

**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**

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<b>4. TITLE AND SUBTITLE</b> A Pharmacokinetic/Pharmacodynamic Study of the Glucocorticoid Receptor Antagonist Mifepristone Combined with Enzalutamide in Castrate-Resistant Prostate Cancer				<b>5a. CONTRACT NUMBER</b>	
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<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> 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.					
<b>15. SUBJECT TERMS</b> Castration Resistant Prostate Cancer (CRPC); Androgen Receptor (AR); Glucocorticoid Receptor (GR); Enzalutamide; Mifepristone; Pharmacokinetic (PK) Pharmacodynamic (PD); Prostate Cancer (PC)					
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Unclassified	Unclassified	unclassified	Unclassified	15	<b>19b. TELEPHONE NUMBER (Include area code)</b>

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## 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, lead 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 extending the study through a no-cost extension to all 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.

<b>Major Task 1: Regulatory Approval: Lead and subsidiary sites</b>	<b>COMPLETE</b>
<b>Major Task 2: Coordinate and Initiate Phase I Portion of Study</b>	<b>COMPLETE</b>
<b>Major Task 3: Complete phase I study</b>	<b>COMPLETE</b>
<b>Major Task 4: Initiation of Phase II</b>	<b>COMPLETE</b>
<b>Major Task 5: Complete Phase II study</b>	<b>COMPLETE</b>
<b>Major Task 6: Data Analysis</b>	<b>Ongoing</b>

**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.

<b>Major Task 1: Regulatory Approval: Lead and subsidiary sites</b>			
	<b>Timeline (months)</b>	<b>Objective complete</b>	<b>Findings, developments, discussion points</b>
<u>Subtask 1:</u> Obtain Regulatory Approval for Research Protocol at UC: COMPLETE			
<u>Subtask 2:</u> 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

<b>Major Task 2: Coordinate and Initiate Phase I Portion of Study</b>			
	<b>Timeline (months)</b>	<b>Objective complete</b>	<b>Findings, developments, discussion points</b>
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	

<b>Major Task 3: Complete phase I study</b>	<b>Timeline (months)</b>	<b>Objective complete</b>	<b>Findings, developments, discussion points</b>
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	Yes	ongoing
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
<i>Milestone Achieved: Completion of phase I study</i>	9-12	Yes	

<b>Major Task 4: Initiation of Phase II</b>			
	<b>Timeline (months)</b>	<b>Objective Complete</b>	<b>Findings, developments, discussion points</b>
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	

<b>Major Task 5: Complete Phase II study</b>			
	<b>Timeline (months)</b>	<b>Objective Complete</b>	<b>Findings, developments, discussion points</b>
Recruitment and enrolment	30-72	Yes	Depending on accrual 2 University of Chicago Network site can be added
Data Capture and Input	30-72	Ongoing	TBD
PK analysis (Batched for Phase II portion of study)	30-72	Ongoing	PK Samples will be collected and batch analyzed at end of accrual
Weekly institutional data safety monitoring board	30-72	Ongoing	Weekly DSM
Monthly safety/oversight teleconference	30-72	Ongoing	Weekly teleconference DSM through University of Chicago Personalized Cancer Care Consortium
Submission of year 2 IND report	21-24	Yes	

to FDA**			
Submission of year 3,4 IND report to FDA**		Yes	
Submission of any protocol amendments to IRB, FDA, HRPO	Continuous	Yes	

<b>Major Task 6: Data Analysis</b>			
Coordinate with Sites for monitoring data collection rates and data quality	30-72	Yes	Ongoing
Perform all analyses according to specifications, share output and finding with all investigators	25-27; 30-72	Yes	See below
Disseminate and report results from Phase I study (abstracts, DOD)**	27-30	Yes	In current protocol. Awaiting national reporting for completion and analysis of phase II
Disseminate and report findings from Phase II study (abstracts, DOD)	52-72	Ongoing	See below
Submit manuscript for publication on results of study	>72 (post award)		
Publication of study results	>72 (post award)		
<i>Milestone Achieved: Report results from data analyses for phase I, Report results for phase II, publish study results</i>	25->60		Completed interim analysis of phase II study.

**\*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 the primary task has been to complete accrual to the phase II study through all 4 sites. We continue discussing the study weekly at our the University of Chicago Personalized Cancer Care Consortium (PCCC) safety monitoring meeting, lead 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 including 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 from those tasks  
 Since the last reporting period, significant recruitment has been completed and the interim analysis has been completed as of 2/6/19 and is included below. Recruitment as of 2/6/19 is as follows.

Count of SUBGROUP DESCRIPTION	
SUBGROUP DESCRIPTION	Total
Phase I: Dose Escalation, Safety, Tolerability	18
Phase II portion, part 2 patients randomized to Enz + Mifepristone	33
Phase II portion, part 2 patients who are randomized to Enz only	33
Phase II, part 1: Pre-randomization	8
Phase II, Part I: post-lead in- non randomized patients	16
Grand Total	108

As noted, there have been 66 patients randomized (n=84 initially planned to randomized per biostatistical plan) on the phase II portion of the study with 2 currently screening. There are 8 patients in the pre-randomization enzalutamide alone lead-in. Sixteen patients experienced progressive disease prior to randomization and were not randomized.

**Efficacy**

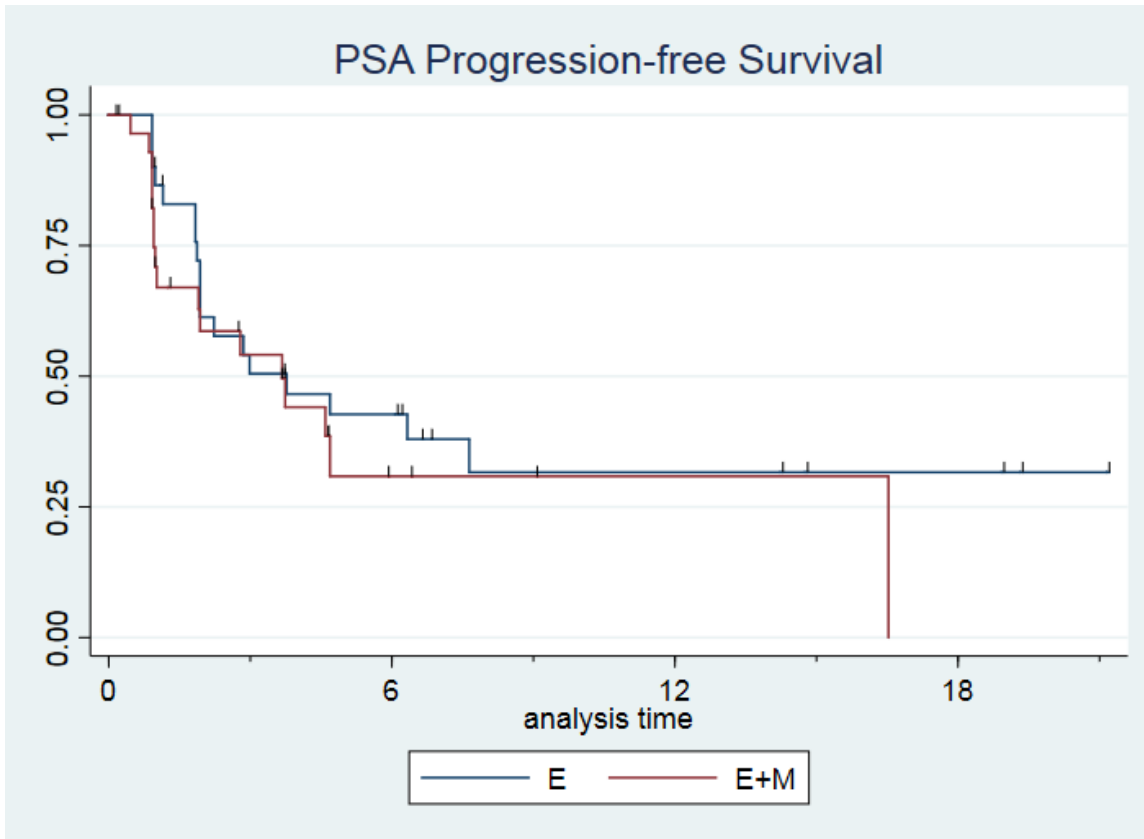
**Cortisol Analysis**

As cortisol is a readout for central GR blockade, cortisol increase was the first condition of the interim analysis. 42 patients had a cortisol value recorded at week 16 (one month from randomization at week 12). Mean cortisol levels were 12.8 (E) vs. 28.3 (E+M), a highly significant difference in favor of the combination arm (p<0.001). Thus, the study drug lead to expected endocrine changes.

**Disease control (PSA progression)**

Per protocol guidelines, an interim analysis was undertaken after 35 progression events. PSA progression was defined as a PSA rise of  $\geq 25\%$  or death

Time to PSA progression is similar in the two treatment arms with 12-month progression-free rates of approximately 31% in both arms (logrank p=0.39):



Cox regression analysis yields a hazard ratio (E+M)/E of  $\exp(0.2902) = 1.34$  in favor of the control (E) arm ( $p=0.4$ ). The conditional power at this first (and only) interim time point is

$$p_1(\theta) = \Phi\left(\frac{-0.85 * \sqrt{35} - 1.28 * \sqrt{70} + (70 - 35) * \frac{1.28+0.84}{\sqrt{70}}}{\sqrt{70 - 35}}\right) = \Phi(-1.16) = 0.12,$$

which is less than 0.25. Thus per protocol, this meets futility assessment for further randomization.

### Safety

The study drugs continue to be well tolerated with no unanticipated. Over the last reporting period, there were no serious adverse events deemed potentially related to study drug and cumulative toxicity is as follows:

Protocol Number and AE	Worst Grade(n, %)					
	0	1	2	3	4	5

IRB13-0979 (n=88)	
ABDOMINAL DISTENSION	. 1 . . . . .
ABDOMINAL PAIN	. 3 1 1 . . . . .
AGITATION	. . 1 . . . . .
ALKALINE PHOSPHATASE INCREASED	. 1 . . . . .
ALOPECIA	. 1 . . . . .
AMNESIA	. 3 1 . . . . .
ANEMIA	. 1.1 . . . . .
ANOREXIA	. 18 4 . . . . .
ANXIETY	. 9 . . . . .
ARTHRALGIA	. 5 1 . . . . .
ARTHRITIS	. 1 2 . . . . .
ATRIAL FIBRILLATION	. . . 1 . . . . .
BACK PAIN	. 6 5 . . . . .
BLADDER SPASM	. . 1 . . . . .
BLOATING	. 1.1 . . . . .
BLOOD BILIRUBIN INCREASED	. 1 . . . . .
BONE PAIN	. 2 . 1 . . . . .
BREAST PAIN	. 1 . . . . .

IRB13-0979	
GAIT DISTURBANCE	. . 1 . . . . .
GASTROESOPHAGEAL REFLUX DISEASE	. 1 . . . . .
GENERALIZED MUSCLE WEAKNESS	. 6 1 . . . . .
GENITAL EDEMA	. 2 . . . . .
GYNECOMASTIA	. 4 1 . . . . .
HEADACHE	. 5 . 1 . . . . .
HEART FAILURE	. . . 1 . . . . .
HEMATURIA	. 4 . . . . .
HOT FLASHES	. 23 3 . . . . .
HYPERGLYCEMIA	. 2 2 . . . . .
HYPERSOMNIA	. 1 . . . . .
HYPERTENSION	. 2 . 1 . . . . .
HYPOGLYCEMIA	. . 1 . . . . .
ILEUS	. . 1 . . . . .
INFECTIONS AND INFESTATIONS - OTHER, SPE	. . 1 . . . . .
INSOMNIA	. 2 2 . . . . .
INTRAOPERATIVE MUSCULOSKELETAL INJURY	. . 1 . . . . .
INVESTIGATIONS - OTHER, SPECIFY	. 1 . . . . .
LARYNGEAL INFLAMMATION	. 1 . . . . .
LOCALIZED EDEMA	. 1 . . . . .
LUNG INFECTION	. . . 1 . . . . .

IRB13-0979	
COGNITIVE DISTURBANCE	. 3 . 1 . . . . .
CONFUSION	. 4 1 . . . . .
CONSTIPATION	. 17 2 . . . . .
COUGH	. 4 . . . . .
CYSTITIS NONINFECTIVE	. 1 1 . . . . .
DEATH NOS	. . . . . 2.3 . . . . .
DEPRESSION	. 3 1 . . . . .
DIARRHEA	. 16 . . . . .
DIZZINESS	. 9 2 . . . . .
DRY SKIN	. 1 . . . . .
DYSGEUSIA	. 1.1 . . . . .
DYSPEPSIA	. 2 . . . . .
DYSPHAGIA	. . . 1 . . . . .
DYSPNEA	. 4 2 . . . . .
EDEMA LIMBS	. 5 1 . . . . .
ENTEROCOLITIS INFECTIOUS	. . . 1 . . . . .
ERECTILE DYSFUNCTION	. 1 . . . . .
FALL	. 3 1 . . . . .
FATIGUE	. 45 16 4 . . . . .
FLU LIKE SYMPTOMS	. 2 . . . . .
FRACTURE	. 1 1 . . . . .

LYMPHOCYTE COUNT DECREASED	. . 1 . . . . .
MEMORY IMPAIRMENT	. 6 . . . . .
MUCOSAL INFECTION	. 1 . . . . .
MUSCLE WEAKNESS LOWER LIMB	. 1 . . . . .
MYALGIA	. . 2 . . . . .
NASAL CONGESTION	. 4 . . . . .
NAUSEA	. 11 2 . . . . .
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIF	. . . 2 1 . . . . .
NEUTROPHIL COUNT DECREASED	. 1 . 1 . . . . .
NON-CARDIAC CHEST PAIN	. 2 . 1 . . . . .
PAIN	. 19 4 1 . . . . .
PAIN IN EXTREMITY	. 2 1 . . . . .
PARESTHESIA	. 1 . . . . .
PELVIC PAIN	. 3 2 1 . . . . .
PERIPHERAL MOTOR NEUROPATHY	. 1 . . . . .
PERIPHERAL SENSORY NEUROPATHY	. 6 . . . . .
PLATELET COUNT DECREASED	. 1 . . . . .
PNEUMONITIS	. . 1 . . . . .
PRODUCTIVE COUGH	. 1 . . . . .
PRURITUS	. 1 . . . . .
RASH ACNEIFORM	. 1 . . . . .



#### **4. IMPACT:**

##### **A. What was the impact on the development of the principal discipline(s) of the project?**

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 includes a clinical trial with a novel GR antagonist with enzalutamide. The trial, supported by the NIH SPORE, has begun to accrue and is using the pharmacology learned from this trial as its foundation.

##### **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**

No further delays have been noted during this reporting period. Accrual has been brisk and is now completed.

##### **C. Changes that had a significant impact on expenditures**

Due to slower than 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 payment to subcontracted sites for their ongoing patients accrued to the trial.

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 is 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	1, 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
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

**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