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

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Szmulewitz, Russell

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

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University of Chicago
5801 S. Ellis Avenue
Chicago, IL 60637

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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. Within the phase I portion, the study will examine the pharmacokinetics and safety of the two drugs in combination. The phase II portion is a multi-site randomized clinical trial of enzalutamide alone or in combination with mifepristone.

15. SUBJECT TERMS

Castration Resistant Prostate Cancer (CRPC); Androgen Receptor (AR); Glucocorticoid Receptor (GR); Enzalutamide; Mifepristone; Pharmacokinetic (PK) Pharmacodynamic (PD); Prostate Cancer (PC)

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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 extention 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.

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	**COMPLETE**
Major Task 6: Data Analysis	**Ongoing**

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 abovc
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	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
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	30-72	Yes	Depending on accrual 2 University of Chicago Network site can be added
Data Capture and Input	30-72	Yes	Final data cleaning is ongoing
PK analysis (Batched for Phase II portion of study)	30-72	Yes	
Weekly institutional data safety monitoring board	30-72	Yes	Weekly DSM
Monthly safety/oversight teleconference	30-72	Yes	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	

Major Task 6: Data Analysis			
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	Yes	Study present as poster presentation at ASCO Genitourinary Symposium 2020
Submit manuscript for publication on results of study	>72 (post award)	Ongoing	Manuscript in draft
Publication of study results	>72 (post award)	Ongoing	Manuscript in draft
Milestone Achieved: Report results from data analyses for phase I, Report results for phase II, publish study results	25->60		Completed interim analysis of phase II study.

Discussion of Accomplishments:

Regulatory/oversight

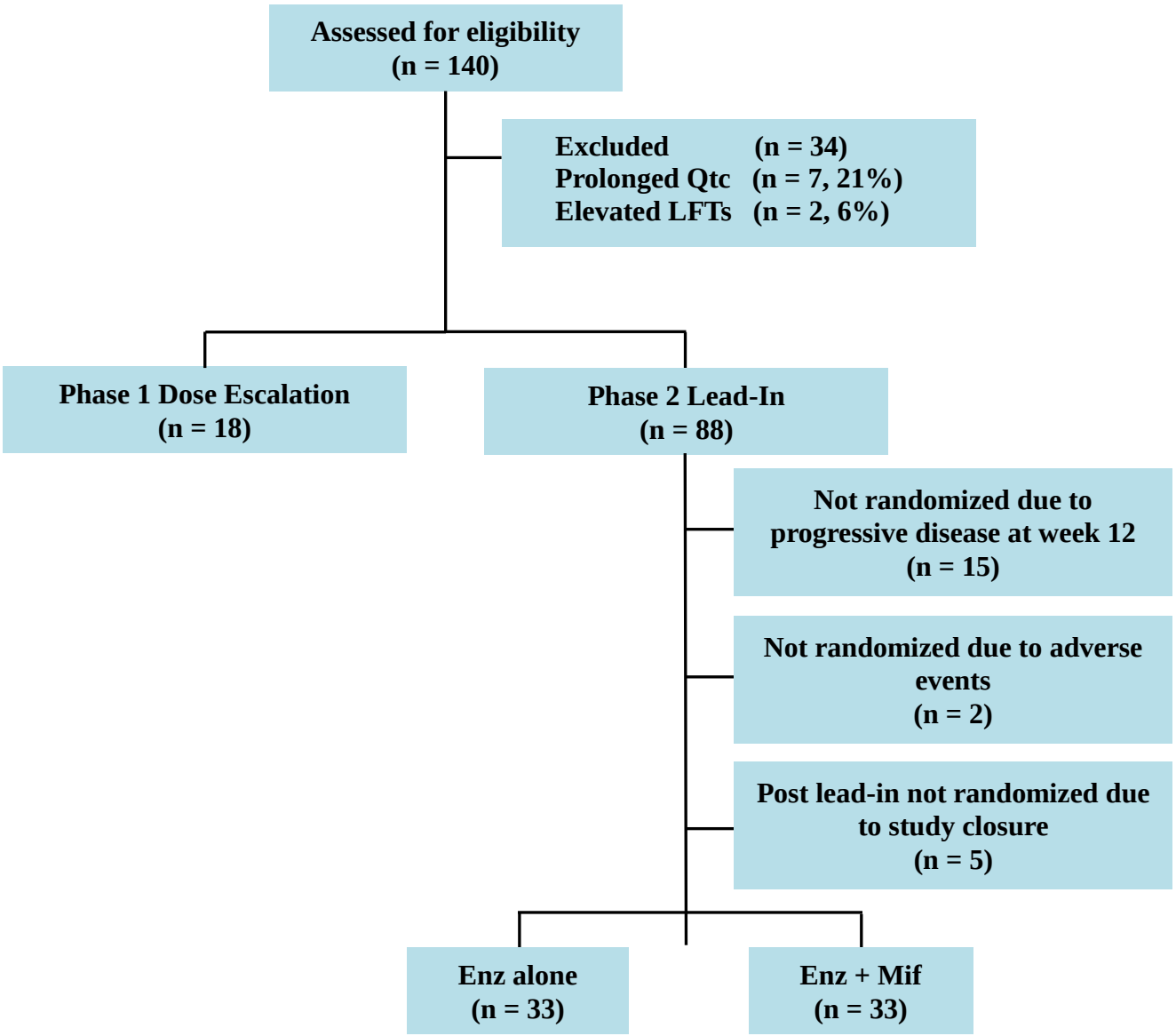
Within this reporting period the primary task was to complete accrual to the phase II study through all 4 sites. We continued discussing the study weekly at our the University of Chicago Personalized Cancer Care Consortium (PCCC) safety monitoring meeting, led by Dr. Walter Stadler, which allows for teleconferencing of affiliate sites on this study. Our independent trial monitor is also present at the weekly DSM, which 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 was reviewed quarterly for safety and data integrity at the University of Chicago Comprehensive Cancer Center High Risk Clinical Trial committee. This committee reported no concerns. 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.

Accrual: Task 2 through 4 were completed prior to this reporting period and were fully reported at the last yearly technical report. Task 5, completion of the phase II trial was accomplished during the final

reporting period. Task 6, analysis of the study and dissemination of results, has been the major task for this reporting period (see below).

As noted in figure 1, there were 66 patients randomized to the phase II, after initial phase I (n=84 initially planned to randomized per biostatistical plan). The most common reasons for eligibility exclusion were elevated liver function studies and prolonged Qtc.

Figure 1: Accrual consort diagram. Enz, enzalutamide; Enz alone, Enz 160mg daily after 12-week enzalutamide monotherapy lead in; Enz+Mif, Enz 120mg and Mif 300 mg daily after 12 week Enz lead-in; LFTs, liver function tests; Mif, mifepristone.



Accrual demographics for the entire study are as follows:

	Overall	Phase I	Phase II (n=88)

	(n=106)	(n=18)	Enz (n=33)	Enz + Mif (n=33)	NR (n=22)
Age, years					
Median (range)	69 (52-58)	70 (55-84)	71 (52-83)	71 (57-85)	68 (52-58)
>75, No. (%)	34 (32)	5 (28)	10 (30)	14 (42)	5 (23)
ECOG PS, No (%)					
0 or 1	46 (43)	10 (56)	13 (39)	16 (49)	7 (32)
2	60 (57)	8 (44)	20 (61)	17 (52)	15 (68)
Race, No. (%)					
White	76 (72)	12 (67)	20 (61)	26 (79)	16 (73)
AA	25 (24)	6 (33)	9 (27)	7 (21)	3 (14)
Asian	2 (2)	0	2 (6)	0	0
Other	3 (3)	0	2 (6)	0	1 (5)
Prior Docetaxel No. (%)	36 (34)	7 (39)	9 (27)	6 (19)	14 (64)
Disease Location, No. (%)					
Bones	73 (69)	16 (89)	22 (67)	19 (58)	16 (73)
Lymph Nodes	57 (54)	11 (61)	17 (52)	18 (55)	11 (50)
Viscera	30 (28)	6 (33)	9 (27)	6 (18)	9 (41)
PSA (ng/mL), median (range)	11.0 (0.1-616)	7.1 (1.5-616)	14.4 (2.2-342)	12.3 (0.2-77.7)	10.4 (0.1-380)

Pharmacokinetics: Given the effect of mifepristone on enzalutamide, PK analyses were performed during the phase I portion, as follows:

	Enz + Metabolite C_{min} (ug/mL) (Mean ± Standard Deviation)		
	Day 29	**Day 57**	**Day 57/29**
Enz 40mg, Mif 300mg*	22.1 ± 6.1	13.5 ± 7.2	0.6 ± 0.2
Enz 80mg, Mif 300mg*	20.1 ± 1.5	14.1 ± 3.3	0.7 ± 0.1
Enz 120mg, Mif 300mg	23.0 ± 5.5	22.4 ± 5.9	1.0 ± 0.2

Efficacy

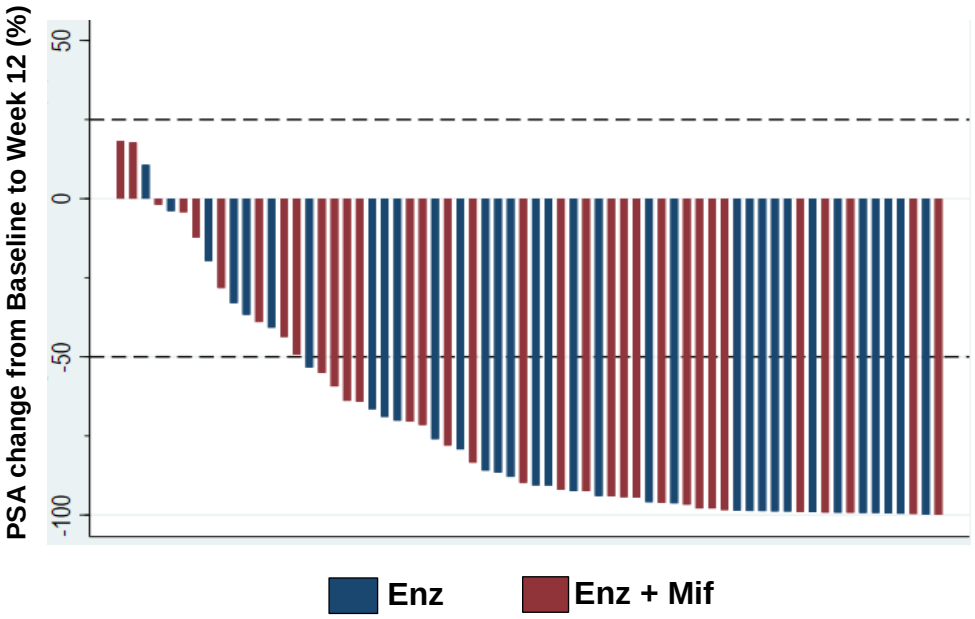
Cortisol Analysis

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.

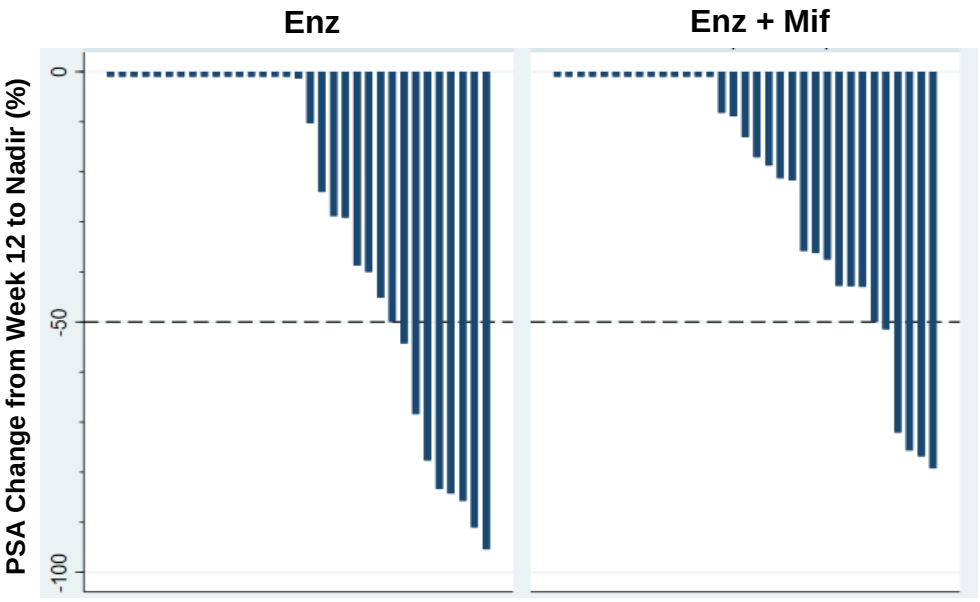
PSA Response

Figure 2. Decrease in prostate-specific antigen (PSA) while receiving treatment during 12-week Enz lead-in. Decrease in PSA while receiving treatment. Waterfall plot showing percent reduction in PSA at (A) 12-week time point after Enz alone lead-in prior to combination with Mif at week 12 and (B) maximum nadir post randomization.

A



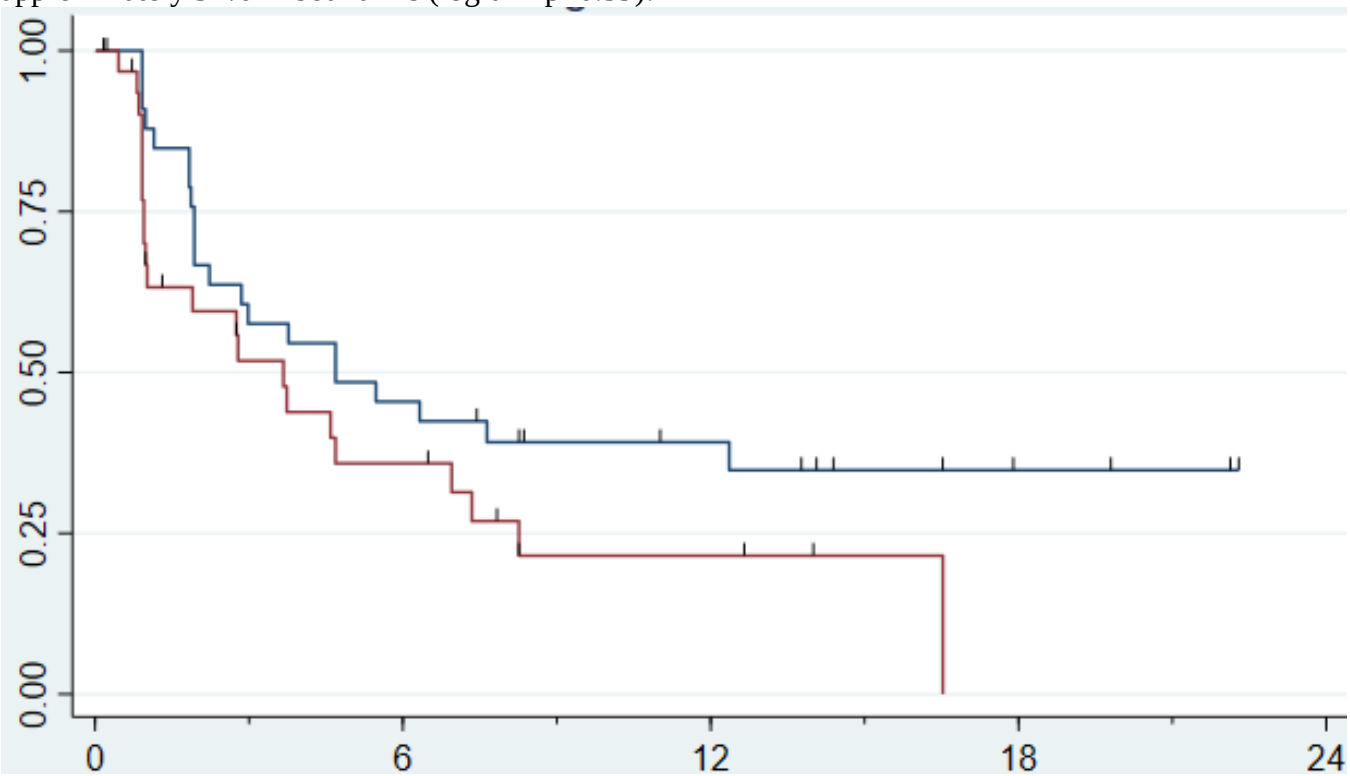
B



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 ≥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

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

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

Safety

The study drugs were well tolerated with no unanticipated. Final safety analysis is as follows:

Adverse Events Summary: Adverse Events of Grade 1 to 3 in ≥15% of Patients in Any Cohort

	Phase 1 No., % (n= 18)		Phase 2: Enz Alone No., % (n = 33)		Phase 2: Enz + Mif No., % (n= 33)	
	All Grade	Grade 3	All Grade	Grade 3	All Grade	Grade 3
Total Adverse Events (No. of patients, %)	16 (89)	3 (22)	29 (88)	5 (15)	30 (91)	6 (18)
Any Serious Adverse Events						
Any AE leading to Treatment Discontinuation						
Any Adverse Event Leading to Death						
Adverse Event	**All Grade**	**Grade 3**	**All Grade**	**Grade 3**	**All Grade**	**Grade 3**
Fatigue	13 (72)	1 (6)	25 (76)	1 (3)	25 (76)	4 (12)
Anorexia	5 (28)	0 (0)	4 (12)	0 (0)	11 (33)	0 (0)
Diarrhea	5 (28)	0 (0)	6 (18)	0 (0)	4 (12)	0 (0)
Hot Flashes	5 (28)	0 (0)	15 (45)	0 (0)	15 (45)	0 (0)
Nausea	5 (28)	0 (0)	3 (9)	0 (0)	3 (9)	0 (0)
Pain	5 (28)	0 (0)	1 (3)	0 (0)	1 (3)	0 (0)
Amnesia	4 (22)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Edema	3 (17)	0 (0)	1 (3)	0 (0)	3 (9)	0 (0)
Generalized Muscle Weakness	0 (0)	0 (0)	2 (6)	0 (0)	8 (24)	0 (0)
Dizziness	2 (11)	0 (0)	1 (3)	0 (0)	5 (15)	0 (0)

AE, adverse event; Enz, Enzalutamide; Enz alone, Enz 160mg daily after 12-week enzalutamide monotherapy lead in; Enz+Mif, Enz 120mg and Mif 300 mg daily after 12 week Enz lead-in; Mif, Mifepristone

Current Study Plans:
The study has completed and final efforts in Task 6 involving data analysis and publication of findings is ongoing and will be completed after completion of this award. The results were presented nationally at the ASCO Genitourinary Oncology Symposium in Feb 2020. Serritella at el., *J Clin Oncol*. 38, 2020 (suppl 6; abstr 91). Final analysis is ongoing and manuscript is in advanced draft.

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 allowed the PI 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.

In addition, the award, and study that it funded, were the foundation of several other grants, including a Prostate Cancer Foundation Challenge Award, which funded the biomarker analyses embedded in this trial. Based on these preliminary results, the PI was able to secure funding as a major project within an NCI SPORE in prostate cancer (P50 CA180995) to support the next iteration of GR-AR antagonist study using a novel GR antagonist.

C. How were the results disseminated to communities of interest?

The results were presented nationally at the ASCO Genitourinary Oncology Symposium in Feb 2020. Serritella at el., *J Clin Oncol*. 38, 2020 (suppl 6; abstr 91). Final analysis is ongoing and manuscript is in advanced draft.

D. What do you plan to do during the next reporting period to accomplish the goals?
NA. This is the final reporting period

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, and requires a 25% dose reduction. 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

Data analysis has not been completed as we are waiting on final correlative data. It is anticipated that manuscript will be submitted in the next quarter following completion of this award.

C. Changes that had a significant impact on expenditures

Nothing to report

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: The results were presented nationally at the ASCO Genitourinary Oncology Symposium in Feb 2020. Serritella at el., *J Clin Oncol*. 38, 2020 (suppl 6; abstr 91).

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