Title:

A phase 1b study of adaptive androgen deprivation therapy for stage IV castration sensitive prostate cancer

PROTOCOL NUMBER:	**MCC 19367**
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PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Principal Investigator:

Signature of Investigator Date

Printed Name of Investigator

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, instructions from Celgene representatives, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

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Protocol Synopsis

11.1 Synopsis

PROTOCOL TITLE: **A phase Ib study of adaptive androgen deprivation therapy for stage IV castration sensitive prostate cancer**	
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DATE PROTOCOL FINAL:	
STUDY DRUG:	Leuprolide, Goserelin, Triptorelin, Relugolix, Darolutamide Abiraterone, Enzalutamide, Apalutamide
INDICATION:	metastatic castration sensitive prostate cancer
STUDY PHASE:	Pilot
BACKGROUND AND RATIONALE: When cure is not feasible, an alternative approach to treat stage IV prostate cancer would be to control tumor burden rather than attempting eradication. Utilizing mathematical modeling based on evolutionary principles, our group has shown that adaptive chemotherapy can successfully control breast and ovarian cancers in preclinical models.[1,2] We then developed a simple mathematical model of the intratumoral evolutionary dynamics in stage IV prostate cancer. This model assumes three competing tumor subpopulations: (i) TP, which express CYP17A1 and produce testosterone; (ii) T+, which require exogenous androgen; and (iii) T-, which are androgen-independent and abiraterone-resistant. The existence of the TP, T+ and T- prostate cancer cells were detected by IHC on lymph node biopsies of castration-naïve lymph node metastasis as well as primary cancers (data not shown). We tested this approach in a pilot study of adaptive abiraterone therapy for patients with metastatic castration resistant prostate cancer. The interim analysis based on 11 patients with a median follow up of 21 months indicate that adaptive abiraterone is feasible and probably non-inferior to the standard continuous abiraterone therapy with less than 50% of abiraterone usage. Five published phase 3 trials tested 2 different approaches built upon the standard continuous androgen deprivation therapy (ADT) with Luteinizing hormone releasing hormone (LHRH) agonist in metastatic castration sensitive prostate	

intermittent versus continuous LHRH analog in subjects with mCSPC and the overall survival data were statistically inconclusive to show the non-inferiority of intermittent versus continuous LHRH analog.[3] Post hoc subgroup analysis showed that patients with high volume/extensive disease (had one or more bone metastases outside the axial and pelvic bones) had 4.9 years median overall survival with intermittent LHRH analog as compared with 4.4 years in the continuous LHRH analog group (hazard ratio for death with intermittent therapy, 1.02; 95% CI, 0.85 to 1.22). The median survival differences between these two treatment approaches are mainly among patients with minimal disease.

For the combinational treatment approach, the phase III CHAARTED trial reported that adding upfront docetaxel chemotherapy to LHRH analog compared to LHRH analog alone prolonged median overall survival by 17 months for patients with newly diagnosed high volume metastatic prostate cancer.[4] The high volume disease was defined as visceral metastasis and or 4 more bone metastasis (at least 1 beyond pelvis and vertebral column). Of note, such prolongation of overall survival was not noted in the patients with low volume metastasis. The median time to progression to the castration resistant stage was 11.7 months for LHRH analog only arm; 20.2 month in the LHRH analog plus docetaxel arm. The phase III double-blind randomized Latitude trial reported that adding upfront abiraterone plus prednisone to LHRH analog compare to LHRH analog plus placebo significantly improved overall survival and radiographic progression free survival in patients with high risk castration-naïve metastatic prostate cancer.[5] The high risk is defined as $\geq$ 2 of 3 risk factors: Gleason $\geq$ 8, $\geq$ 3 bone lesions, or measurable visceral metastases. Of note, only 5% patients had liver metastasis. Most recently, the phase 3 TITAN and the phase 3 ENZAMET trial reported improvement in overall survival by adding potent AR antagonist to LHRH analog compare to LHRH analog plus placebo at year 2 (TITAN trial with apalutamide) and year 3 (ENZAMET trial with enzalutamide).[10, 11] This clinical benefit were seen in patients with low as well as high volume metastasis.

We tested our competition model of TP (testosterone producing), T+ (testosterone dependent) and T- (testosterone independent) prostate cancer cells with the retrospective data on >100 patients with mCSPC, and found that a shorter course of LHRH analog as compared to > 6 months of LHRH analog used in the intermittent LHRH analog arm of SWOG 9346 would be more effective to preserve the T+ population and delay the progression to the castration resistant stage. The TP population is the target of abiraterone, which blocks cancer cells' production of testosterone through Cyp17. The success of the Latitude trial confirmed our observation with the Cyp 17 immunohistochemistry that a significant percentage of TP cells were present in the

primary as well as castration naïve metastatic sites (> 30% based on IHC). Although the Latitude trial showed that continuous targeting both the T+ and TP prostate cancer cells improved survival for patients with high-risk castration naïve metastatic, we hypothesize that such survival benefit can be extended further with a treatment strategy adapted to the changes in the percentage of TP, T+, T- prostate cells under the selective pressure of treatment.

To develop adaptive therapy for mCSPC, we propose this pilot feasibility study to use PSA response, and testosterone level to guide the treatment with LHRH analog and AR directed therapy (abiraterone plus prednisone, enzalutamide, or apalutamide).

STUDY OBJECTIVES:

Primary: Test the feasibility of adaptive ADT in patients with asymptomatic mCSPC

Secondary: Assess the clinical benefits of adaptive ADT by comparing to historical controls

Exploratory objectives/correlative studies:

1. Detect the intra-tumor heterogeneity of AR and Cyp17 IHC stains on FFPE blocks of primary prostate cancer and or metastatic lesions
2. Refine the mathematical model for adaptive ADT
3. To develop imaging habitat biomarkers to track diseases progression using the patients scans and compare with conventional progression variables (like PSA).
4. Compare IHC, immunofluorescence and imaging biomarkers with a retrospective cohort of mCSPC patients who underwent continuous ADT as standard of care
5. Detect and track the changes of AR alterations in tumor cell free DNA

STUDY DESIGN:

This is a prospective pilot study on 16 subjects with mCSPC.

STUDY ENDPOINTS:

Primary: percentage of subjects who remain on study at month 12 from first dose of ADT

Secondary: Median time to PSA progression and median time to radiographic progression.

STUDY DURATION: 30 months enrollment period	**TOTAL SAMPLE SIZE:** 16
DOSING REGIMENS: During the treatment phase LHRH analog will be given every 4 or 12 weeks at the discretion of the treating physician; abiraterone will be given at 1000 mg daily along with 5 mg daily prednisone, enzalutamide will be given at 160 mg daily, and apalutamide will be given at 240 mg daily. It is at the discretion of the study investigator to choose one of these AR directed therapies.	**STUDY DRUG SUPPLIES:** LHRH analog, and AR directed therapy (abiraterone and prednisone, enzalutamide darolutamide or apalutamide) are prescribed as standard of care and continue to be covered by patients' insurance.

1.2 Investigational Plan:

Subjects with asymptomatic mCSPC and no liver metastasis will be consented and screened during a run in period with 12 to 16 weeks of LHRH analog, and 8 to 12 weeks AR directed therapies (abiraterone plus prednisone, enzalutamide, darolutamide or apalutamide). A total of 16 eligible subjects who achieve >75% PSA decline after the 12 to 16 weeks *run-in period* will be enrolled. Both LHRH analog and AR directed therapy will be stopped after study enrollment. PSA and testosterone level will be measured during the run-in period and then every 6 weeks after study enrollment. Baseline imaging studies with CT and bone scan will be performed at the time of study enrollment and then be performed every 18 weeks while on study. If a subject develops radiographic progression while being off therapies with LHRH analog and AR directed therapy, these scans will be considered the new baseline scans for this subject.

Adaptive therapy

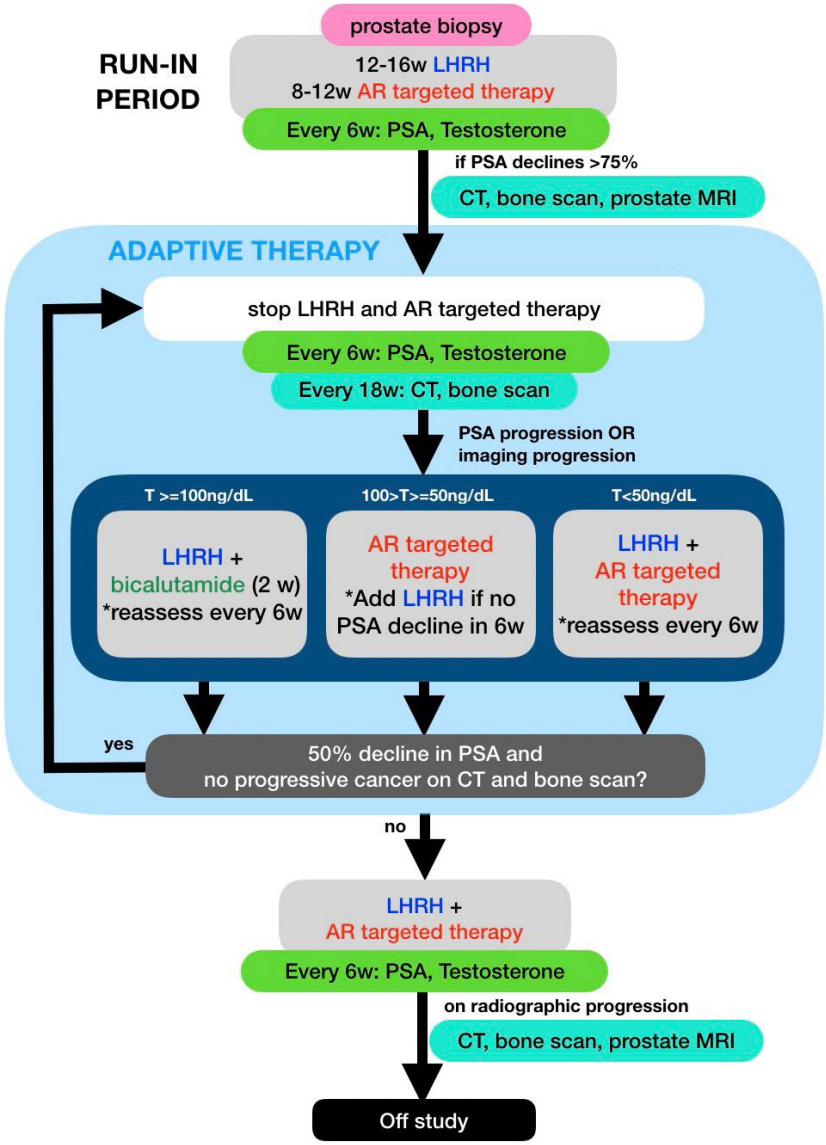
Treatment will be restarted if subjects develop PSA or radiographic progression per prostate cancer working group (PCWG)3 criteria[6] while being off treatment. The selection of treatment will be based on subject's testosterone level (***Figure 1 Schema***):

1. If the testosterone level is > 100 ng/dl, LHRH analog will be restarted with 2 weeks of bicalutamide bridging and continued until PSA declines 50% or more in 2 measurements at least 2 weeks apart. AR directed therapy will be added if 50% decline of PSA can't be achieved after 6 weeks of therapy with LHRH analog.
2. If the testosterone level is between 50 and 100 ng/dl, AR directed therapy will be restarted and continued till PSA decline 50% or more in 2 measurements at least 2 weeks apart. LHRH analog will be added if the 50% decline of PSA can't be achieved after 6 weeks of therapy with AR directed therapy.
3. If the testosterone level is below 50, combined therapy with LHRH analog and AR directed therapy will be restarted.

Treatment will be discontinued after achieving 50% or more decline of PSA. For subjects who restarted therapy for radiographic progression, no progressive cancer needs to be documented on the post treatment scans along with PSA response prior to stopping therapy and proceeding with the surveillance phase. Subjects will be off study if radiographic progression is noted while on combined treatment with LHRH analog and AR directed therapy. Of note, patients in the prior phase 3 prostate cancer trials with AR directed therapy did not discontinue treatment until they develop radiographic disease progression.[5, 7,8]

Early Stopping Rule: The study will be terminated early if 2 or more of the first 6 enrolled and evaluable subjects discontinue study within a year of study enrollment due to radiographic progression while on LHRH analog, and AR directed therapy. A subject is not considered evaluable until he has been enrolled and treated per study protocol for 12 months or longer. The interim analysis will be conducted after 6 enrolled subjects became evaluable. The study enrollment should continue prior to the interim analysis. Study enrollment will be held at the time of interim analysis and then reopen if less than 2 of the first 6 enrolled evaluable subjects discontinue study within a year of study enrollment due to radiographic progression while on LHRH analog and AR directed therapy.

Figure 1. Study Schema



*Bicalutamide bridging is not required if LHRH antagonist, relugolix is used. Adding AR targeted therapy is recommended if < 50% PSA reduction is achieved 6 weeks into restarting LHRH

1.3 Schedule of Study Assessments *

Treatment Phase	Screening and run-in period	Adaptive Therapy		End of Study
Procedures	Every 4 weeks (±7 days)	Every 6 weeks (±7 days)	Every 18 weeks (±7 days)	4-6 weeks after being taken off study therapy
Informed consent	X			
Record anti-cancer therapies				X
Physical examination, vital signs, weight	X[1]	X		X
ECOG performance status	X[1]	X		X
CBC w/ diff		X		X
Complete metabolic panel	X	X		X
PSA, diagnostic	X[1]	X[3]		X
Total testosterone level	X[1]	X[3]		X
Bone scan, CT abdomen, and pelvis	X[2]		X[4]	
Record adverse events	X	X		X
Blood collection for tumor cell free DNA			X[5]	
Archival tissue (prostate biopsy or radical prostatectomy) and/or biopsy of a metastatic lesion[5]	X			X (optional)

[1]The visit and blood draw frequencies during the run-in period will be at the discretion of the treating physician.

[2] These scans are required if it has been > 16 weeks between patient's last scan and study enrollment. These scans are not required to determine patient's eligibility. It can be performed within 2 weeks of study enrollment..

[3] If needed, PSA and testosterone can be repeated in 2 weeks to confirm response or progression

[4] Chest CT will be added if a subject is known to have lung metastasis

[5] This is an optional research blood collection. A minimum of 2 collections are recommended for each consented subject.

[6] These archival tissues will be collected and used for IHC for AR and Cyp17. If tissue diagnosis is not performed, biopsy of the prostate gland and or a metastatic lesion is required for study enrollment. A fresh biopsy is recommended if the original tissue diagnosis was > 5 years old. End of study biopsy is optional.

[#]Consent and screening will occur during the 12-16 week run in period. Subjects will be enrolled after they meet the eligibility criteria after at least 12 weeks but no more than 16 weeks of combined treatment with LHRH analog and AR targeted therapy.

Glossary of Abbreviation

ADT	Androgen deprivation therapy
AE	Adverse event
AJCC	American Joint Committee on Cancer (www.cancerstaging.org)
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AST	Aspartate transaminase
BMP	Basic metabolic profile
CFR	Code of Federal Regulations
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCs	Circulating tumor cells
CYP	Cytochrome P450
CMP	Complete metabolic profile
CRPC	Castration resistant prostate cancer
FDA	Food and Drug Administration
GCP	Good Clinical Practice guidelines
GI	Gastrointestinal
IHC	Immunohistoschemistry
LHRH	Luteinizing hormone releasing hormone
mCSPC	Metastatic castration sensitive prostate cancer
mCRPC	Metastatic castration resistant prostate cancer
OS	Overall survival
PCWG3	Prostate Cancer Working Group 3
PFS	Progression-free survival
PSA	Prostate specific antigen
rPFS	Radiographic progression-free survival
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious adverse event
SRC	Scientific review board
ULN	Upper limit of normal

2 Background and Rationale

2.1 Prostate cancer and prostate cancer treatment

Prostate cancer is the most common non-cutaneous cancer diagnosed in men and the second-highest cause of death for men in the United States. It was estimated that in 2016 there would be 180,890 new cases diagnosed and 26,120 deaths from prostate cancer. Approximately 30% of patients will develop recurrent prostate cancer after initial definitive local therapy.

Androgen deprivation therapy (LHRH analog) with surgical castration or chemical castration with LHRH analog remains as the cornerstone of treatment for metastatic prostate cancer. Despite the initial good response to LHRH analog, prostate cancer will eventually progress with castrate level of serum testosterone (<50ng/dl). This is the stage defined as castration resistant prostate cancer (CRPC). Nearly all prostate cancer-specific deaths occur after patients develop metastatic castration-resistant prostate cancer (mCRPC).[9]

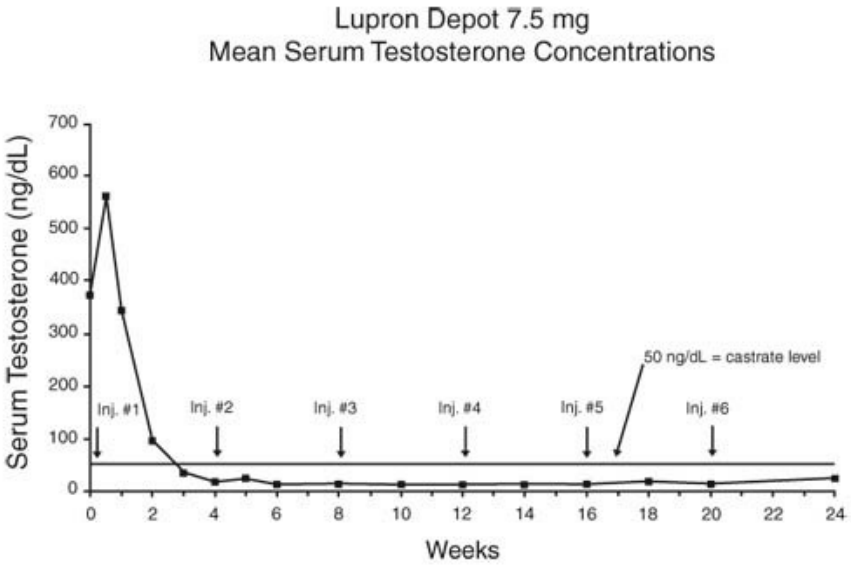


Figure 2. Pharmacodynamics of every 4 weeks injection with 7.5mg Lupron/Leuprolide

Leuprolide, Goserelin, and Triptorelin are the most commonly used LHRH agonists for LHRH analog. Administration of LHRH agonist led to an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a

transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrogen and estradiol in premenopausal females). However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels in 3 weeks and the testosterone level reaches a nadir within 8 weeks (Figure 2).

Three pivotal phase 3 trials tested 2 different approaches built upon the standard continuous androgen deprivation therapy (LHRH analog) in metastatic castration sensitive prostate cancer (mCSPC). The SWOG 9346 study compared intermittent versus continuous LHRH analog in subjects with mCSPC and the overall survival data were statistically inconclusive to show the non-inferiority of intermittent versus continuous LHRH analog.[3] Post hoc subgroup analysis showed that patients who had high volume/extensive disease (had one or more bone metastases outside the axial and pelvic bones) had 4.9 years median overall survival with intermittent LHRH analog as compared with 4.4 years in the continuous LHRH analog group (hazard ratio for death with intermittent therapy, 1.02; 95% CI, 0.85 to 1.22). The median survival differences between these two treatment approaches are mainly among patients with minimal disease.

The phase III CHAARTED trial slightly modified the definition of high volume disease by including visceral metastasis and requires a minimum of 4 bone metastases in patients without visceral metastases. Adding upfront Docetaxel chemotherapy to LHRH analog for this group of patients prolonged median overall survival by 17 months compared to LHRH analog alone.[4] Such prolongation of overall survival was not noted in the patients with low volume metastasis. The median time to progression to the castration resistant stage was 11.7 months for LHRH analog only arm; 20.2 month in the LHRH analog plus docetaxel arm.

Most recently, the phase III double-blind randomized Latitude trial reported that adding upfront AR directed therapy to LHRH analog compared to LHRH analog plus placebo significantly improved overall survival and radiographic progression free survival in patients with high risk castration-naïve metastatic prostate cancer.[5] The high risk is defined as ≥ 2 of 3 risk factors: Gleason ≥ 8, ≥ 3 bone lesions, or measurable visceral metastases. Of note, only 5% patients had liver metastasis. Overall survival was 34.7 months in the LHRH analog arm and not reached in the LHRH analog AR directed therapy arm at a median follow up of 30.4 month. Median time to PSA progression was 33 months and median time to radiographic progression was 33.3 months in the LHRH analog AR directed therapy arm.

We tested our competition model of TP (testosterone producing), T+ (testosterone dependent) and T- (testosterone independent) prostate cancer cells with the retrospective data on >100 patients with mCSPC, and found that a shorter course of LHRH analog as compared to > 6 months of LHRH analog used in the intermittent LHRH analog arm of SWOG 9346 would be more effective to preserve the T+ population and delay the progression to the castration resistant stage (see Section 2.2). The TP population is the target of abiraterone, which blocks cancer cells' production of testosterone through cyp17. The success of the Latitude trial confirmed our observation with the cyp 17 immunohistochemistry that a significant percentage of TP cells were present in the primary as well as castration naïve metastatic sites (> 30% based on IHC). Although the Latitude trial showed that continuous targeting both T+ and TP prostate cancer cells improved survival for patients with high risk castration naïve metastatic disease,[5] we hypothesize that such survival benefit can be extended further with a treatment strategy adapted to the changes in the percentage of TP, T+, T- prostate cells under the selective pressure of treatment.

To develop adaptive therapy for mCSPC, we propose this pilot feasibility study to use PSA response, and testosterone level to guide the treatment with LHRH analog and/or AR directed therapy.

2.2 Rationale and Mathematical Modeling for adaptive LHRH analog

A mathematical model of intratumoral evolutionary dynamics was developed for an ongoing trial using adaptive abiraterone for treatment of mCRPC (NCT02415621). Interim analyses of the trial results have been consistent model predictions. Here we will use this same parsimonious mathematical model of intratumoral evolutionary dynamics. The model is considered parsimonious because it focuses only on the role of testosterone in prostate cancer growth and defines tumor subpopulations solely on their interactions with androgens. This is clearly a simplified model, but it has been successful in predicting observed clinical outcomes in our initial adaptive therapy trial for mCRPC, a stage that is more enriched with intratumoral heterogeneity compared to mCSPC.

Evolutionary subpopulations

We assume three competing phenotypes: (i) T+ cells requiring exogenous androgen; (ii) TP cells expressing CYP17A1 and producing testosterone; and (iii) T- cells that are androgen-independent. These populations are consistently observed in clinical specimens.

Lotka-Volterra model

We use Lotka-Volterra competition equations to model the interactions among the T+, TP and T- cell types, i= 1, 2, and 3. The LV equations require parameterization of growth rates, r_i, carrying capacities, K_i, and the competition matrix, a_ij.

$$\frac{dx_i}{dt} = r_i x_i \left(1 - \frac{\sum_{j=1}^{3} a_{ij} x_j}{K_i}\right)$$

Growth Rate and Carrying Capacity Setup

Since virtually all prostate cancers respond to LHRH analog, we assumed that T+ cells are the fittest population in the absence of therapy. Fitness of TP and T- cells are diminished by the cost of utilizing other means of survival and proliferation. The growth rates are calculated from published doubling times of cell lines (PMID: 26146646; 18782595; 11040447). T+ is based on the LNCaP cell line with a doubling time of 28 hours. TP is based on H295R cell lines which "retain the ability to produce adrenal androgens" with an average doubling time of 39.5 hours. T- cells are based on the C4-2 and C4-2B cells lines with a doubling time of 48 hours. In this way, each 'time unit' in the model is equal to one day.

$r_{T+} = 0.5941$
$r_{TP} = 0.4212$
$r_{T-} = 0.3466$

In a naïve, untreated tumor population, we assume that all three cell types have the same carrying capacity, $K_1=K_2=K_3=100$. When LHRH analog is applied we assumed the carrying capacity of T+ derives entirely from "cheating" – i.e. utilizing the publically available testosterone produced by the TP cells so we set $K_1 = 0.5x_2$, allowing each TP cell to support the growth of 0.5 T+ cells. Both T- and TP keep the same carrying capacity: $K_2=K_3=100$. The carrying capacity of T+ cells are reduced by LHRH analog in the form of symmetrical sigmoidal decay calibrated to testosterone measurements (Figure 2).

$K_1 = K_{exo} + K_{endo}$ where $K_{exo} = d + \frac{a-d}{1+\left(\frac{t}{c}\right)^b}$ with

$a = 100$
$b = 2.905$
$c = 8.526$
$d = 0$
$K_{endo} = 0.5 * x_2$

The recovery of testosterone after ending LHRH analog is not well defined. The fastest recovery seems to be about 2 months. To capture these dynamics, the recovery of testosterone is modeled using a sigmoidal function.

$$K_1 = K_{exo} + K_{endo} \quad \text{where} \quad K_{exo} = d + \frac{a-d}{1+\left(\frac{t}{c}\right)^b} \quad \text{with}$$

$a = 100$
$b = 4.805$
$c = 42.20515$
$d = 100$
$K_{endo} = 0.5 * x_2$

Competition Coefficient Setup

The diagonal values are set to unity to maintain logistic growth in the absence of other cell types. Optimization techniques were used to define the other values for the competition matrix a_{ij}.

Maximizing T+

	T+	TP	T-	Final Density
T+	***1***	*0*	*0*	*99.99*
TP	*1*	***1***	*1*	*8.03*
T-	*1*	*1*	***1***	*8.96*

For the naïve (pre-Lupron) matrix, the final population frequency of T+ was maximized. The resulting matrix is below. This results in a final population density of T+ = 99.99. When T+ is maximized the frequency of TP = 8.03 and T- = 8.96. The above table shows that T+ does not suffer any ill effects from TP or T- cells. Both TP and T- cells suffer the full effect of competition with the other cell types.

For the LHRH analog matrix, there are multiple objectives to optimize for that represent different groups of patients:

1. Maximizing T+ or Minimizing T- (results in the same matrix)
2. T+ frequency equal to TP frequency
3. Maximizing T-.
4. Others?

1) Maximizing T+ or Minimizing of T-

	T+	TP	T-	Final Frequencies
T+	***1***	*0*	*0*	*44.98*
TP	*0*	***1***	*0*	*93.72*
T-	*1*	*1*	***1***	*11.97*

2) T+ frequency equal to TP frequency – This is the one used for all the results.

	T+	TP	T-	Final Frequencies
T+	***1***	*0*	*0*	*24.40*
TP	*1*	***1***	*1*	*49.90*
T-	*1*	*1*	***1***	*22.34*

3) Maximizing T-

	T+	TP	T-	Final Frequencies
T+	***1***	*0*	*1*	*0.002*
TP	*0*	***1***	*1*	*50.82*
T-	*0*	*0*	***1***	*57.50*

Each of these matrices describes a different qualitative patient group. The first matrix where T+ is maximized represents the scenario where there is a maximal amount of T+ remaining to prevent competitive release from T-. The second matrix where T+ and TP are present in less density and there is a more substantial group of T- represents what I assume to be the most common patient group (not best case, but not worst case). The last matrix represents the worst case scenario where all of the T+ cells will die off very quickly and only TP will remain to prevent competitive release. All patients will fall on a spectrum of these matrices, though these 3 give a good representation of the dynamics we may expect to see.

PSA Setup

Because the direct correlation between tumor cell count and serum PSA is unknown, we naïvely assume that each cell produces one unit of PSA per unit time. We also assume that 50% of the PSA decays out of the serum each time step. In this way, the simulated serum PSA is defined by

$$\frac{dPSA}{dt} = \sum_{i=1}^{3} x_i - 0.5 * \mathrm{PSA}$$

The evolutionary strategy tested in the protocol relies on the fitness advantage of the T+ cells in the absence of LHRH analog. That is, in the presence of LHRH analog, the TP and T- cells are fitter and proliferate while the T+ population decline. Without any perturbation of this system, the resistant cells will rapidly dominate. However, we propose that by removing therapy, we reverse these fitness advantages. Thus, the tumor will indeed regrow but, critically, the fitness advantage of the T+ cells in the absence of LHRH analog allows them to proliferate at the expense of the TP and T- cells. Thus, when the tumor returns to its pretreatment size, it will have a mix of subpopulations that

is nearly identical to that of the tumor prior to therapy. In other words, it remains responsive to LHRH analog.

So, why have intermittent androgen therapy trials not been shown to be more effective for mCSPC? Our modeling results (Figure 3) demonstrate that the 7 months of LHRH analog induction phase and the minimum of 6 months of treatment phase used in the SWOG 9346 trial would significantly reduce the T+ population so that the tumor consisted almost entirely of TP and T- phenotypes. Thus, because competitive release has already occurred, cycling of therapy provide no evolutionary benefit.

As shown in Figure 3, we calculated that best results will be obtained by maximally shortening the induction period. Each patient should be evaluated with PSA and testosterone levels at 4 weeks intervals following the initial injection. Therapy should be withdrawn after testosterone level reaches a nadir. The model predicts that this approach will typically permit multiple on/off treatment cycles allowing prolonged tumor control while also allowing the patients to remain untreated for at least half of the time on trial thus reducing the physical and psycho-social adverse effects of LHRH analog.

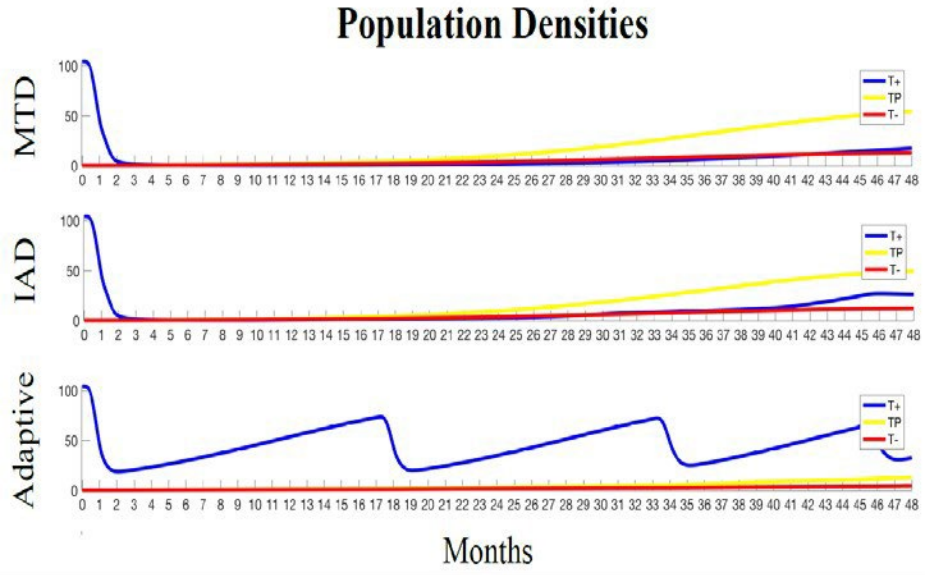


Figure 3. Computer simulations using models and parameters found in the text of the protocol. The top row shows a typical outcome for standard maximal tolerated dose (MTD) therapy. Continuous LHRH analog selected for resistant phenotypes (TP and T-). For the intermittent therapy we assumed an 8 month induction period of MTD LHRH analog as outlined in the published protocols. We find this resulted in population dynamics almost identical to that of MTD. Consistent with published reports, we find this provides no clinical benefit over continuous LHRH analog. In the bottom row, we model an evolution-based intermittent therapy in which there is no or minimal induction period. Treatment is withdrawn when PSA declines below 50% of the pretreatment level and then started again only when the PSA returns to the pretreatment level. As shown, the models suggest this strategy allows the T+ cells to remain the dominant intratumoral population so that tumor remains responsive

In patients with high risk mCSPC, adding continuous abiraterone plus prednisone to LHRH analog has become the standard of care based on the Latitude trial. Continuous suppression of the T+ and TP populations will lead to the dominance of the T- population, the most aggressive prostate cancer. This is particularly concerning given most patients with high risk prostate cancer have a Gleason score 8 or above. To develop adaptive therapy for high risk mCSPC, we will use PSA response, and testosterone level to guide the treatment with LHRH analog and or AR targeted therapy in this pilot feasibility study. The percentage of T+ and TP populations will be assessed with IHC for AR and cyp17 on the prostate biopsies and or biopsy of a metastatic lesion. Changes in the TP and T+ populations will be modeled based on the changes in the PSA and testosterone levels.

3 Study Objectives and Endpoints

3.1 Objectives

Primary: Test the feasibility of adaptive LHRH analog in patients with asymptomatic mCSPC

Secondary: Assess the clinical benefits of adaptive LHRH analog by comparing to historical controls.

Exploratory objectives/correlative studies:

1. Detect the intra-tumor heterogeneity of AR and Cyp17 IHC stains on FFPE blocks of prostate tumors and or metastatic lesions
2. Refine the mathematical model for adaptive ADT
3. To develop imaging habitat biomarkers to track diseases progression using the patients' CT and bone scans and compare with conventional progression variables (like PSA).
4. Compare the IHC, immunofluorescence and imaging biomarkers with a retrospective cohort of mCSPC patients who underwent continuous LHRH analog as standard of care
5. Detect and track the changes of AR alterations in tumor cell free DNA

3.2 Endpoints

Primary: Percentage of subjects who remain on study at month 12 from first dose of LHRH analog

Secondary: Median time to PSA progression and median time to radiographic progression while on LHRH analog, and AR directed therapy.

4 Screening and Eligibility

4.1 Inclusion criteria: patients must meet all of the following criteria

1. Histologically or cytologically confirmed adenocarcinoma of the prostate
2. >75% PSA decline after 12 to 16 weeks of run in period with LHRH analog, and AR directed therapy
3. Performance status ECOG 0-1
4. Adequate organ function:

   Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) must be < 2.5 x upper limit of normal (ULN), total bilirubin < 1.5 X ULN, estimated creatinine clearance must be >40 mL/min, absolute neutrophil count (ANC) > 1500/l, hemoglobin above 9 g/dl, platelet count > 100,000/l
5. Stable medical condition, including the absence of acute exacerbations of chronic illnesses, serious infections or major surgery within 28 days prior to study enrollment
6. Ability to give written informed consent

4.2 Exclusion criteria: any of the following is a criterion for exclusion from the study

1. Prior LHRH analog with LHRH analogue for non-metastatic prostate cancer within 12 months prior to study enrollment; or > 3 months of LHRH analog in the metastatic setting.
2. Prior treatments with TAK-700/Orteronel, ketoconazole, abiraterone, darolutamide, apalutamide or enzalutamide for more than 12 weeks.
3. Documented central nervous system metastases or liver metastasis
4. Prior surgical castration
5. Requiring opioids for cancer related pain
6. Treatment with any investigational compound within 30 days prior to the first dose of study drugs
7. Diagnosis or treatment for another systemic malignancy within 2 years before the first dose of study drugs, or previously diagnosed with another malignancy &

have any evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

8. Uncontrolled hypertension despite appropriate medical therapy (blood pressure of greater than 160 mmHg systolic and 100 mmHg diastolic at 2 separate measurements no more than 60 minutes apart during the Screening period). Note: Patients may be rescreened after adjustments of antihypertensive medications
9. Unstable symptomatic ischemic heart disease, ongoing arrhythmias of Grade > 2 (NCI CTCAE, version 5.0), New York Association Class III or IV heart failure
10. Known human immunodeficiency virus (HIV) infection, active chronic hepatitis B or C not contained with anti-viral therapy, life threatening illness unrelated to cancer, or any serious medical or psychiatric illness that could, in investigator's opinion, potentially interfere with participation in this study.
11. Known GI disease or GI procedure that could interfere with the GI absorption or tolerance of study drugs, including difficulty swallowing tablets.
12. Subjects with delayed healing of wounds, ulcers, and/or bone fractures
13. Inability to comply with protocol requirements

5 Investigational Plan

Subjects with asymptomatic mCSPC and no liver metastasis will be consented and screened during a run in period with 12 to 16 weeks of LHRH analog, and 8 to 12 weeks AR directed therapies (abiraterone plus prednisone, enzalutamide, darolutamide, or apalutamide). A total of 16 eligible subjects who achieve >75% PSA decline after the 12 to 16 weeks *run-in period* will be enrolled. Both LHRH analog and AR directed therapy will be stopped after study enrollment. PSA and testosterone level will be measured during the run-in period and then every 6 weeks after study enrollment. Baseline imaging studies with CT and bone scan will be performed at the time of study enrollment and then be performed every 18 weeks while on study. If a subject develops radiographic progression while being off therapies with LHRH analog and AR directed therapy, these scans will be considered the new baseline scans for this subject.

Adaptive therapy

Treatment will be restarted if subject develops PSA or radiographic progression per prostate cancer working group (PCWG)3 criteria[6] while on off treatment surveillance. The selection of treatment will be based on subject's testosterone level (***Figure 1 schema***):

1. If the testosterone level is > 100 ng/dl, LHRH analog will be restarted with 2

weeks of bicalutamide bridging and continued until PSA declines 50% or more in 2

measurements at least 2 weeks apart. AR directed therapy will be added if 50% decline of PSA can't be achieved after 6 weeks of therapy with LHRH analog.

2. If the testosterone level is between 50 and 100 ng/dl, AR directed therapy will be restarted and continued till PSA decline 50% or more in 2 measurements at least 2 weeks apart. LHRH analog will be added if the 50% decline of PSA can't be achieved after 6 weeks of therapy with AR directed therapy.
3. If the testosterone level is below 50, combined therapy with LHRH analog a n d AR directed therapy will be restarted.

Treatment will be discontinued after achieving 50% or more decline of PSA. For subjects who restarted therapy for radiographic progression, no progressive cancer needs to be documented on the post treatment scans along with PSA response prior to stopping therapy and proceeding with the surveillance phase. Subjects will be off study if radiographic progression is noted while on combined treatment with LHRH analog and AR directed therapy. Of note, patients in the prior phase 3 prostate cancer trials with AR directed therapy did not discontinue treatment until they develop radiographic disease progression.[5,7,8]

Early Stopping Rule: The study will be terminated early if 2 or more of the first 6 enrolled subjects discontinue study within a year of study enrollment due to radiographic progression while on LHRH ANALOG, and AR directed therapy. A subject is not considered evaluable until he has been enrolled and treated per study protocol for 12 months or longer. The interim analysis will be conducted after 6 enrolled subjects became evaluable. The study enrollment should continue prior to the interim analysis. Study enrollment will be held at the time of interim analysis and then reopen if less than 2 of the first 6 evaluable subjects discontinue study within a year of study enrollment due to radiographic progression while on LHRH analog and AR directed therapy.

6 Visit schedule and assessments

Screening Assessments and all on study scheduled visits and assessments are outlined in Section 1.3.

6.1 Drug Administration

LHRH analog with injections of monthly or every 3 months depot dosage of LHRH agonist like Leuprolide (preferred), Goserelin, or Triptorelin will be administered as standard of care. When LHRH analog is restarted with a testosterone level above 100, adding 2 weeks of oral

bicalutamide bridging at 50 mg daily is required for the potential testosterone flare. This bicalutamide bridging is also considered as standard of care. Bicalutamide bridging is not required if LHRH antagonist, relugolix is used.

Abiraterone 1000mg taken daily with empty stomach plus prednisone 5mg once a day with food, enzalutamide 160mg taken daily with or without food, or apalutamide 240mg taken daily with or without food will be prescribed as the standard of care and dispensed by the specialty pharmacy designated by patients' insurance. Medication diaries are not required. Diaries are not required due to medication being standard-of-care, and compliance not being a primary end-point or objective of the study. Participant should be informed to use a condom and another effective method of birth control if he is having sex with a woman of childbearing potential. These measures are required during and for at least one week after treatment with abiraterone, enzalutamide or apalutamide.

When abiraterone is discontinued per study protocol, prednisone tapering is not required. If prednisone tapering is chosen, the dose, frequency and length of prednisone tapering will need to be recorded in clinic visit notes.

6.2 Toxicity Assessment and reporting of adverse events

NCI CTAE version 5.0 will be used for toxicity assessment. Please refer to abiraterone, enzalutamide, and apalutamide FDA approval label for known toxicities of these AR directed therapies.

Adverse events will be collected after a patient is consented for the study and until 6 weeks after being taken off study therapy. An adverse event (AE) for the purpose of this protocol is the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) occurring after study enrollment even if the event is not considered to be related to starting or stopping study treatments. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy (e.g., any hematologic abnormality that requires transfusion). In addition, isolated abnormal laboratory values that are considered clinically significant (e.g., cause study discontinuation or constitutes in and of itself a serious adverse event) should be recorded on the Adverse Events CRF. AE will be assessed at the clinic visits as specified in the protocol. Toxicity will be scored using CTCAE Version 5.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP homepage (HTTP://CTEP.INFO.NIH.GOV).

Any event that that is life threatening, requires inpatient hospitalization, prolongs hospitalization (excluding emergency room visits), results in persistent or significant disability or incapacity or results in death would be considered a serious adverse event (SAE). Other important medical events that may not result in death, be life-threatening or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the

patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. All serious, related adverse events (and unanticipated) will be reported and documented on forms as required by institutional guidelines and forwarded directly to the IRB in

electronic version within 2-5 business days of becoming aware of the event. Disease progression or symptomatic progression will be considered as AE during the adaptive therapy period.

6.3 Dose Reduction

Dose reduction of abiraterone is allowed if subjects develop grade 3 or 4 fatigue or liver enzyme abnormalities for more than 2 weeks.

Level 1 dose reduction is defined as 750 mg daily

Level 2 dose reduction is defined as 500 mg daily

Dose escalation to the full dose, i.e. 1000mg daily is allowed after these AEs are resolved. The lowest dose of abiraterone permitted is 500 mg daily. Subjects will be taken off study treatment if abiraterone related grade 3 or 4 AEs do not resolve within 3 weeks after being off abiraterone.

Dose reduction of enzalutamide or apalutamide is allowed if subjects develop grade 3 or 4 fatigue for more than 2 weeks

Level 1 dose reduction of enzalutamide is defined as 120 mg daily

Level 2 dose reduction of enzalutamide is defined as 80 mg daily

Level 1 dose reduction of apalutamide is defined as 180 mg daily

Level 2 dose reduction of apalutamide is defined as 120 mg daily

Dose escalation to the full dose is allowed for enzalutamide and apalutamide. The lowest dose of enzalutamide permitted is 80 mg daily, and the lowest dose of apalutamide permitted is 120 mg daily. Subjects will be taken off study treatment if apalutamide or enzalutamide related grade 3 or 4 AEs do not resolve within 3 weeks after being off treatment.

Switching from one AR directed therapy to another is allowed if the subjects develop poor tolerance or grade 3 or 4 AR directed therapy related AEs.

Dose reductions are not applicable to prednisone, bicalutamide or LHRH analog with LHRH analogs.

7 Criteria for evaluation and Endpoint definition

7.1 Measurability of Lesions

Measurable disease:

1. Non lymph node lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) by ≥ 1.0 cm with CT or MRI scans. All tumor measurements must be recorded in decimal fractions of centimeters.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in SHORT AXIS (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan

The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less.

Non-measurable disease:
All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, and previously radiated lesions that have not progressed are considered non-measurable.

7.2 Progression Criteria

Given death and symptomatic progression are rare events in this patient population; Median time to PSA progression and median time to radiographic progression while on LHRH analog, AR directed therapy was chosen as secondary endpoints. Radiographic progression is defined by any of the following criteria:

1. Progression of measurable lesions per RECIST 1.1 criteria. Twenty percent increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over pretreatment baseline if no decrease during therapy) using the same imaging techniques as baseline, as well as an absolute increase of at least 0.5 cm.

2. Progression on bone scan is defined as 2 or more new lesions on radionuclide bone scans. Should two or more new bone lesions be evident at the first assessment on treatment (Month 3), two or more additional new lesions must be evident on a confirmatory assessment at least 8 weeks or later (at investigator's discretion). This confirmation recommended by PCWG3 due to the bone scan flare during initial therapy and is not required when 2 or more new lesions first appear after Month 3.

3. Unequivocal progression evidenced by appearance of 2 or more new measurable lesions at least 2 cm in short axis.

Performance Status

Patients will be graded according to the ECOG Performance Status Scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

7.3 Endpoint definitions

Primary: percentage of subjects who remain on study at month 12

This endpoint is descriptive and superiority to continuous LHRH analog can be demonstrated statistically so long as 2 or fewer men of the 16 have progressed at month 12 (see statistical consideration)

Secondary: Median time to PSA progression and median time to radiographic progression while on LHRH analog, AR directed therapy**.**

Such time intervals start with the first dose of LHRH analog for mCSPC and the definition of PSA progression and radiographic progression will be based on the PCWG3 criteria.[6] This was 33 months with continuous LHRH analog and abiraterone in the phase 3 Latitude trial.[5]

7.4 Exploratory objectives/correlative studies

Archival tissue from primary prostate cancer and/or metastatic lesions will be collected at screening and at the time of study discontinuation due to cancer progression. If tissue diagnosis is not performed, biopsy of the prostate gland and or a metastatic lesion is required for study enrollment. A fresh biopsy is recommended if the original tissue diagnosis was > 5 years old. IHC for AR and Cyp 17 will be performed at Moffitt's tissue core. If funds allow, these tumor samples will also be submitted for targeted exome sequencing. Analysis of CT and bone scan imaging biomarkers will be performed by Dr. Gillies' group.

Through the chart review protocol MCC17610, we have identified 307 metastatic prostate cancer cases treated at Moffitt Cancer Center between 2010 and 2016. We are identifying a retrospective cohort of patients among these 307 cases that would match the current study populations. No more than 120 FFPE blocks on this retrospective cohort of patients will be requested for TMA construction and IHC stains for AR, Cyp17. CT and bone scan images will be de-identified and used for imaging biomarker analysis.

Circulating tumor cell free DNA (cfDNA) has been increasingly used to assess and monitor the genomic alterations that may be associated with treatment response. Mutations in AR ligand binding domain (exon 8) were detected in cfDNA and were reported as a resistance mechanism to abiraterone and enzalutamide. The AR T878A mutation has been particularly associated with resistance to abiraterone. The detection on AR mutations and AR amplification will be performed at Dr. Liang Wang's lab. To improve the detection rate, this test will be performed in patients with > 2 bone metastases or lung metastases. The timing of the blood collection would be within 2 weeks of radiographic progression either on or off treatment. Three lavender tubes will be used for cfDNA collection at each collection point.

8 Statistical Considerations

Statistics will be descriptive for the primary and secondary endpoints.

Sample Size Justifications: For patients enrolled in the trial we expect the probability of progression at one year to be less than 12%. The study would be considered feasible if less than 2 of the first 16 evaluable subjects have progression to the castration resistant stage at year one from the first LHRH analog treatment for mCSPC.

9 Minority Accrual

We will work with social workers to identify the resources that may help minorities' enrollment in clinical trials.

10 Regulatory Considerations

10.1 Scientific Review Committee (SRC) and Institutional Review Board approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. Moffitt's SRC conducts a formal internal peer review of all clinical protocols and general scientific oversight of interventional clinical research. Protocols are reviewed for scientific merit, adequate study design, safety, availability of targeted study population, and feasibility of timely completion of all proposed research projects to be conducted by its assigned programs at the Cancer Center. The SRC is responsible for evaluating the risk/benefit assessment and corresponding data and safety monitoring plan as part of the scientific review and approval process. The review of this protocol by the IRB and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of IRB approval must be submitted by the Investigator to the SRC and IRB for approval. The Investigator is also responsible for notifying the IRB of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB prior to use.

10.2 Informed consent

The Investigator or delegated research staff must obtain informed consent of a subject or his designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files.

10.3 PI responsibility

The PI of each study is ultimately responsible for every aspect of the design, conduct and actions of all members of the research team. This includes the final analysis of the protocol.

In all cases, the PI of the study will have primary responsibility for ensuring that the protocol is conducted as approved by the SRC and IRB. The PI will ensure that the monitoring plan is followed, that all data required for oversight of monitoring are accurately reported to Moffitt's protocol monitoring committee and IRB as required, that all adverse events are reported according to protocol guidelines, and that any adverse actions reflecting patient safety concerns are appropriately reported.

10.4 Subject confidentiality

Moffitt affirms the subject's right to protection against invasion of privacy. In order to maintain patient confidentiality, all case report forms, study reports and communications relating to the study will identify patients by initials and assigned patient numbers. In compliance with United States federal regulations, Moffitt requires the Investigator to permit representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

10.5 Study records requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's evaluation checklists; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or

magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

10.6 Monitoring of the study and regulatory compliance

The Principal Investigator and the Clinical Research Coordinator assigned to the case will be primarily responsible for maintaining all study related documents including the clinical research forms. Oncore is Moffitt's clinical trial database of record for all CRF entries and will be verified with source documentation. The review of medical records within PowerChart will be done in a manner to assure that patient confidentiality is maintained. Regulatory documents and case report forms will be reviewed routinely for accuracy, completeness and source verification of data entry, validation of appropriate informed consent process, adherence to study procedures, and reporting of SAEs and protocol deviations according to Moffitt's Monitoring Policies.

10.7 Protocol modifications

No modifications will be made to the protocol without the agreement of the investigators. Changes that significantly affect the safety of the patients, the scope of the investigation, or the scientific quality of the study will require Scientific Review Committee and Institutional Review Board approval prior to implementation, except where the modification is necessary to eliminate apparent immediate hazard to human subjects. Any departures from the protocol must be fully documented in the case report form and the source documentation.

10.8 The Protocol Monitoring Committee (PMC) and Internal Monitoring

The PMC meets monthly and reviews accrual, patterns and frequencies of all adverse events, protocol violations and when applicable, internal audit results. The PMC ensures the safety of patients and the validity and integrity of data. PMC reviews SAEs, deviations, Interim analysis, interim and final reports from the external Data Monitoring Committee (DMC) as well as audits both internally and externally. The PMC can make the following determinations, Accepted, Acceptable with Corrective Action and Tabled. Investigators of studies, which are designated to be reviewed by the PMC for data and safety monitoring, shall provide an interim analysis report of the study's progress and summary of adverse events and deviations based on the phase of the study and the associated risk of the study or more often if applicable. The external DSMB (if applicable) shall forward its report for high-risk studies designated for external review at least annually or more often if applicable.

Internal monitoring

Data will be captured in Oncore, Moffitt's Clinical Trials Database. Regulatory documents and case report forms will be reviewed routinely for accuracy, completeness and source verification of data entry, validation of appropriate informed consent process, adherence to study procedure, and reporting of SAEs and protocol deviations according to Moffitt's Monitoring Policies.

10.9 Suspension/Termination

The PMC and/or the IRB may vote to suspend or terminate approval of a research study not being conducted in accordance with the IRB, the Cancer Center and/or regulatory requirements or that has been associated with unexpected problems or serious harm to subjects. The PMC/IRB will notify the PI in writing of such suspension or terminations. It is the responsibility of the PMC/IRB Chairperson to ensure prompt written notification of any suspensions or terminations of PMC/IRB approval to the relevant Federal Agencies, including OHRP, FDA, the study sponsor/funding source and if applicable, the Affiliate Program.

The responsible clinical investigator as well as Moffitt has the right to discontinue this study at any time for reasonable medical or administrative reasons, which could be but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality.
- Inaccurate or incomplete data collection.
- Falsification of records.
- Failure to adhere to the study protocol.

A written notification of termination will be issued.

11 References

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