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

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: $\left(\frac{(140-age)\times weight[kg]}{serum\ creatinine\left[\frac{mg}{dL}\right]\times 72}\right)\times 0.85$

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

- 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.

- 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.

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.

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

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

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

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:

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.

- 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.

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.