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

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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 guarter 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             |                              |                       |  |  |  |  |
|--|------------------------------|-----------------------|--|--|--|--|
|  | Timelin<br>e<br>(months<br>) | Objective<br>complete | Findings, developments, discussion<br>points   |  |  |  |
| Subtask 1: Obtain Regulatory Ap  | pproval for R                | Research Protoco      | ol at UC: COMPLETE   |  |  |  |
| <u>Subtask 2:</u> Obtain Regulatory Ap<br>for Research Protocol at PCCTC | pproval<br>sites             | _                     |  |  |  |  |
| PCCTC site identification  |                              | Yes                   | The trial is now open at NorthShore<br>University (D. Shevrin PI) and at<br>Karmanos Cancer Center (Heath).<br>Depending on accrual 2 University of<br>Chicago Network site can be added |  |  |  |
| Scientific and IRB<br>submission at PCCTC sites                          | 25-28                        | Yes                   | Regulatory documents sent to sites above   |  |  |  |
| Coordination of Clinical<br>Trials Agreement (CTA) at<br>PCCTC sites     | 25-28                        | Yes                   | Active central CTA agreements are<br>already in place between the University<br>of Chicago and PCCTC sites as well as<br>University of Chicago and                                       |  |  |  |
| Scientific Review Approval<br>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         Objective         Findings, developments, discussion    |                              |                       |  |  |  |  |

|  | (months) | 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 | Timeline | Objective | Findings, developments, discussion points |
|------------------------------|----------|-----------|---|
| I study                      | (months) | complete  |   |
| 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<br>to FDA                  | 9-12       | Yes | Yearly IND reports submitted   |
| Submission of any protocol<br>amendments to IRB, FDA, HRPO | Continuous | Yes | Personnel and minor clarification<br>amendments submitted to IRB. No<br>significant changes that mandated<br>HRPO submission |
| Milestone Achieved: Completion<br>of phase I study         | 9-12       | Yes |  |

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

| Major Task 5: Complete Phase II study               |                      |                               |   |  |  |
|---|----------------------|-------------------------------|---|--|--|
|   | Timeline<br>(months) | Objecti<br>ve<br>Comple<br>te | Findings, developments, discussion<br>points  |  |  |
| Recruitment and enrolment                           | 30-72                | Yes                           | Depending on accrual 2 University of<br>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<br>University of Chicago Personalized<br>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  | Major Task 6: Data Analysis |         |  |  |  |  |  |
|--|-----------------------------|---------|--|--|--|--|--|
| Coordinate with Sites for<br>monitoring data collection rates<br>and data quality  | 30-72                       | Yes     | Ongoing  |  |  |  |  |
| Perform all analyses according to<br>specifications, share output and<br>finding with all investigators                        | 25-27; 30-<br>72            | Yes     | See below  |  |  |  |  |
| Disseminate and report results<br>from Phase I study (abstracts,<br>DOD)   | 27-30                       | Yes     | In current protocol. Awaiting national reporting for completion and analysis of phase II |  |  |  |  |
| Disseminate and report findings<br>from Phase II study (abstracts,<br>DOD)   | 52-72                       | Yes     | Study present as poster presentation at<br>ASCO Genitourinary Symposium 2020             |  |  |  |  |
| Submit manuscript for publication on results of study  | >72 (post<br>award)         | Ongoing | Manuscript in draft  |  |  |  |  |
| Publication of study results   | >72 (post<br>award)         | Ongoing | Manuscript in draft  |  |  |  |  |
| Milestone Achieved: Report<br>results from data analyses for<br>phase I, Report results for phase<br>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.

<u>Accrual:</u>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 | demograp | hics for | the entire | study are | as follows: |
|---------|----------|----------|------------|-----------|-------------|
|---------|----------|----------|------------|-----------|-------------|

|   | Overall | Phase I | Phase II (n=88) |
|---|---------|---------|-----------------|
| - |         |         |                 |

|                                | (n=106)           | ( <b>n=18</b> )  | Enz<br>(n=33)     | Enz + Mif<br>(n=33) | NR<br>(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<br>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),<br>median (range) | 11.0<br>(0.1-616) | 7.1<br>(1.5-616) | 14.4<br>(2.2-342) | 12.3<br>(0.2-77.7)  | 10.4<br>(0.1-380) |

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

|                      | Enz + Metabolite C <sub>min</sub> (ug/mL)<br>(Mean ± Standard Deviation) |                |               |  |
|----------------------|--|----------------|---------------|--|
|                      | Day 29   | Day 57         | Day 57/29     |  |
| Enz 40mg, Mif 300mg* | 22.1 ± 6.1   | $13.5 \pm 7.2$ | $0.6 \pm 0.2$ |  |
| Enz 80mg, Mif 300mg* | $20.1 \pm 1.5$   | $14.1 \pm 3.3$ | $0.7 \pm 0.1$ |  |
| Enz 120mg, Mif 300mg | $23.0 \pm 5.5$   | 22.4 ± 5.9     | $1.0 \pm 0.2$ |  |

<u>Efficacy</u> 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.





#### 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

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

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<br>No., %<br>(n= 18) |         | Phase 2: Enz Alone<br>No., %<br>(n = 33) |         | Phase 2: <u>Enz</u> + <u>Mif</u><br>No., %<br>(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 <u>after</u> 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<br>Month, source of<br>funding |
|---|---|---|
| Name: Russell Szmulewitz,<br>MD<br>Affiliated Institution:<br>University of Chicago | Study Role(s): Principal Investigator<br>Responsibilities: Study oversight and<br>conduct                                   | 1, University of<br>Chicago internal<br>funds |
| Name: Elia Martinez, RN,<br>OCN<br>Affiliated Institution:<br>University of Chicago | Study Role(s): Research Nurse<br>Responsibilities: Coordinates research<br>activities for the patients on the study         | 2   |
| Name: Julie Gruczynski<br>Affiliated Institution:<br>University of Chicago          | Study Role(s): Study Coordinator<br>Responsibilities: Data manager for the<br>study; took over role from Jaclyn<br>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