting guidelines set forth in Section 16.2.

10 STUDY PROCEDURES

10.1 Screening Evaluations

- Informed Consent
- Review of Inclusion/Exclusion Criteria
- Review of Medical History
- Vital Signs, including height, weight, blood pressure, pulse, and temperature
- Physical Exam
- ECOG Performance Status
- Laboratory assessments:
  - CBC with differential
  - CMP, including Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, and Urea Nitrogen
  - Urinalysis
  - Prostate-specific antigen (PSA)
  - Testosterone
- CT scans of chest/abdomen/pelvis
- Whole body bone scan

10.2 On Treatment Evaluations

After the patient is determined to be eligible and is registered on the trial he will be randomized 1:1 using block randomization to ADT + abiraterone or ADT + docetaxel. Treatment will occur per standard of care at the discretion of the treating physician. Radiographic disease assessment will be performed per clinical indication and at the time of progression. Study visits time points will be based on day 1 of treatment and follow a consistent schedule, regardless of treatment delays. Patients will be followed until disease progression or for 18 months, whichever occurs first.

10.2.1 Day 1 (Month 0) and at Months 3, 6, 9, 12, 18

- Archival Tissue Submission. This should be performed anytime between registration and prior M3 visit.
- Laboratory assessments:
  - Prostate-specific antigen (PSA)
- Correlative Blood Collection – Only months 0 (prior to treatment), 3, 6, and 18 or at progression, if prior. (optional)
- Questionnaires:
  - FACT-P-TOI
  - FACT/GOG-NTX

- To avoid duplicate FACT answers, subjects only need to complete the 11 additional questions that specifically address sensory and motor neuropathy symptoms within the FACT/GOG-NTX. [Appendix C]

- PROMIS Fatigue

- Tissue may be procured from a standard of care biopsy at any point while on study.
- Month 3 Only – Overall Treatment Utility (OTU) form to be completed by treating physician
- Month 18 Only, if patient has not progressed prior - Was It Worth It (WIWI) questionnaire and End of Study Evaluation Form to be completed by patient

10.2.2 At the time of Progression, if prior to M18 visit

- Correlative Blood Collection
- Tissue may be procured from a standard of care biopsy at the time of progression.
- CT scans of chest/abdomen/pelvis
- Whole body bone scan
- Was It Worth It (WIWI) questionnaire and End of Study Evaluation Form to be completed by patient

11 CRITERIA FOR EVALUATION AND ENDPOINT

11.1 Safety

Routine safety and tolerability may be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

Physical Examination

Complete and symptom-directed physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner).

Vital Signs

Vital signs (blood pressure, respiratory rate, pulse rate and temperature) will be obtained per institutional practice. Height and weight will be taken at screening.

Safety Laboratory Determinations

Laboratory evaluations will be performed as noted in the flow chart.

11.2 Efficacy

Prostate-specific antigen will be evaluated throughout treatment to determine optimal PSA response in both arms as well as PSA-PFS time points between treatment arms. This study will use the PCGW3 criteria to define PSA-PFS[18]. PCWG3 defines PSA progression as the date that an increase of 25% or more and absolute increase of 2 ng/mL or more from the nadir are documented. For patients who had an initial PSA decline during treatment, this must be confirmed by a second value 3 or more weeks later.

12 STATISTICAL CONSIDERATIONS

12.1 Primary Objective and Endpoint

To assess the impact of abiraterone and docetaxel on total quality of life between screening and month 12 of the study. The Functional Assessment of Cancer Therapy -Prostate (FACT-P) questionnaire will be administered at baseline and month 12. The FACT-P is a 39 item questionnaire that measures health-related quality of life in men with prostate cancer.[14] The FACT-P Trial Outcome Index (TOI) is the sum of the Physical Well-Being (PWB), Functional Well-Being (FWB), and Prostate Cancer Subscales (PCS). TOI Scores will be quantified and compared between treatment arms.

12.2 Statistical Hypothesis

We hypothesize that abiraterone will have improved quality of life measurements at month 12 compared to docetaxel based on comparison of data from CHAARTED[8] and LATITUDE.[7]

12.3 Secondary Objective and Endpoint

- FACT/GOG-NTX: The FACT/GOG-NTX is a 38 item questionnaire that assesses patient self-report of neuropathy.[15] It is a combination of the 27-item FACT-G (which is also part of the FACT-P) plus 11 additional questions that specifically address sensory and motor neuropathy symptoms.
- PROMIS Fatigue: The PROMIS Fatigue scale is a 7-item self-report measure designed to assess severity, frequency, and daily pattern of fatigue (www.nihpromis.com). It has been validated in cancer populations.[16]

12.4 Sample Size Determination

We hypothesize that patients on the ADT + Abiraterone arm will experience a superior overall QOL at month 12 after enrollment in the study. Cella (2008) reports that a minimally important difference in FACT-P TOI is a (standardized) effect size of 0.42 – 0.57. Power was calculated via simulations in R using a Gaussian approximation for FACT-TOI analyzed using a mixed effects model with fixed effects for treatment arm and categorical assessment time and a random intercept for each subject. We assumed correlation = 0.5 between baseline and follow up FACT-P TOI. We computed power for a comparison of the standardized change in FACT-P TOI from baseline to 12 months. With the above assumption 40 subjects with complete data per group will provide 80% power to detect a standardized effect size difference of 0.56 between the randomized groups at two sided alpha = 0.05.

The sample size of 80 patients is calculated based on the number of patients with complete data. If there are patients with incomplete follow up data, they will contribute to the intent to treat population. We assume 10% of patients will have incomplete data. To account for this increased uncertainty the sample size will be increased to 89.

12.5 Statistical Methods

Quality Of Life Endpoints

The primary and secondary outcome variables are patient reported quality of life, including the FACT-P TOI (the primary outcome variable), and FACT/GOG NTX and PROMIS Fatigue

(secondary outcome variables) assessed at baseline, 3, 6, 9, 12, and 18 months. Each of these outcomes will be analyzed using Gaussian repeated measures mixed-effects models. The models will contain random intercepts, fixed effects for each follow up assessment time and interaction terms for treatment arm and follow up assessment time. The primary analysis will be use a modified intent-to-treat strategy. Multiple imputation methods will be used to impute missing questionnaire data for each subject who completes a baseline questionnaire. The mixed effects models will also be used to report the mean and standard error of the change from baseline at each of the follow up time points at which the questionnaires are administered (3, 6, 9, 12, 18 months). The area under the curve from 0 to 12 months will also be reported. Joint modeling of longitudinal FACT-P TOI and survival may be used as an additional sensitivity analysis to explore changes in QOL over time.

The primary hypothesis is that patients on the ADT + Abiraterone arm will experience a superior overall QOL at month 12 after enrollment in the study. This single primary hypothesis will be tested at the two sided 0.05 significance level (unadjusted) using the interaction term between treatment arm and the 12 month follow up time from the mixed effects model for FACT-P TOI described above. Tests of interaction between treatment arm and the 12 month follow up time will also be performed for the models for FACT/GOG NTX and PROMIS Fatigue at the two sided 0.05 significance level (unadjusted).

PSA Response and PSA Progression Free Survival

PSA will be measured every three months while on study. The proportion of subjects experiencing a 50% and 90% reduction in PSA as defined by the Prostate Cancer Working Group 3 will be reported for each study arm, along with exact 95% confidence intervals (Clopper-Pearson). The proportion of PSA responders as defined by each of the above criteria will be compared between treatment arms using Fisher's Exact test at the two sided 0.05 significance level (unadjusted).

PSA Progression free survival (PSA-PSF) will be plotted using Kaplan-Meier methods. PSA-PFS will be compared between the treatment arms using a log-rank test at the two sided 0.05 significance level (unadjusted). Subjects that have not experience PSA progression at the end of study will be censored for PSA progression at the time of last on-study PSA evaluation.

13 REGISTRATION GUIDELINES

Study related screening procedures can only begin once the patient has signed a consent form.

Patients must meet all of the eligibility requirements listed above prior to registration.

Patients must be registered before receiving any study treatment and must begin treatment within 42 days after randomization.

To register eligible patients on study, complete a Clinical Trials Office Patient Registration Form and submit to CTORegistrations@hci.utah.edu.

14 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of (electronic or paper) forms for each patient that provides a record of the data generated according to the protocol. CRF's should be created prior

to the study being initiated and updated (if applicable) when amendments to the protocol are IRB approved. These forms will be completed on an on-going basis during the study. The medical records will be source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility and attention to detail by a member of the Research Compliance Office. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log. The data will be reviewed no less than annually by the Data and Safety Monitoring Committee. The Investigator will allow the Data and Safety Monitoring Committee or Research Compliance Office personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

Data capture should be restricted to endpoints and relevant patient information required for planned manuscripts.

15 SPECIAL INSTRUCTIONS

15.1 Correlative Studies

15.1.1 Correlative Tissue Samples

Available archival tissue will be sent to Foundation Medicine to test for biomarkers of disease response and prediction of treatment effect, such as, but not limited to: next generation sequencing of tumor DNA and whole transcriptome analysis. NGS may be performed to assess for changes to tumor suppressors and the androgen receptor, as these have been demonstrated to be mechanisms of resistance to therapy.

If the patient consents to the optional tissue, up to 4 research cores will be collected any time the patient has a standard of care biopsy while on study. Testing may include, but is not limited to:

- Multiomics platforms
- Immunohistochemistry
- Flow cytometry

Specimen collection and processing instructions can be found in the lab manual.

15.1.2 Correlative Blood Samples

If the patient consents to provide optional blood samples, up to 54mL of peripheral blood will be collected at the timepoints listed in the study calendar. Testing may include, but is not limited to:

- Circulating tumor cells (CTC) detection, enumeration, and characterization
- Cytokine/chemokine/interferon assays
- Genomic analysis
- Proteomic analyses
- Flow Cytometry
- Detection of somatic and germline DNA alterations by targeted sequencing of cell-free DNA.

- Detection of androgen receptor splice variant 7 (ARV7) by droplet digital PCR (ddPCR).

Specimen collection and processing instructions can be found in the lab manual.

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Informed consent

Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB-approved version.

16.1.1 Participation of Children

Patients must be at least 18 years of age to participate.

16.2 Institutional Review

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements) and any other applicable patient-facing documents. The investigator should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information.

The investigator or designee should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures. Data and Safety Monitoring Plan

A Data and Safety Monitoring Committee (DSMC) is established at Huntsman Cancer Institute (HCI) to ensure the well-being of patients enrolled on Investigator Initiated Trials that do not have an outside monitoring review. The roles and responsibilities of the DSMC are set forth in the NCI-approved Data and Safety Monitoring (DSM) plan. The activities of the committee include reviewing adverse events (including SAEs), deviations, important medical events, significant revisions or amendments to the protocol, and approving cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not be resumed until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

This is a multicenter treatment study classified as high risk per the NCI-approved DSM plan.

Each high-risk study will be assigned a physician member of the DSMC as medical monitor, or in rare cases, an external medical monitor. The medical monitor will be notified of all serious adverse events (SAEs). Specific notifications will also be issued when a dose-limiting toxicity is encountered and when the MTD dose is defined. Approval of the medical monitor is required for all dose escalations. All serious adverse events (SAEs) occurring in patients treated at HCI or its affiliates will also be reviewed by the full DSMC monthly. The full committee will also review all toxicities for patients on treatment and within 30 days of their last treatment on a quarterly basis.

Each high-risk study will also be assigned a dedicated research compliance officer who will monitor the trial. High-risk studies will be monitored by RCO personnel after the first patient is enrolled and every three months thereafter during active enrollment. The RCO monitor will review the study status and summarize enrollment, toxicities, SAEs, dose escalation, statistical endpoints (e.g., stopping rules), deviations, etc. for the full DSMC membership at the regularly scheduled meetings. Amendments which increase risk, change dosing, or impact study objectives will be reviewed by the DSMC and approved by the PRMC and IRB. High-risk trials will be formally reviewed by the DSMC after the first patient is enrolled and then quarterly thereafter.

An initial audit of high-risk studies will be conducted by the RCO approximately one year after enrollment begins and annually thereafter. Audits of high-risk studies may be conducted more frequently as requested by the DSMC, IRB, PRMC, RCO management, or the PI.
Adverse Events and Serious Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for AE and SAE reporting.

16.2.1 Adverse Events (AEs)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they are considered clinically significant by the treating investigator, or require therapy to treat.

Collection of adverse events will begin after the first dose of study drug and end at the Month 18 visit or 30 days after the last dose of study drug if the patient is removed for progression prior to this time point.

The safety profile for the drugs involved in this study have been characterized extensively in previous clinical trials and standard clinical contexts. As such, safety data collection for this study will be limited to ≥ Grade 3 adverse events as defined by CTCAE v5.0.

Information about adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be abstracted from standard investigator clinic notes and recorded in the patient's study chart, at the interval noted in the study calendar.

Adverse events meeting the aforementioned recording criteria should be further evaluated, either through abstraction of standard investigator clinic notes or through direct correspondence with the treating investigator to determine:

1. The severity grade based on CTCAE v5.0 (grade 1-5)
2. Its relationship to the study drugs (definite, probable, possible, unlikely, not related)
3. Its duration (start and end dates or if continuing at final exam)

4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it constitutes an SAE

All adverse events will be treated as medically appropriate.

All CTCAE v5.0 Grade 3 and above adverse events should be followed until its resolution or the patient discontinues study, and assessment should be made at the interval noted in the study calendar (or more frequently, if necessary) of any changes in severity, suspected relationship to the study intervention, interventions employed to treat it, and outcome.

16.2.2 Serious Adverse Event (SAE)

Information about all serious adverse events, as defined below, will be collected and recorded. A serious adverse event is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Causes congenital anomaly or birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition

Collection of serious adverse events will begin at enrollment and end 30 after the last dose of study treatment or until a new cancer treatment is initiated, whichever happens the soonest.

Any death from any cause while a patient is receiving treatment on this protocol or up to 30 days after the last dose of protocol treatment, or any death which occurs more than 30 days after protocol treatment has ended but which is felt to be treatment related, must be reported.

Toxicities which fall within the definitions listed above must be reported as an SAE regardless if they are felt to be treatment related or not.

16.3 SAE Reporting Requirements

A MedWatch 3500A form must be completed to document each observed SAE and submitted to compliance@hci.utah.edu as soon as possible, but no later than 1 working day of first knowledge or notification of event.

The Research Compliance Office will appropriately report these SAEs to the DSMC and/or the IRB of record according to the requirements described below:

DSMC Notifications:

- Fatal or life-threatening events meeting the definition of an SAE will be reported within 7 calendar days after first knowledge of the event by the investigator.
- All other events meeting the SAE criteria above will be reported within 15 calendar days after first knowledge of the event by the investigator.
- Events that meet expedited reporting (serious, unexpected suspected adverse reactions) will be reported to the FDA and IRB, as applicable.

IRB Notification:

1. Events will be submitted to the IRB of record per local guidelines.

16.4 Reporting of Pregnancy

Although pregnancy is not considered an adverse event, it is the responsibility of investigators or their designees to report the pregnancy of a male subjects' female partner as an unanticipated problem involving risk as noted above. Pregnancies or lactation that occurs during the course of the trial or within 30 days of completing the trial must be reported to the DSMC, IRB, and FDA as applicable. All female partners of subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events.

16.5 Protocol Amendments

Any amendments or administrative changes to an IRB approved protocol will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all subjects included in the trial.

Any amendments to the protocol that significantly affect the safety of subjects, scope of the investigation, or the scientific quality of the study are required to submit the amendment for FDA review.

16.6 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The sponsor requires the **prompt reporting** to HCI RCO of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance

16.7 FDA Annual Reporting

This study is IND exempt therefore there are no annual reporting requirements to the FDA.

16.8 Clinical Trials Data Bank

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the Clinical Trials Office.

16.9 Record Keeping

Per 21 CFR 312.57, the Investigator records shall be maintained for a period of 2 years following the date a marketing application is approved; or, if no application is filed or the application is not approved, until 2 years after the investigation is discontinued and the FDA is notified.

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Appendix A: FACIT Administration Guidelines

The FACIT scales are designed for patient self-administration, but can also be administered by interview format. For self-administration, patients should be instructed to read the brief directions at the top of the page. After the patient's correct understanding has been confirmed, he/she should be encouraged to complete every item in order without skipping any. Some patients may feel that a given question is not applicable to them and will therefore skip the item altogether. **Patients should be encouraged to circle the response that is most applicable.** If, for example, a patient is not currently receiving any treatment, the patient should circle "not at all" to the question "I am bothered by side effects of treatment."

Appendix B: FACT-P

Patient Name: _____ Patient ID: _____

Date: _____

FACT-P (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 past 7 days.**

	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

English (Universal)
Copyright 1987, 1997

FACT-P (Version 4)

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

	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

FACT-P (Version 4)

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

	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

Appendix C: FACT/GOG – NTX

Patient Name: _____ Patient ID: _____

Date: _____

FACT/GOG-NTX (Version 4)

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

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4
NTX 5	I have joint pain or muscle cramps	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
NTX 7	I get a ringing or buzzing in my ears	0	1	2	3	4
NTX 8	I have trouble buttoning buttons	0	1	2	3	4
NTX 9	I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4

English (Universal)
Copyright 1987, 1997

Appendix D: PROMIS Fatigue

Patient Name: _____ Patient ID: _____

Date: _____

Fatigue - Short Form 7a

Please respond to each question by marking one box per row.

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
FATEXP20	How often did you feel tired?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP5	How often did you experience extreme exhaustion?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP18	How often did you run out of energy?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP33	How often did your fatigue limit you at work (include work at home)?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP30	How often were you too tired to think clearly?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP21	How often were you too tired to take a bath or shower?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP40	How often did you have enough energy to exercise strenuously?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

2 May 2016
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Appendix E: ECOG/KPS Conversion Table

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—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—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare 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 personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

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Appendix F: Overall Treatment Utility Form

Patient Name: _____ Patient ID: _____

Date: _____

Overall Treatment Utility (OTU)

OTU is a novel clinical outcome measure incorporating objective and subjective measures of anticancer efficacy, tolerability and acceptability, assessed 12 weeks after starting treatment and condensed into a simple 3-point score.

OTU may be regarded as asking the clinician: *"With the benefit of hindsight, are you glad you gave this treatment?"* and asking the patient: *"With the benefit of hindsight, are you glad you received it?"*: OTU is scored as good, intermediate or poor, corresponding to "yes", "uncertain" or "no" replies to these questions.

To score OTU, the patient is assessed 12 weeks after randomisation (acceptable window 10-14 weeks), using the following criteria:

1. **Clinical benefit?** Categorised as:

   a. Both radiologically progression-free (RECIST response or stable disease) and no clinical deterioration[1], as assessed by treating consultant

   b. Either radiological progression (RECIST progressive disease) or clinical deterioration, as assessed by treating consultant

2. **Tolerable and acceptable?** Categorised as:

   a. All of the following:
      - no SAE or SUSAR attributed to treatment
      - no episodes of grade ≥3 non-haematological toxicity
      - patient response to LHA[2] Q37 ("How much has your treatment interfered with your normal daily activities?") is not "Very much"
      - patient response to LHA[2] Q38 ("How worthwhile do you think your treatment has been?") is not "Not at all"

   b. Any of the following:
      - an SAE or SUSAR attributed to treatment
      - an episode of grade ≥3 non-haematological toxicity
      - patient response to LHA[2] Q37 ("How much has your treatment interfered with your normal daily activities?") is "Very much"
      - patient response to LHA[2] Q38 ("How worthwhile do you think your treatment has been?") is "Not at all"

Scoring:

Good OTU:	Patient is alive and scores 1a/2a
Intermediate OTU:	Patient is alive and scores 1a/2b or 1b/2a
Poor OTU:	Patient is alive and scores 1b/2b, or patient is dead

[1] Clinical deterioration = clear clinical evidence of cancer progression which has not been confirmed radiologically.
[2] LHA = Limited Heath Assessment. Please see webappendix pages 9-13 for full details of the LHA.

Investigator Signature Date

Appendix G: Was It Worth It Questionnaire

To be completed by Physician, Nurse, or CRA:

Patient Name: _____ Date: _____

Patient Number: _____

Participating in a clinical trial / research study is a personal choice and an individual experience. We would like to get your feedback on your experience in this research study.

Directions: Please answer each question by circling Y (for yes), N (for no), or U (for uncertain).

1. Was it worthwhile for you to participate in this research study? Y N U

2. If you had to do it over, would you participate in this research study again? Y N U

3. Would you recommend participating in this research study to others? Y N U

4. Overall, did your quality of life change by participating in this research study? *(circle one response)*

It improved It stayed the same It got worse

5. Overall how was your experience participating in this research study? *(circle one response)*

Better than I expected The same as I expected Worse than I expected

6. If there was one thing that could have been done to improve your experience in this research study, what would it be?

---

7. Would you like to talk to someone about your concerns? Yes No

(circle one response)

Appendix H: End of Study Evaluation Form

Patient Name: _____ Patient ID: _____

Date: _____

Which one of the following phrases best describes you at this time? *(Mark one with an X.)*

- ☐ Normal, no complaints, no symptoms of disease
- ☐ Able to carry on normal activity, minor symptoms of disease
- ☐ Normal activity with effort, some symptoms of disease
- ☐ Care for self, unable to carry on normal activity or do active work
- ☐ Require occasional assistance but able to care for most of personal needs
- ☐ Require considerable assistance for personal care
- ☐ Disabled, require special care and assistance
- ☐ Severely disabled, require continuous nursing care

Appendix I: Extent of Metastases Form

Patient Name: _____ Patient ID: _____

Date: _____

For purposes of this study, extent of metastases will be defined in accordance with the CHAARTED trial. 'High Volume' disease is defined as 'Yes' to question 1. Also patient may qualify as 'High Volume' by answering 'Yes' to question 2 and 3. Otherwise, patients are defined as 'Low Volume'.

1. Presence of visceral metastases (Y/N): _____
2. ≥ 4 Bone lesions (Y/N):_____
3. ≥1 bone lesion outside of the vertebral column and pelvis (Y/N): _____

Extent of disease determination (High/Low Volume):_____

_____

Investigator Signature Date