Title: Abiraterone with Discontinuation of Gonadotropin-Releasing Hormone Analogues in Metastatic Prostate Cancer

NCT03565835
IRB#: 2017-8506
IRB Approval Date: 01/27/2025

PROTOCOL TITLE

Abiraterone with Discontinuation of Gonadotropin-Releasing Hormone Analogues in Metastatic Prostate Cancer

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TITLE	Abiraterone with Discontinuation of Gonadotropin-Releasing Hormone Analogues in Metastatic Prostate Cancer
BACKGROUND	Abiraterone inhibits the CYP17A enzyme, which is a critical enzyme in androgen biosynthesis. Abiraterone has regulatory approval in metastatic castration-resistant prostate cancer (mCRPC) in both chemotherapy-naïve and in the post-docetaxel setting based upon results from two randomized

	phase III studies. Abiraterone is also proven to extend survival in the metastatic, hormone-naïve population based on two phase III studies. Abiraterone is a castrating agent, but, other than a small first in human study, all clinical studies have been done in conjunction with gonadotropin-releasing hormone (GnRH) analogues. Maintaining castrate level of serum testosterone is critical in the treatment of metastatic prostate cancer. It is unknown if GnRH analogues must be continued to maintain castrate levels of serum testosterone in patients treated with abiraterone.
STUDY PHASE	Single arm feasibility study
OBJECTIVES	**Primary objective:** • To assess the proportion of patients with a non-castrate testosterone level (>50 ng/dl) when abiraterone acetate plus prednisone is used without GnRH analogues in metastatic prostate cancer. **Secondary objectives:** • To measure serum luteinizing hormone (LH) level in patients with metastatic prostate cancer treated with abiraterone acetate plus prednisone without a GnRH analogue. • To measure PSA response rate, radiographic progression-free survival (rPFS) and median overall survival in patient with metastatic prostate cancer treated with abiraterone acetate plus prednisone without a GnRH analogue. • To monitor the safety profile of abiraterone acetate plus prednisone without a GnRH analogue in metastatic prostate cancer.
STUDY DESIGN	• In this single-arm, phase II study patients with metastatic prostate cancer will be treated with abiraterone acetate and prednisone without a GnRH analogue. • During the treatment period, blood work will be monitored to determine if testosterone rises to non-castrate levels.

	• **Data will be utilized from Montefiore Medical Center Cancer Registry for a Comparison Group**
NUMBER OF PATIENTS	A total of 36 patients will be enrolled.
ELIGIBILITY	**Inclusion Criteria** 1) The patient must be able to provide study-specific informed consent prior to study entry 2) Age ≥ 18 3) ECOG Performance Status 0-2 4) Pathologically proven diagnosis of prostate adenocarcinoma 5) Patients must have metastatic prostate cancer 6) Patients may have mCRPC or may have metastatic castration-sensitive disease. 7) Patients must be maintained on a GnRH analogue (agonist (leuprolide, goserelin, triptorelin, histerelin, deslorin) or antagonist (degarelix)) 8) The patient and the investigator have decided that the next line of cancer therapy will be abiraterone plus prednisone and the initial dose of abiraterone will be 1000 mg daily. Or patients may already be on abiraterone with prednisone at a dose of 1000 mg daily along with a GnRH analogue. 9) Lab values meeting the following criteria a) Total testosterone level of <50 ng/dl b) Total bilirubin < 2.0 X Upper Limit of Normal (ULN) c) Aspartate aminotransferase (AST) ≤ 3 X ULN d) Alanine aminotransferase (ALT) ≤ 3 X ULN e) Absolute Neutrophil Count > 1.5 K/mm^3 f) Platelets > 100 K/mm^3 g) Hemoglobin ≥9.0 g/dL h) calculated creatinine clearance ≥ 30 mL/min according to the following formula Calculated creatinine clearance = $\frac{(140 - age) \times wt\ (kg)}{72 \times creatinine\ (mg/dl)}$

	Exclusion Criteria 10) History of bilateral orchiectomy 11) History of hypopituitarism 12) For patient not yet started on abiraterone with prednisone, uncontrolled hypertension (systolic blood pressure >170 mm Hg or diastolic blood pressure >100 mm Hg) 13) Patients must not have New York Heart Association Class III or IV heart failure at the time of screening. Patients must not have any unstable angina, myocardial infarction, or serious uncontrolled cardiac arrhythmia within 6 months prior to registration 14) Any other serious illness or medical condition that the principal investigator feels would make the patient a poor candidate for this study

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1 Study Objectives

1.1 Primary objective:

- To assess the proportion of patients with a non-castrate testosterone level (>50 ng/dl) when abiraterone acetate plus prednisone is used without GnRH analogues in metastatic prostate cancer.

1.2 Secondary objectives:

- To measure serum luteinizing hormone (LH) level in patients with metastatic prostate cancer treated with abiraterone acetate plus prednisone without a GnRH analogue.
- To measure PSA response rate, radiographic progression-free survival (rPFS) and median overall survival in patient with metastatic prostate cancer treated with abiraterone acetate plus prednisone without a GnRH analogue.
- To monitor the safety profile of abiraterone acetate plus prednisone without a GnRH analogue in metastatic prostate cancer.

2 Background and Rationale

Prostate cancer is the second most commonly diagnosed malignancy in men around the world with an estimated 1,111,700 new cases and 307,500 deaths per year.[1] Metastatic prostate cancer is characterized by a period during which suppression of serum testosterone with androgen deprivation therapy (ADT) is sufficient to control disease. Unfortunately, this period is followed by transition to castration-resistance during which progression occurs despite continued suppression of testosterone. This is referred to as metastatic castration-resistant prostate cancer (mCRPC). Formerly, this disease state was known as hormone-refractory prostate cancer. This term is no longer used as it is now known that androgen receptor (AR) signaling remains critical to disease progression in castration-resistant disease.[2] That prostate-specific antigen (PSA) rises in the setting of progression in mCRPC exemplifies this point as PSA is an androgen-regulated gene. Maintaining castrate level of serum testosterone is critical in the treatment of mCRPC as rising serum testosterone levels is expected to drive disease progression. The clinical relevance of targeting androgen signaling in mCRPC is demonstrated by the survival advantage of the second-

generation androgen pathway targeted agents, abiraterone acetate and enzalutamide, in this disease state.[3, 4]

2.1 Abiraterone in mCRPC

Abiraterone inhibits the CYP17A enzyme, a critical enzyme in androgen biosynthesis in both the testicles and the adrenal glands. Abiraterone has regulatory approval in metastatic castration-resistant prostate cancer (mCRPC) in both chemotherapy-naïve and in the post-docetaxel setting based upon results from the COU-AA-301 and COU-AA-302 clinical trials, respectively.[3, 4] In both clinical trials, abiraterone 1000 mg daily plus prednisone 5 mg twice per day, when used in conjunction with GnRH analogues, prolonged median OS.

2.2 Abiraterone in metastatic, hormone-naïve prostate cancer

Two phase III studies evaluating abiraterone acetate in the metastastic, hormone-naïve setting were presented at the American Society of Clinical Oncology (ASCO) annual meeting in 2017. LATITUDE was a placebo-controlled, phase III trial evaluating abiraterone 1000 mg daily and prednisone 5 mg daily versus placebo in patients with newly diagnosed, metastatic hormone naïve prostate cancer who were just beginning ADT. There were two primary endpoints (OS and rPFS). Abiraterone with prednisone improved OS (median not yet reached v. 34.7 months, HR 0.62; P<0.001) and rPFS (33.0 vs. 14.8 months, HR 0.47; P<0.001).[5] STAMPEDE was a phase III trial evaluating abiraterone 1000 mg daily plus prednisolone 5 mg daily with ADT versus ADT alone in metastatic, hormone-naïve prostate cancer. The primary endpoint was OS and abiraterone with prednisolone improved OS (HR 0.63; P<0.001).[6] This level 1 evidence is changing the standard of care for metastatic, hormone-naïve prostate cancer and it is anticipated that abiraterone will receive regulatory approval in this treatment setting.

2.3 Abiraterone Without GnRH Analogues

The first paper to describe abiraterone acetate was published in 1994.[7] In this article, a number of inhibitors of CYP17A were described. Among the most potent was abiraterone acetate (CB7630) the active metabolite of which (abiraterone or CB7598) was shown to suppress serum testosterone in mice with a compensatory increase in luteinizing hormone (LH). The first in human

dose escalation study of abiraterone acetate was published one decade later.[8] This was a small study that investigated the use of abiraterone in three patient cohorts:

A) 16 patients with prostate cancer treated with GnRH agonists who were treated with a single dose of abiraterone (up to 500 mg)

B) 4 patients with a history of prostate cancer who had been treated with GnRH agonists in the past but had recovered serum testosterone to non-castrate values and were treated with a single dose of abiraterone (up to 500 mg)

C) 6 patients with a history of prostate cancer (5 of 6 with previous GnRH agonist) and all with non-castrate testosterone levels. Patients were treated with multiple doses of abiraterone. An initial 3 patients were treated with abiraterone at 500 mg. All 3 had inadequate testosterone suppression. 3 patients were then treated with abiraterone at 800 mg for multiple doses. All 3 patients treated at 800 mg daily had suppression of testosterone but 2 of these had a compensatory rise in LH that led to an increase in testosterone. For this reason, future development of abiraterone was done in conjunction with GnRH analogues.

2.4 Testosterone Recovery Following Discontinuation of GnRH Analogues

A number of publications have reported on testosterone recovery in prostate cancer patients following discontinuation of long-term GnRH analogues.[9-11] In a recent report from Planas et. al. testosterone recovery was monitored in patients with prostate cancer that had been maintained on GnRH analogues for a median duration of 74.6 months.[9] The median age was 71.5 years. The mean time to recovery of testosterone to non-castrate level (> 50ng/dl) was 14.5 months for patients maintained on GnRH analogues for <60 months and was 29.3 months for patients that had been maintained on GnRH analogues for > 60 months. LH recovery was more rapid with half of patients showing a rise in LH by 6 months from discontinuation of the GnRH analogue.

2.5 Characteristics of Patients Treated with Abiraterone

In the COU-AA-302 phase III clinical trial, abiraterone + prednisone was compared to placebo + prednisone in chemotherapy-naïve patients with asymptomatic to mildly symptomatic mCRPC.[4] Patients were maintained on GnRH analogues through the duration of the study. The starting dose of abiraterone was 1000 mg daily. Prednisone was dosed at 5 mg BID. The median age in the abiraterone group and the placebo group were 71 and 70 years, respectively. The median duration

of GnRH analogues in the abiraterone and placebo groups prior to study entry were 40.4 and 40.8 months, respectively. This illustrates that the population treated with abiraterone is an elderly population that has typically been on long term GnRH analogues.

2.6 Rationale for Discontinuation of GnRH Analogue when Abiraterone is Used in Metastatic Prostate Cancer

As has been demonstrated, the recovery of testosterone following cessation of GnRH analogues is often sluggish in patients maintained on long-term ADT. In the reports cited previously, this sluggish testosterone recovery is in the absence of ongoing hormone therapy. Abiraterone is a potent inhibitor of CY17A which is critical for androgen synthesis in the testicles. We suspect that testosterone recovery, should it occur, would likely occur slowly in patients w/ metastatic prostate cancer maintained on abiraterone with discontinuation of GnRH analogue.

We believe the cessation of GnRH analogues during the use of abiraterone plus prednisone in metastatic prostate cancer is reasonable if serum testosterone is monitored. This clinical trial is designed to determine the probability of testosterone recovery to non-castrate levels when GnRH analogues are discontinued during the use of abiraterone with prednisone in patients with metastatic prostate cancer. .

3 Eligibility Criteria and Registration

3.1

Inclusion Criteria

1) The patient must be able to provide study-specific informed consent prior to study entry
2) Age ≥ 18
3) ECOG Performance Status 0-2
4) Pathologically proven diagnosis of prostate adenocarcinoma
5) Patients must have metastatic disease
6) Patients may have mCRPC or may have metastatic castration-sensitive disease.
7) Patients must be maintained on a GnRH analogue (agonist (leuprolide, goserelin, triptorelin, histerelin, deslorin) or antagonist (degarelix))

8) The patient and the investigator have decided that the next line of cancer therapy will be abiraterone plus prednisone and the initial dose of abiraterone will be 1000 mg daily. Or patients may already be on abiraterone with prednisone at a dose of 1000 mg daily along with a GnRH analogue.
9) Lab values meeting the following criteria
   a) Total testosterone level of <50 ng/dl
   b) Total bilirubin < 2.0 X Upper Limit of Normal (ULN)
   c) Aspartate aminotransferase (AST) ≤ 3 X ULN
   d) Alanine aminotransferase (ALT) ≤ 3 X ULN
   e) Absolute Neutrophil Count > 1.5 K/mm^3
   f) Platelets > 100 K/mm^3
   g) Hemoglobin ≥9.0 g/dL
   h) calculated creatinine clearance ≥ 30 mL/min according to the following formula

$$\text{Calculated creatinine clearance} = \frac{(140 - \text{age}) \times \text{wt (kg)}}{72 \times \text{creatinine (mg/dl)}}$$

3.2 Exclusion Criteria

1) History of bilateral orchiectomy
2) History of hypopituitarism
3) For patient not yet started on abiraterone with prednisone, uncontrolled hypertension (systolic blood pressure >170 mm Hg or diastolic blood pressure >100 mm Hg)
4) Patients must not have New York Heart Association Class III or IV heart failure at the time of screening. Patients must not have any unstable angina, myocardial infarction, or serious uncontrolled cardiac arrhythmia within 6 months prior to registration
5) Any other serious illness or medical condition that the principal investigator feels would make the patient a poor candidate for this study

3.3 Screening Evaluation

Within 30 days prior to registration

A. Blood work for CBC, Chem 7, LFTs, PSA, Testosterone, LH
B. Complete history, physical examination, vital signs, review of medications and ECOG performance status.

3.4 Registration Procedures

Patients will be registered through the Office of Clinical Trials at Montefiore Medical Center (Phone number: 718-379-6861). The signed informed consent document and the completed cpdmu patient registration form must be provided to the Office of Clinical Trials (cpdmu-registration@montefiore.org) at the time of registration and prior to patient treatment.

At the time of registration, all eligibility criteria must be reviewed. It is the treating physician's responsibility to ensure that patients meet all eligibility criteria. To facilitate this an eligibility checklist is provided in the appendix of this protocol.

4 Study Design

4.1 General Design

This is a single arm, open label feasibility clinical trial that will include patients with metastatic prostate cancer who are mainted on a GnRH analogue and are already being treated with or will be beginning therapy with abiraterone plus prednisone. For patients being initiated on abiraterone with prednisone or for those patients already on abiraterone with prednisone, the GnRH analogue will be discontinued. LH and testosterone will be measured during screening and during therapy with abiraterone. Monitoring of the patient would be according to the standard of care with the exception that the GnRH analogue would be discontinued. Treatment on the protocol would continue until abiraterone is permanently discontinued or until testosterone rises to a non-castrate value (> 50 ng/dl). Should testosterone become non-castrate, the treating investigator would remove the patient from the protocol and resume ADT with a GnRH analogue. In this scenario, abiraterone and prednisone would be continued at the discretion of the investigator based upon expectation of ongoing benefit to the patient.

4.2 Study Calendar

The following assessments should be done within 30 days prior to registration

A. Blood work for CBC, Chem 7, LFTs, PSA, Testosterone, LH

B. Complete history, physical examination, vital signs, review of medications and ECOG performance status.

	Screening	Q12 Wk[1] (+/-1 wk)	EOT	Follow up Q12 Wks (+/-4 wks)
History and Physical Examination	**X**	**X**	**X**	
Vital Signs	**X**	**X**	**X**	
AE Assessment	**X**	**X**	**X**	
ECOG PS	**X**	**X**	**X**	
CBC	**X**			
Chemistry	**X**			
LFTs[2]	**X**			
PSA	**X**	**X**	**X**	
Testosterone	**X**	**X**	**X**	
LH	**X**	**X**	**X**	
Tumor Assesment[3]	**X**	**X**	**X**	
Subsequent Therapy				**X**[4]
Survival				**X**

AE: Adverse Event, CBC: complete blood count, EOT: end of trial visit, LFTs: liver function tests, LH: luteinizing hormone PS: Performance Status, PSA: Prostate-Specific Antigen
[1]The first study visit should occur within 28 days of registration onto this study.
[2]LFT monitoring is required at the initiation of abiraterone and periodically during ongoing therapy. The investigator should refer to the abiraterone package insert to ensure that LFTs are monitored according to standard practice
[3]Tumor assessments are not required but will be done at the discretion of the investigator. Tumor assessments done during study therapy will be recorded.
[4]For prostate cancer

4.3 Primary Objective

- To assess the proportion of patients with a non-castrate testosterone level (>50 ng/dl) when abiraterone acetate plus prednisone is used without GnRH analogues in metastatic prostate cancer.

4.4 Secondary Objectives

- To measure serum luteinizing hormone (LH) level in patients with metastatic prostate cancer treated with abiraterone acetate plus prednisone without a GnRH analogue.

- To measure PSA response rate, radiographic progression-free survival (rPFS) and median overall survival in patient with metastatic prostate cancer treated with abiraterone acetate plus prednisone without a GnRH analogue.
- To monitor the safety profile of abiraterone acetate plus prednisone without a GnRH analogue in metastatic prostate cancer.

5 Therapy

5.1 Abiraterone

Abiraterone is an inhibitor of the CYP17A enzyme and is FDA-approved in combination with prednisone for the treatment of mCRPC. The recommended starting dose is 1000 mg once daily in combination with prednisone at 5 mg BID. Abiraterone is supplied as 250 mg tablets.

5.2 Drug Supply and Accountability

Abiraterone and prednisone will be prescribed the study investigator. Prescriptions will be sent to commercial pharmacies. Abiraterone and prednisone will not be provided by this research study and will instead be billed to the patient's insurance..

5.3 Administration

Administration will be as per the product label. Per the label, abiraterone should be taken on an empty stomach. Abiraterone should be taken at least two hour after the most recent meal and patients should wait at least one hour after taking abiraterone to eat their next meal. Once patients begin taking abiraterone, patients must begin taking prednisone.

5.4 Compliance

Compliance with study drug will be documented with the use of pill logs.

5.5 Initial Dose and Dose Adjustments

The dosing of abiraterone and prednisone will follow the package insert. It is anticipated that all patients on this protocol will begin abiraterone at 1000 mg once daily on an empty stomach. All

patients will also begin taking prednisone. Dose adjustments will be at the discretion of the treating investigator but are expected to follow dose adjustment recommendations as per the package insert.

5.6 Monitoring for Benefit and Safety

While on protocol, all decisions regarding imaging will be the discretion of the treating investigator and will follow local standard of care procedures. The investigator will assess for adverse events at each study visit and will follow the package insert and standard procedures for dose holding, dose modification and discontinuation of study therapy. Blood work for safety including monitoring of the basic metabolic and liver function tests will be done according to standard practice. Per the FDA package insert, liver function tests should be checked prior to beginning abiraterone, monitored at 2 week intervals for the first 3 months of therapy and then monthly while on abiraterone. Patients treated on this protocol will be monitored according to this guideline. The FDA package insert also states that potassium should be checked prior to initiating abiraterone and that serum potassium should be monitored for hypokalemia monthly during ongoing therapy with abiraterone.

5.7 Abiraterone Warnings and Precautions

Please see the abiraterone FDA package insert for full prescribing information. The key aspects of the package insert are summarized herein.

According to the FDA package insert there are three warnings and precautions:

1) Mineralocorticoid excess: Use abiraterone with caution in patients with a history of cardiovascular disease. The safety of abiraterone in patients with LVEF < 50% or NYHA Class II to IV heart failure in Study 2 was not established. Control hypertension and correct hypokalemia before treatment. Monitor blood pressure, serum potassium and symptoms of fluid retention at least monthly.
2) Adrenocortical insufficiency: Monitor for symptoms and signs of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

3) Hepatotoxicity: Can be severe and fatal. Monitor liver function and modify, interrupt, or discontinue abiraterone dosing as recommended.

5.8 Adverse Reactions

The most common adverse reactions (≥10%) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

The most common laboratory abnormalities (>20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

5.9 Drug Interactions

CYP3A4 Inducers: Avoid concomitant strong CYP3A4 inducers during abiraterone treatment. If a strong CYP3A4 inducer must be co-administered, increase the abiraterone dosing frequency.

CYP2D6 Substrates: Avoid co-administration of abiraterone with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate.

5.10 Use in Specific Populations

Do not use abiraterone in patients with baseline severe hepatic impairment (Child-Pugh Class C)

5.11 GnRH Analogues with Abiraterone

As previously mentioned in this protocol, the entirety of the clinical development of abiraterone has been done so in conjunction with continuation of GnRH analogues. According to the product label, patients being treated with abiraterone should be informed that they need to maintain treatment with GnRH analogues during therapy with abiraterone and prednisone.

6 Study Procedures

6.1 Identification of Study Subjects

Patients with metastatic prostate cancer being treated with ongoing ADT with a GnRH analogue and are already being treated with abiraterone and prednisone or who will begin abiraterone with prednisone will be offered participation in this protocol. Patients will be identified at the Montefiore Einstein Center for Cancer Care.

6.2 Screening Period

Patients who are being offered abiraterone acetate plus prednisone will be offered participation in this trial. Prior to participating in any study procedures, patients will be provided with an ICF. In the event that a patients agrees to participate and signs the ICF they will screened for participation in this trial.

If they are not yet prescribed abiraterone and prednisone but have signed the ICF, they will be prescribed abiraterone and prednisone. Abiraterone and prednisone will be provided by a commercial pharmacy and will not be provided through participation in this study.

6.2.1 Studies Required for Screening

Within 30 days prior to registration

A. Blood work for CBC, Chem 7, LFTs, PSA, Testosterone, LH
B. Complete history, physical examination, vital signs, review of medications and ECOG performance status.
C. The history of GnRH analogue use will be recorded. The agent, dose and dates administered will be recorded. The duration of first GnRH analogue injection will be noted as will the date of the last injection prior to trial participation.

6.3 Study Visits

The first study visit will occur within four weeks (+/- 1 week) of registration. Subsequent study visits will be every 12 weeks (+/- 1 week). Procedures at study visits will include

A. Blood work for PSA, Testosterone, LH
B. Complete history, physical examination, vital signs, review of medications and ECOG performance status.

6.4 End of Treatment Visit

A. Blood work for PSA, Testosterone, LH
B. Complete history, physical examination, vital signs, review of medications and ECOG performance status.

6.5 Follow Up

Patients will be monitored at 12 week intervals (+/- 4 weeks) after discontinuation of study therapy for determination of subsequent therapies and survival.

7 Endpoints

7.1 Evaluation of Primary Objective

The primary objective of this clinical trial is to determine if serum total testosterone levels become non-castrate (≥50 ng/dl) when abiraterone acetate plus prednisone is used without GnRH analogues in patients with metastatic prostate cancer. We will monitor testosterone at 12 week intervals. The proportion of patients with a castrate level of serum total testosterone (<50 ng/dl) after 24 weeks will be the primary endpoint. If a patient is not on abiraterone for 24 weeks as a consequence of disease progression, intolerance or other reason the patient will be replaced. However, if the patient is found to have a testosterone level of ≥ 50 ng/dl while on abiraterone they will not be replaced and this data point will be used for evaluating the primary objective. The proportion of patients with a castrate level of serum testosterone at each 12-week interval will be reported.

7.2 Additional endpoints.

- To measure serum luteinizing hormone (LH) level in patients with metastatic prostate cancer treated with abiraterone acetate plus prednisone without a GnRH analogue. We will record LH values at 12 week intervals and will report the median time until LH rises to be within the normal range when abiraterone acetate plus prednisone is used without GnRH analogues in metastatic prostate cancer.
- To measure PSA response rate, radiographic progression-free survival (rPFS) and median overall survival in patient with metastatic prostate cancer treated with abiraterone acetate plus prednisone without a GnRH analogue.

- To monitor the safety profile of abiraterone acetate plus prednisone without a GnRH analogue in metastatic prostate cancer.

7.3 Duration of Clinical Trial Participation

Patients will continue on clinical trial therapy until abiraterone is permanently discontinued, serum total testosterone rises to ≥50 ng/dl, a GnRH analogue is given, withdrawl of consent, intolerable adverse events, at the time of radiographic progression of disease according to the guidelines of the Prostate Cancer Clinical Trials Working Group 3[12], at the time of clinical progression, or when the investigator feels as though it is the patient's best interest to discontinue therapy in this clinical trial. Following discontinuation of clinical trial therapy with abiraterone and prednisone, patients will be followed at 12 week intervals for survival and subsequent prostate cancer therapy.

8 Statistical Considerations

This primary aim of this feasibility study is to evaluate the of the proportion of patients whose testosterone rises to a non-castrate value (≥50 ng/dl) when abiraterone and prednisone are used without a GnRH analogue in the treatment of mCRPC. The secondary objectives are to measure levels of serum LH, PSA response rate, rPFS and median overall survival in these study participants.

The demographic and clinical characteristic of the study participants will be summarized numerically using descriptive statistics and graphically (e.g. boxplots). The frequency of participants with castrate level of testosterone (<50 ng/dl) will be presented as proportion along with its 95% Clopper-Pearson exact confidence interval. The serum LH levels will be presented as mean with 95% confidence interval, log transformation will be performed in case of non-normal distribution of LH values. If after transformation, normality is not satisfied, we will present it as median and inter quartile range (IQR).

For survival analyses, we will plot Kaplan-Meier survival curves for outcomes of rPFS and overall survival from time from start of treatment. The probability of survival will be presented at different time points.

Sample size justification:

This is a feasibility study and no formal power calculation is performed. Based on our experience,

we assume that the abiraterone and prednisone without GnRH provides approximately 80% non-castrate level of serum total testosterone level. Under this assumption, a sample size of 30 will produce a 95% confidence interval with a width equal to 0.31 using Clopper_Pearson exact formula (i.e. 0.61, 0.92). Patient dropout is anticipated to be approximately 20%. Therefore it is anticipated that 36 patients will be accrued to assess the primary endpoint in 30 patients.

8.1 Subject Accrual

Approximately 40 patients with metastatic prostate cancer are prescribed abiraterone + prednisone annually at our center. Assuming that 25% of these patients are enrolled onto this study, it is estimated that patient recruitment will take approximately 3-4 years.

9 Regulatory considerations

9.1 Protection of Human Subjects

The Investigators will ensure that patients, or their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks and other critical issues regarding this clinical trial. Patients will be required to provide informed consent prior to participating in any aspect of this research. The preparation of the informed consent form is the responsibility of the primary investigator and will include all elements required by CFR 21 Part 50.25 and the local IRB.

9.2 Compliance with the Protocol and Protocol Revisions

The study must be conducted as described in this approved protocol. All revisions to the protocol must be provided to the primary investigator. The primary investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

10 Data Handling and Record Keeping

10.1 Confidentiality

Study subject information will be kept confidential and managed according

to the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of source documents include: clinical notes, hospital records, laboratory results, results of imaging studies and the actual images from imaging studies, subjects' diaries or evaluation checklists, pharmacy dispensing records and other records from the pharmacy, all data generated from the research lab pertaining to this research, subject files, and any other information that is collected for or generated during subject participation in this clinical trial.

10.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must

be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

11 Data Safety and Monitoring Boards

All trials initiated by the Montefiore Medical Center are subject to oversight by the Data Safety Monitoring Board (DSMB). This board meets two times per year with any additional meetings scheduled when needed. The responsibilities are as follows:

- Familiarize themselves with the research protocol (s)
- Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.
- The DSMB reviews trial performance information such as accrual information.
- The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
- All adverse events are reviewed by the committee with assurances that these have been in fact sent for review to all pertinent IRBs.
- Review of reports of related studies to determine whether the monitored study needs to be changed or terminated.
- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).
- Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial. The study leadership will provide information on cumulative toxicities and relevant recommendations to the local PI to be shared with their IRB's.

12 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject and does not necessarily have to have a causal relationship with study

treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of treatment. During clinical trials, AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject.

AEs will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial intervention or medication. All AEs considered related to trial intervention or medication will be followed until resolution, even if this occurs post-trial.

12.1 Adverse Event Definitions

Adverse Event (AE): Any new, undesirable medical experience or change of an existing condition that occurs during or after treatment, whether or not considered product-related.

Serious Adverse Event (SAE): An AE occurring at any dose that results in any of the following outcomes (CFR 312.32)

- Death
- Life-threatening adverse experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability or incapacity
- Congenital anomaly / birth defect.

Important medical events that may not be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the SAE definition. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Unexpected Adverse Event: An AE that is not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the investigator's brochure or package insert.

Life-threatening: Any adverse experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

AEs will use the descriptions and grading scales found in the revised Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

12.2 Adverse Event Reporting

Adverse events (AEs) will be recorded from the time of consent and for at least 30 days after treatment discontinuation, regardless of whether or not the event(s) are considered related to trial medications. All AEs considered related to trial medication will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

12.3 Serious Adverse Event Reporting

12.3.1 Study Center (Site) Requirements for Reporting SAEs

Investigators and other site personnel must report all SAEs occurring during the course of the study within 24 hours of discovery via phone, email, or fax. This includes both SAEs unrelated and related to the investigational product. In general, SAEs assessed as clearly being due to disease progression, and not due to study drug(s), should be excluded from AE reporting. Study-specific clinical outcomes of death because of disease progression are exempt from SAE reporting, unless the investigator deems them related to use of the study drug. Hospitalization for radical prostatectomy is not an SAE.

The definition of "related" being that there is a reasonable possibility the drug caused the adverse experience.

Unrelated	The Adverse Event is *clearly not related* to the investigational agent(s)
Unlikely	The Adverse Event is *doubtfully related* to the investigational agent(s)
Possible	The Adverse Event is *may be related* to the investigational agent(s)
Probable	The Adverse Event is *likely related* to the investigational agent(s)
Definite	The Adverse Event is *clearly related* to the investigational agent(s)

The following steps will be taken to report promptly and document accurately any SAE, even if it may not appear to be related to the study treatment:

- Report the SAE to the PI and the treating physician by email, telephone or fax within 24 hours of becoming aware that a patient has experienced an SAE.
- Record the SAE accurately on the AE page of the patient's CRF.
- Using the standard IRB-SAE report form, submit all known patient information within 24 hours of SAE occurrence to the clinical trial office to submit to IRB and DSMB. Date and sign each report before submission. Include the following information (or as much as possible to obtain and still report the event within 24 hours):
  - Study protocol number and indication
  - Study site and investigator's identification
  - Patient's ID (patient number and initials), age or date of birth, and sex
  - Date of enrollment
  - Description of SAE, including date of onset and duration, severity, and outcome
  - Date of first and most recent (last) dose administered
  - Action taken regarding study treatment
  - Relationship of SAE to study treatment
  - Concomitant medications, including regimen and indication
  - Intervention, including concomitant medications used to treat SAE
  - Pertinent laboratory data/diagnostic tests conducted and date
  - Pertinent medical history of patient
  - Date of hospital admission/discharge
  - Date of death (if applicable)

Within 10 days of initial IRB notification, the PI is required to submit a completed Adverse Event Report to the IRB. The treating physicians should perform appropriate diagnostic tests and therapeutic measures and submit all follow-up substantiating data, such as diagnostic test reports and autopsy report to the PI, IRB, and DSMB.

12.3.2 Death and Immediately Life-Threatening Events

Any death and immediately life-threatening event from any cause while a patient is receiving trial treatment on this protocol or up to 30 days after the last dose of trial treatment, or any death and immediately life-threatening event occurring more than 30 days after trial treatment has ended but which is felt to be treatment related must be reported within 24 hours of discovery of the event. All deaths must be reported primarily for the purposes of SAE reporting; however, deaths due unequivocally to progression are not SAEs. The primary investigator, IRB and DSMB should be notified and their reporting procedure followed.

13 References

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14. Appendices

14.1 Eligibility Checklist

Inclusion Criteria

1) The patient must be able to provide study-specific informed consent prior to study entry **Yes/No**
2) Age ≥ 18 **Yes/No**
3) ECOG Performance Status 0-2 **Yes/No**
4) Pathologically proven diagnosis of prostate adenocarcinoma **Yes/No**
5) Patients must have metastatic prostate cancer **Yes/No**
6) Patients may have mCRPC or may have metastatic castration-sensitive disease. **Yes/No**
7) Patients must be maintained on a GnRH analogue (agonist (leuprolide, goserelin, triptorelin, histerelin, deslorin) or antagonist (degarelix)) **Yes/No**
8) The patient and the investigator have decided that the next line of cancer therapy will be abiraterone plus prednisone and the initial dose of abiraterone will be 1000 mg daily. Or patients may already be on abiraterone with prednisone at a dose of 1000 mg daily along with a GnRH analogue. **Yes/No**
9) Lab values meeting the following criteria **Yes/No**
   a) Total testosterone level of <50 ng/dl
   b) Total bilirubin < 2.0 X Upper Limit of Normal (ULN)
   c) Aspartate aminotransferase (AST) ≤ 3 X ULN
   d) Alanine aminotransferase (ALT) ≤ 3 X ULN
   e) Absolute Neutrophil Count > 1.5 K/mm^3
   f) Platelets > 100 K/mm^3
   g) Hemoglobin ≥9.0 g/dL
   h) calculated creatinine clearance ≥ 30 mL/min according to the following formula

$$\text{Calculated creatinine clearance} = \frac{(140 - \text{age}) \times \text{wt (kg)}}{72 \times \text{creatinine (mg/dl)}}$$

Exclusion Criteria

10) History of bilateral orchiectomy **Yes/No**
11) History of hypopituitarism **Yes/No**

Yes/No

12) For patient not yet started on abiraterone with prednisone, uncontrolled hypertension (systolic blood pressure >170 mm Hg or diastolic blood pressure >100 mm Hg) **Yes/No**

13) Patients must not have New York Heart Association Class III or IV heart failure at the time of screening. Patients must not have any unstable angina, myocardial infarction, or serious uncontrolled cardiac arrhythmia within 6 months prior to registration **Yes/No**

14) Any other serious illness or medical condition that the principal investigator feels would make the patient a poor candidate for this study **Yes/No**

14.2 Pill Log

Patient ID _____ Patient Initials _____ Month _____ Year_____

Take abiraterone once daily on an empty stomach. While taking abiraterone you must continue taking prednisone. If you have forgotten a dose and it is less than 12 hours until the next dose, you

should skip the missed. Please call your study doctor at (718)405-8505 if you experience any side effects or if you have any concerns or questions. Remember to bring this pill diary to each study visit.

Day		Date	Time	Number of 250 mg tablets taken	Comments
1	Abiraterone				
2	Abiraterone				
3	Abiraterone				
4	Abiraterone				
5	Abiraterone				
6	Abiraterone				
7	Abiraterone				
8	Abiraterone				
9	Abiraterone				
10	Abiraterone				
11	Abiraterone				
12	Abiraterone				
13	Abiraterone				
14	Abiraterone				
15	Abiraterone				
16	Abiraterone				
17	Abiraterone				
18	Abiraterone				
19	Abiraterone				
20	Abiraterone				
21	Abiraterone				
22	Abiraterone				
23	Abiraterone				
24	Abiraterone				
25	Abiraterone				
26	Abiraterone				
27	Abiraterone				
28	Abiraterone				
29	Abiraterone				
30	Abiraterone				
31	Abiraterone				

Patient Signature _____ Date _____

Research Staff Signature _____ Date _____