AWARD NUMBER: W81XWH-14-1-0021

TITLE: A Pharmacokinetic/Pharmacodynamic Study of the Glucocorticoid Receptor Antagonist Mifepristone Combined with Enzalutamide in Castrate-Resistant Prostate Cancer

PRINCIPAL INVESTIGATOR: Russell Szmulewitz

CONTRACTING ORGANIZATION: The University of Chicago
Chicago, IL 60637-5418

REPORT DATE: December 2017

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
December 2017	Annual	1 Dec 2016 – 30 Nov 2017

4. TITLE AND SUBTITLE
A Pharmacokinetic/Pharmacodynamic Study of the Glucocorticoid Receptor Antagonist Mifepristone Combined with Enzalutamide in Castrate-Resistant Prostate Cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-14-1-0021

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Russell Szmulewitz

E-Mail: rszmulew@medicine.bsd.uchicago.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Chicago
5841 S. Maryland Avenue
Chicago, IL 60637

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This is a Clinical Exploration Award funding a clinical trial for patients with metastatic, castration resistant prostate cancer (CRPC). For patients with metastatic CRPC, there are few established therapeutic options and the prognosis remains dire. The overarching goal of this award is to build on concept that under the selective pressure of androgen receptor (AR) targeted therapies, prostate cancer adapts. One way it adapts is by upregulating another hormone receptor, the glucocorticoid receptor (GR), which may compensate for diminished AR activity. The clinical trial within this award is a phase I/II clinical trial of the GR antagonist mifepristone in combination with the FDA-approved AR antagonist enzalutamide. The first objective is, within the context of a phase I clinical trial, to establish safe and pharmacologically active doses of the two drugs for use in combination for daily dosing. The second objective is to use pharmacodynamic biomarkers to support the hypothesis that GR antagonism in combination with AR antagonism will delay CRPC progression. During this funding period, two additional sites have opened the study and are now actively recruiting. This has greatly facilitated accrual. Thus far the combination of mifepristone and enzalutamide has been well tolerated with no dose limiting toxicities. During the next year, the goal is to complete enrollment for the phase II trial.

15. SUBJECT TERMS
Castration resistant prostate cancer (CRPC); Androgen Receptor (AR); Glucocorticoid receptor (GR); Enzalutamide; Mifepristone; Pharmacokinetic (PK) Pharmacodynamic (PD); Prostate

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	13	19b. TELEPHONE NUMBER *(include area*

Table of Contents

1 INTRODUCTION:

This award is a Clinical Exploration Award funding a clinical trial for patients with metastatic, castration resistant prostate cancer (CRPC). For patients with metastatic CRPC, there are few established therapeutic options and the prognosis remains dire. The overarching goal of this translational research award is to build on concept that under the selective pressure of androgen receptor (AR) targeted therapies, prostate cancer adapts. One way it adapts is by upregulating another hormone receptor, the glucocorticoid receptor GR), which may compensate for diminished AR activity. The clinical trial within this award is a phase I/II clinical trial of the GR antagonist mifepristone in combination with the FDA-approved AR antagonist enzalutamide. The two major objectives of the award correspond to the two phases of the trial that will be articulated in more detail within the "Accomplishments" section of the report. The first objective is within the context of a phase I clinical trial to establish safe and pharmacologically active doses of the two drugs for use in combination for daily dosing. This will be completed at the lead site. The second objective is to use pharmacodynamic biomarkers to support the hypothesis that GR antagonism in combination with AR antagonism will delay CRPC progression. This portion of the study will be a multiple-institutions study, led by the lead site.

2 KEYWORDS

The following are key words that will be used in this report
Castration resistant prostate cancer (CRPC)
Androgen Receptor (AR)
Glucocorticoid receptor (GR)
Enzalutamide
Mifepristone
Pharmacokinetic (PK)
Pharmacodynamic (PD)
Prostate specific antigen (PSA)

3 ACCOMPLISHMENTS:

A. What were the major goals of the project?
Please note that a revised statement of work (SOW) was submitted 10/2017 as part of a no-cost extension to allow study completion.

As stated in the revised SOW, the major tasks for the study, with projected timeline are listed as follows. Specific activities accomplished, in concordance with SOW during this quarter will be detailed in the next section.

Major Task 1: Regulatory Approval: Lead and subsidiary sites	**COMPLETE**
Major Task 2: Coordinate and Initiate Phase I Portion of Study	**COMPLETE**
Major Task 3: Complete phase I study	**COMPLETE**
Major Task 4: Initiation of Phase II	**COMPLETE**
Major Task 5: Complete Phase II study	**Months 30-60**
Major Task 6: Data Analysis	**Months 30-60**

B. What was accomplished under these goals?
The following tables summarize the objectives/subtasks to be accomplished during this reporting period specifically, with comments when pertinent.

Major Task 1: Regulatory Approval: Lead and subsidiary sites			
	Timeline (months)	**Objective complete**	**Findings, developments, discussion points**
Subtask 1: Obtain Regulatory Approval for Research Protocol at UC: COMPLETE			
Subtask 2: Obtain Regulatory Approval for Research Protocol at PCCTC sites			
PCCTC site identification		Yes	The trial is now open at NorthShore University (D. Shevrin PI) and at Karmanos Cancer Center (Heath). Depending on accrual 2 University of Chicago Network site can be added
Scientific and IRB submission at PCCTC sites	25-28	Yes	Regulatory documents sent to sites above
Coordination of Clinical Trials Agreement (CTA) at PCCTC sites	25-28	Yes	Active central CTA agreements are already in place between the University of Chicago and PCCTC sites as well as University of Chicago and
Scientific Review Approval PCCTC sites	25-28	Yes	See above
IRB Approval PCCTC Sites	25-30	Yes	See above

Major Task 2: Coordinate and Initiate Phase I Portion of Study			
	Timeline (months)	**Objective complete**	**Findings, developments, discussion points**
Finalization of data capture forms	1-3	Yes	
Site initiation training at UC	1-3	Yes	
Screening and Registration of first patient on phase I at UC	1-3	Yes	

Major Task 3: Complete phase I study	Timeline (months)	Objective complete	Findings, developments, discussion points
Recruitment and enrolment	1-24	Yes	See below
PK analysis	3-27	Yes	See below
Weekly institutional data safety monitoring board	1-36	Yes	Ongoing
Monthly safety/oversight teleconference	27-48	NA	Will begin with multi-site participation
Submission of year 1 IND report to FDA	9-12	Yes	Yearly IND reports submitted
Submission of any protocol amendments to IRB, FDA, HRPO	Continuous	Yes	Personnel and minor clarification amendments submitted to IRB. No significant changes that mandated

			HRPO submission
Milestone Achieved: Completion of phase I study	9-12	Yes	

Major Task 4: Initiation of Phase II			
	Timeline (months)	**Objective Complete**	**Findings, developments, discussion points**
Finalize Recommended phase II dose	25-27	Yes	Phase II dose was determined based on phase I to be enzalutamide 120mg and mifepristone 300mg, both daily
Finalize Data Capture forms for phase II **	9-12	Yes	
Orientation and training of sites for phase II trial	25-27	Yes	See above.
First patient randomized on phase II trial	27-30	Yes	

Major Task 5: Complete Phase II study			
	Timeline (months)	**Objective Complete**	**Findings, developments, discussion points**
Recruitment and enrolment	27-48	Yes	Depending on accrual 2 University of Chicago Network site can be added
Data Capture and Input	15-48	Ongoing	TBD
PK analysis (Batched for Phase II portion of study)	33-48	Ongoing	PK Samples will be collected and batch analyzed at end of accrual
Weekly institutional data safety monitoring board	25-48	Ongoing	Weekly DSM
Monthly safety/oversight teleconference	25-48	Ongoing	Weekly teleconference DSM through University of Chicago Personalized Cancer Care Consortium
Submission of year 2 IND report to FDA	21-24	Yes	
Submission of year 3 IND report to FDA	33-36	Yes	
Submission of any protocol amendments to IRB, FDA, HRPO	Continuous	Yes	

***Note: No items within SOW to be completed on task 6 during this reporting period as this task is post completion of accrual to phase II.**

Discussion of Accomplishments:

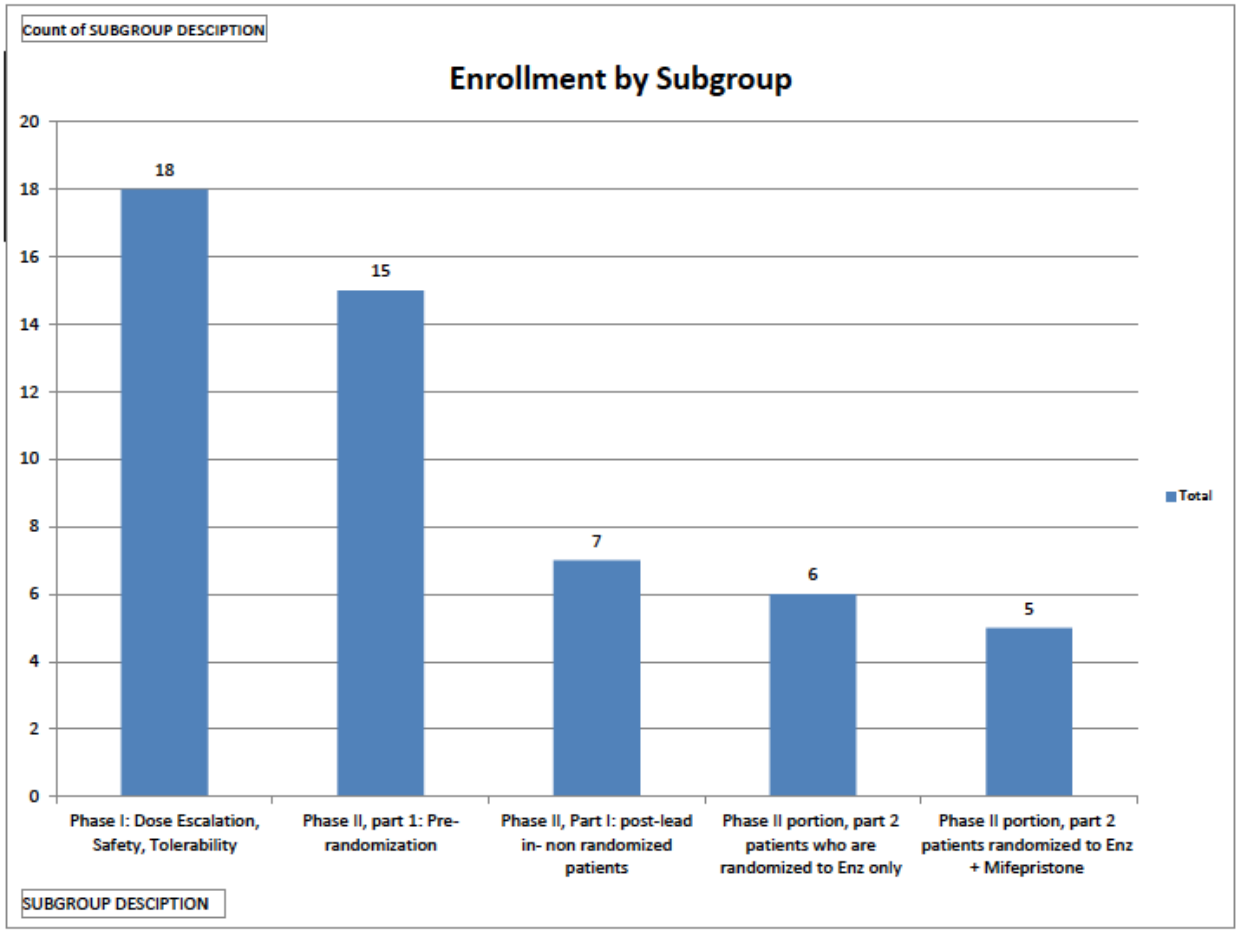
Regulatory/oversight

Within this reporting period (year 5) the primary task has been to ramp up accrual to the phase II study through opening of sites as the Phase I is now complete. There were no dose limiting toxicities; however, one patient did come off study electively during the DLT period for grade 2 fatigue and memory changes. These are anticipated side effects of the two study drugs.

We continue discussing the study weekly at our the University of Chicago Personalized Cancer Care Consortium (PCCC) safety monitoring meeting, led by Dr. Walter Stadler, which allows for teleconferencing of affiliate sites on this study. Our independent trial monitor is also present at the weekly DSM, which includes a discussion of potential subjects available for recruitment. In addition, as the protocol is an investigator initiated trial and the University of Chicago has intellectual property involving the underlying concept of dual GR and AR blockade, over the last reporting period, as suggested by the University of Chicago IRB, the protocol is continues to be reviewed for safety and data integrity at the University of Chicago Comprehensive Cancer Center High Risk Clinical Trial committee. This committee meets quarterly and there have been no issues reported. Finally, there was a routine Cancer Center audit of the trial for data integrity during the last reporting period that reported no major protocol deviations.

Task 2 and 3 (phase I trial) were completed prior to this reporting period and were fully reported at the last yearly technical report. There are no further details to report.

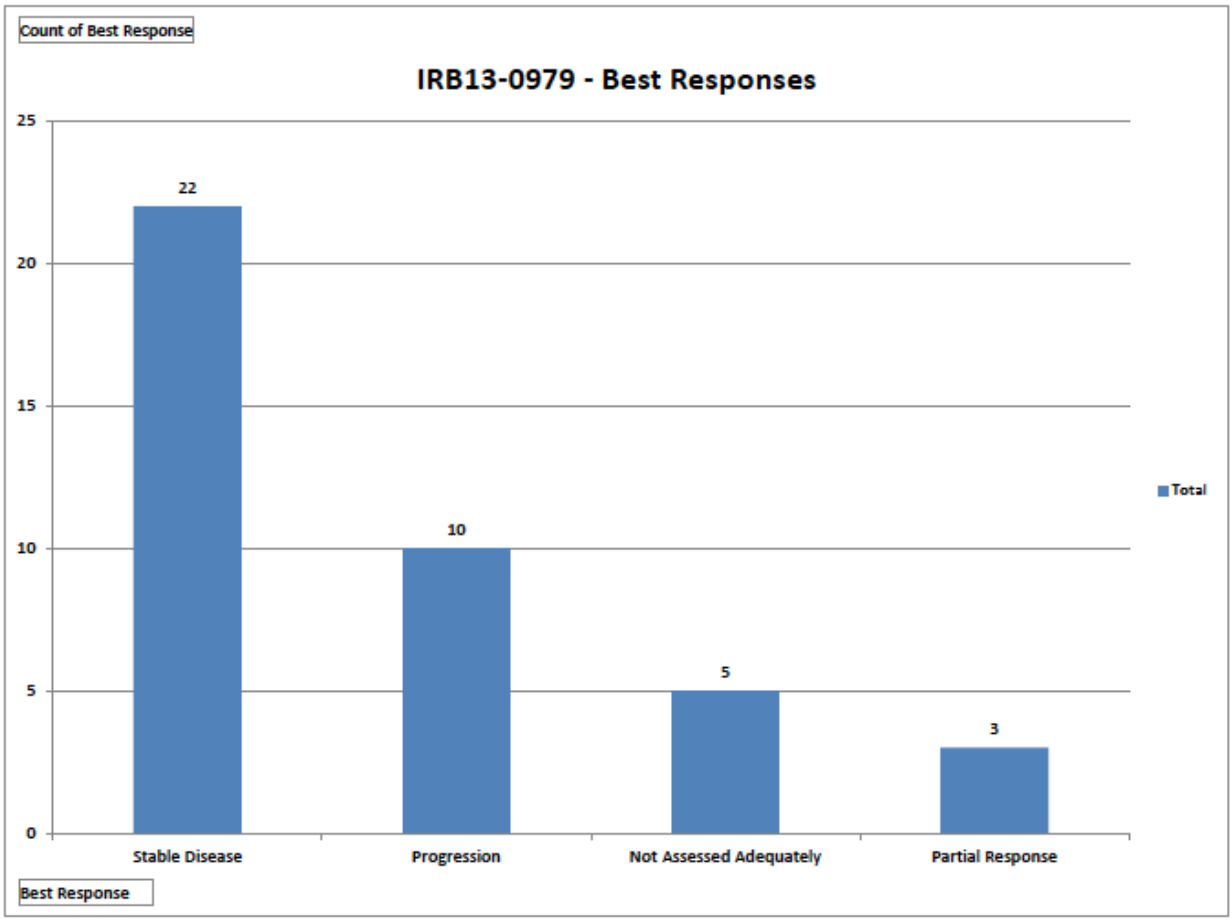
Since the last reporting period, two additional sites have opened the study and are now actively recruiting. Recruitment has thus increased over the last six months. Per protocol, we will not analyze the two randomized cohorts independently for the primary progression and secondary response endpoints. Recruitment as of 11/30/17 is as follows.



As noted, there have been 33 patients enrolled to phase II portion of the study with two currently screening. There are 15 patients in the 12 week enzalutamide lead in at present awaiting randomization.

Efficacy

As noted above, the efficacy outcomes for the phase II will not be fully reported until study completion. In aggregate, with respect to RECIST response, the majority of patients experienced stable disease, which is expected in patients with bone-only metastatic disease. There have been partial responses and a cohort of patients whose best RECIST response was progression as follows.



Safety

The study drugs continue to be well tolerated with no unanticipated. Over the last reporting period, there were two serious adverse events including one grade 3 renal failure due to urinary obstruction and one grade 3 pain. Neither were related to study drug.

The cumulative incidence of adverse events through the study for phase II patients is as follows (data collection ongoing).

Protocol Number and AE	Worst Grade(n, %) 1	2	3
IRB13-0979 (n=25) (All Phase II subjects)			
ABDOMINAL PAIN	1 4.0	1 4.0	.
ANOREXIA	6 24.0	1 4.0	.
ANXIETY	4 16.0	.	.
ARTHRALGIA	1 4.0	.	.
ARTHRITIS	1 4.0	2 8.0	.
BACK PAIN	2 8.0	2 8.0	.
BONE PAIN	1 4.0	.	.
COGNITIVE DISTURBANCE	1 4.0	.	.
CONFUSION	2 8.0	.	.
CONSTIPATION	6 24.0	.	.
COUGH	1 4.0	.	.
DEPRESSION	1 4.0	.	.
DIARRHEA	5 20.0	.	.
DIZZINESS	3 12.0	.	.
EDEMA LIMBS	1 4.0	.	.
ERECTILE DYSFUNCTION	1 4.0	.	.
FALL	1 4.0	.	.
FATIGUE	16 64.0	2 8.0	2 8.0
GYNECOMASTIA	2	.	.
	8.0	.	.
HEADACHE	5 20.0	.	.
HEMATURIA	2 8.0	.	.
HOT FLASHES	10 40.0	1 4.0	.
HYPERTENSION	1 4.0	.	.
INSOMNIA	1 4.0	.	.
MEMORY IMPAIRMENT	1 4.0	.	.
MUSCLE WEAKNESS LOWER LIMB	1 4.0	.	.
NASAL CONGESTION	1 4.0	.	.
NEUTROPHIL COUNT DECREASED	. .	. .	1 4.0
PAIN	5 20.0	2 8.0	.
PELVIC PAIN	. .	1 4.0	.
PERIPHERAL SENSORY NEUROPATHY	2 8.0	.	.
RASH MACULO-PAPULAR	. .	1 4.0	.
RENAL AND URINARY DISORDERS - OTHER, SPE	1 4.0	1 4.0	.
RENAL CALCULI	. .	. .	1 4.0
RESTLESSNESS	1 4.0	.	.
SINUS DISORDER	1 4.0	.	.
SKIN INFECTION	1 4.0	.	.
UPPER RESPIRATORY INFECTION	. .	3 12.0	.
URINARY FREQUENCY	1 4.0	1 4.0	.
URINARY INCONTINENCE	.	1	.
outAE2			
	.	4.0	.
URINARY RETENTION	1 4.0	1 4.0	.
URINARY TRACT INFECTION	. .	2 8.0	.
URINARY TRACT OBSTRUCTION	. .	. .	1 4.0
UROSTOMY LEAK	1 4.0	.	.
WHITE BLOOD CELL DECREASED	. .	. .	1 4.0

What opportunities for training and professional development has the project provided?

This award was not intended for professional development as it is not a training award. Nonetheless, the trial has allowed the PI, a junior investigator, to work as a lead investigator on a complex, multi-site clinical trial. As such provided the PI an opportunity to present trial progress at the PCCTC semi-annual meetings as well as present and participate in monthly teleconference. The PCCTC meetings are attended by representatives from ~15 leading prostate cancer research institutions and included multiple thought leaders in the field. The PI is able to share trial progress, which was an excellent learning opportunity.

C. How were the results disseminated to communities of interest?
There were no results to report during this reporting period.

D. What do you plan to do during the next reporting period to accomplish the goals?
The principal goal during the next reporting period is to complete enrollment for the phase II trial. There are two other PCCC network sites interested in opening the trial, with start up costs covered by the PI's discretionary funds, should NCE be approved to facilitate accrual goal.

4. IMPACT:

A. What was the impact on the development of the principal discipline(s) of the project?
The clinical trial has not completed and we do not have full results. Therefore, there are no significant impacts to the prostate cancer field as of yet. However, one key impact is that our trial is the first to our knowledge of enzalutamide in combination with another drug that is a pharmacologic inhibitor of enzalutamide metabolism. Enzalutamide metabolism is complex and involved multiple hepatic enzymes. We have shown that a strong inhibitor of CYP2C8/9 and CY3A4 essentially decreases clearance of enzalutamide by half. Beyond our trial, these data may have an impact as enzalutamide is considered in combination with other drugs.

Specifically, the University of Chicago and Northwestern are partners on a NIH SPORE in Prostate Cancer Award, which began in the last year. The PI of this DOD award was awarded a Major Project grant within this SPORE to further interrogate GR and AR. This will include a clinical trial with a novel GR antagonist with enzalutamide. The trial design for this trial, supported by the NIH SPORE, was informed by the PK data from this award.

B. What was the impact on other disciplines?
This study is the first study of mifepristone at 300mg daily dosing in an advanced cancer population. GR antagonism is a potential therapeutic maneuver for other cancers, such as breast cancer. We have shown that daily dosing of mifepristone in patients with advanced cancer is safe. This is impactful as the knowledge of its safety in this population can be used as the drug is developed in other cancers.

C. What was the impact on technology transfer?
The University of Chicago was granted a US patent on the concept of dual AR and GR antagonism based on preclinical work, which was licensed to Corcept Therapeutics, in part due to enthusiasm surrounding this currently ongoing clinical trial.

D. What was the impact on society beyond science and technology?
Nothing to report

5. CHANGES/PROBLEMS:

A. Changes in approach and reasons for change
There have been no changes in approach to this research award.

B. Actual or anticipated problems or delays and actions or plans to resolve them

It should be noted that there were barriers to fully accomplishing Major Task 3 prior to this reporting period that have been reported previously and are now resolved. Although accrual increasing with other sites opening, accrual to the trial remains slower then anticipated. This will be improved by opening two additional PCCC network sites, which have been identified and are agreeable to open pending complete approval of pending NCE. Start up costs will be covered through discretionary funds as further site start up costs not covered in DOD budget. Another unanticipated potential issue is that preliminarily, a larger proportion of patients than anticipated have been unable to randomize due to early progression. This does not impact the ultimate number needed to randomize but will potentially increase total accrual if trend persists.

C. Changes that had a significant impact on expenditures

Due to slower then anticipated progress in completing the phase I study, the phase II with site activation was slower than anticipate necessitating NCE. We have submitted a second No Cost Extension to allow completion of accrual.

From an expenditure standpoint, all expenditures budgeted for outside site accruals have been separated from the internal University of Chicago operating budget and will not be affected by the extension. These funds are available to support their accrual provided NCE approved. In the fourth year and beyond, salary support for the PI and study personnel at University of Chicago will therefore be provided through internal funds. This has been discussed with and agreed upon by the Section Chief and senior co-Investigator on this study, Dr. Stadler. There are no expenditure changes otherwise.

D. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents: Nothing to report.

E. Significant changes in use or care of human subjects: Nothing to report

F. Significant changes in use or care of vertebrate animals: Nothing to report

G. **Significant changes in use of biohazards and/or select agents:** Nothing to report

6. PRODUCTS:

A. Publications, conference papers, and presentations: Abstract on the trial, including PK results from phase I were reported at ASCO 2016, in poster, written abstract form.
http://meetinglibrary.asco.org/content/170508-176

B. Website(s) or other Internet site(s): Nothing to report

C. Technologies or techniques: Nothing to report

D. Inventions, patent applications, and/or licenses: Nothing to report

E. Other Products: Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

A. What individuals have worked on the project?

Key Study Personnel	Study Roles and Responsibilities	Nearest Person Month, source of funding
Name: Russell Szmulewitz, MD Affiliated Institution: University of Chicago	Study Role(s): Principal Investigator Responsibilities: Study oversight and conduct	2, University of Chicago internal funds
Name: Elia Martinez, RN, OCN Affiliated Institution: University of Chicago	Study Role(s): Research Nurse Responsibilities: Coordinates research activities for the patients on the study	2, University of Chicago internal funds
Name: Julie Gruczynski Affiliated Institution: University of Chicago	Study Role(s): Study Coordinator Responsibilities: Data manager for the study. Took over role from Jaclyn Peterson	2, University of Chicago internal funds
Name: Walter Stadler, MD Affiliated Institution: University of Chicago	Study Role(s): Co-Investigator Responsibilities: Assist PI with patient accrual, research activities and data analysis	0.5 month, University of Chicago internal funds
Name: Peter ODonnell, MD Affiliated Institution: University of Chicago	Study Role(s): Co-Investigator Responsibilities: Assist PI with patient accrual	0
Name: Chadi Nabhan, MD Affiliated Institution: University of Chicago	Study Role(s): Co-Investigator Responsibilities: Assist PI with patient accrual	0
Name: Mark Ratain Affiliated Institution: University of Chicago	Study Role(s): Co-Investigator Responsibilities: Assist PI with data acquisition and analysis	0.5 month, University of Chicago internal funds
Name: Theodore Karrison, PhD Affiliated Institution: University of Chicago	Study Role(s): Biostatistician Responsibilities: Generation of randomization algorithm and assistance with data analysis	1, University of Chicago internal funds
Name: Amanda Spratt, CCRP Affiliated Institution: University of Chicago	Study Role(s): Independent Safety Monitor Responsibilities: Oversee study accuracy of interventions, adherence to protocol guidelines, review study recruitment and the weekly data safety monitoring minutes for the trial and coordinate/oversee review of data matching and data collection across the trial. Member of the University of Chicago High Risk Protocol Committee, where this study is reviewed quarterly.	1, University of Chicago internal funds

B. Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to report

C. What other organizations were involved as partners?
Pfizer/Medivation supports free enzalutamide for the clinical trial. Corcept Therapeutics supports the study with free mifepristone for the clinical trial.

8. SPECIAL REPORTING REQUIREMENTS
None

9. APPENDICES
None